CONTROL OF SLEEP AND WAKEFULNESS

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Brown RE, Basheer R, McKenna JT, Strecker RE, McCarley RW. Control of Sleep and Wakefulness. *Physiol Rev* 92: 1087–1187, 2012; doi:10.1152/physrev.00032.2011.—This review summarizes the brain mechanisms controlling sleep and wakefulness. Wakefulness promoting systems cause low-voltage, fast activity in the electroencephalogram (EEG). Multiple interacting neurotransmitter systems in the brain stem, hypothalamus, and basal forebrain converge onto common effector systems in the thalamus and cortex. Sleep results from the inhibition of wake-promoting systems by homeostatic sleep factors such as adenosine and nitric oxide and GABAergic neurons in the preoptic area of the hypothalamus, resulting in large-amplitude, slow EEG oscillations. Local, activity-dependent factors modulate the amplitude and frequency of cortical slow oscillations. Non-rapid-eye-movement (NREM) sleep results in conservation of brain energy and facilitates memory consolidation through the modulation of synaptic weights. Rapid-eye-movement (REM) sleep results from the interaction of brain stem cholinergic, aminergic, and GABAergic neurons which control the activity of glutamatergic reticular formation neurons leading to REM sleep phenomena such as muscle atonia, REMs, dreaming, and cortical activation. Strong activation of limbic regions during REM sleep suggests a role in regulation of emotion. Genetic studies suggest that brain mechanisms controlling waking and NREM sleep are strongly conserved throughout evolution, underscoring their enormous importance for brain function. Sleep disruption interferes with the normal restorative functions of NREM and REM sleep, resulting in disruptions of breathing and cardiovascular function, changes in emotional reactivity, and cognitive impairments in attention, memory, and decision making.

I. INTRODUCTION

The purpose of sleep is one of the great unsolved mysteries of biology and has fascinated people for millennia. Although the function or functions of sleep are still unresolved, great progress has been made in understanding the brain mechanisms that control sleep and wakefulness. An understanding of these mechanisms is of paramount importance to our society. Sleeping tablets are among the most widely prescribed medicines, and disturbances in sleep are associated with a wide range of medical and psychiatric conditions. Conversely, an increase in sleep is one important mechanism that the body uses to combat infection and maintain optimal health. Adequate sleep is also essential for optimal cognitive function; lack of sleep has been implicated in major industrial disasters as well as car and workplace accidents. In this unusually comprehensive review we summarize current knowledge regarding the brain mecha-

nisms which control wakefulness, non-rapid-eye-movement (NREM) sleep, and rapid-eye-movement (REM) sleep.

A. Characteristics of Sleep-Wake States

Sleep is defined in the sleep laboratory, in both humans and animals, by recording the electrical field activity of large groups of cortical neurons and muscle cells. Thus scalp electrodes record the electroencephalogram (EEG), electrodes placed on or in skeletal muscles record the electromyogram (EMG), whereas electrodes placed over or near the muscles responsible for horizontal eye movement record the electro-oculogram (EOG). Deep brain electrodes are used to record the activity of individual brain areas or individual neurons. These so-called polysomnographic recordings are used to define the states of wakefulness and sleep as follows (FIGURE 1): wakefulness is defined by low-voltage fast EEG activity (LVFA) and high muscle tone, NREM sleep is characterized by high-amplitude low-frequency EEG and decreased muscle tone, whereas REM sleep has LVFA coupled with a complete loss of muscle tone (REM muscle atonia) and characteristic rapid eye movements which contrast with the slow rolling eye movements observed during NREM. Further characteristics of these three states and the brain circuitry which generates them are discussed in sections II–IV. A summary of studies involving
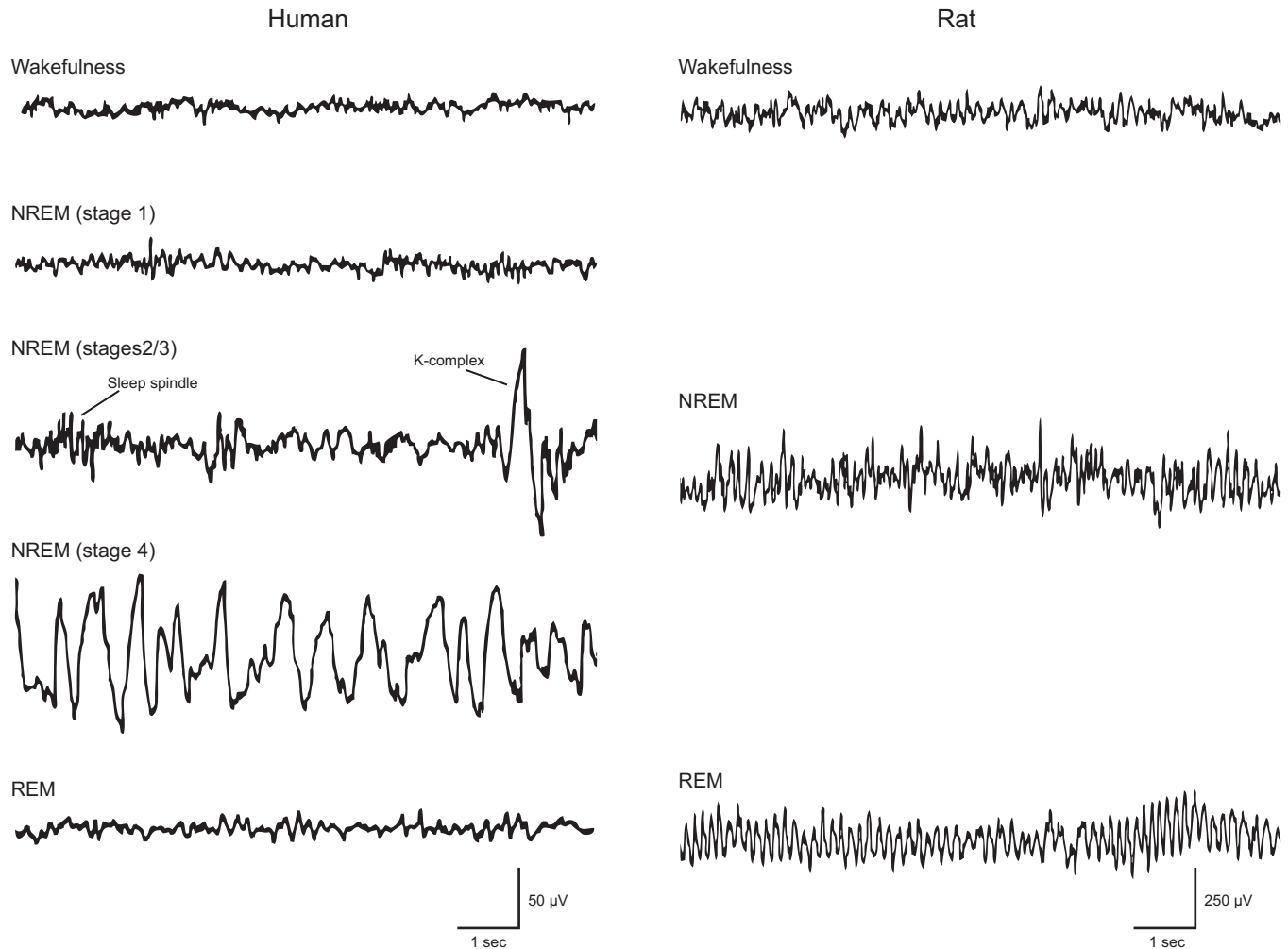
Human

Wakefulness

NREM (stage 1)

NREM (stages2/3)

Sleep spindle

K-complex

NREM (stage 4)

REM

50 μV

1 sec

Rat

Wakefulness

NREM

REM

250 μV

1 sec

FIGURE 1. Electroencephalographic (EEG) recordings in the human and rat capture differences between vigilance states (wakefulness, NREM sleep, and REM sleep). Wakefulness in both species is characterized by low-amplitude/high-frequency activity. Note that high-frequency beta and gamma activity is not easily visible at this slow timescale. In the human, NREM sleep begins in stage 1, the prevalent EEG frequency begins to slow, with strong alpha activity at posterior sites and theta activity at anterior sites. In NREM sleep stages 2/3, both sleep spindles (7–14 Hz) and K-complexes are seen, as the EEG amplitude increases and frequency further slows. In NREM sleep stage 4, also known as slow wave sleep, strong delta (0.5–4 Hz) activity is evident, accompanied by a large increase in amplitude. During REM sleep, the EEG returns to a profile similar to wakefulness, with low-amplitude and high-frequency activity. In the rodent, NREM sleep is usually not parsed into separate stages. NREM sleep exhibits a significant increase of delta range activity, as well as an increase in amplitude. REM sleep is defined by the strong synchronous theta range (7–9 Hz) activity, probably generated in the hippocampus. Human EEG recordings are adapted from Purves et al. (1028). Note the voltage scales are not matched between species.

inactivation of different parts of the brain controlling sleep and wake is provided in **TABLE 1**. The location of these brain regions is shown in **FIGURE 2**.

B. Control of Sleep Timing and Intensity

The timing, depth, and duration of sleep are controlled by the interaction of time of day (circadian control, process C) and by the duration of prior wakefulness (homeostatic control, process S) as proposed in the two-process model of Borbely (122). The cellular mechanisms in the suprachiasmatic nucleus (SCN) which generate circadian rhythms are not covered herein, since they have been reviewed extensively elsewhere (1263). The output pathways from the SCN that control the circadian timing of NREM and REM sleep are covered in sections III and IV. Homeostatic control of sleep is also covered in these sections.

C. Effects of Sleep Loss on Cognition

An important function ascribed to sleep is offline processing of information encountered during the day and consolidation of memory. Conversely, loss of sleep, either voluntarily or due to an underlying medical disorder, is as-

Table 1. *Inactivation of brain regions/neurotransmitter systems and effects on sleep-wake behavior*

Brain Area/System Targeted	Inactivation Technique	Effect on Sleep-Wake and EEG
Brain stem		
Midbrain/pontine reticular formation	Transections in cat (136–138, 580, 730, 1393).	Loss of cortical activation during waking and REM sleep.
	Cerveau isole: mesencephalic transection immediately caudal to the third nerve nuclei (effects contrast with encephale isole: intact sleep-wake with transection at C1 level of spinal cord).	Loss of forebrain signs of REM sleep.
	Brain stem damage in human patients (980).	Coma.
	Transection at caudal pontine or prebulbar level (1341, 1393).	Loss of REM sleep and of the ability of pontine carbachol to elicit tonic and phasic REM components.
	Electrolytic lesions in cat (730).	Loss of cortical activation (not observed when lateral sensory pathways were interrupted). Coma like state.
	Neurotoxic lesions: ibotenic acid lesions in cat (302) or rat (758).	Temporary increase in EEG slow waves but no long-term effects (cat). One week coma like state for combined PH/MPRF lesions. Recovery occurred. No effect (rat).
Dorsolateral pons including the dorsal subcoeruleus (=sublaterodorsal nucleus or peri-locus coeruleus alpha) or dorsal pontine nucleus oralis (PnO)	Electrolytic (387, 388, 495, 498, 569, 893, 900, 1111, 1121, 1122).	Very large lesions:
	Neurotoxic: kainic acid (577, 1122, 1394), ibotenic acid (758), NMDA (682, 683), hypocretin 2-saporin (100), quisqualic acid (606).	Loss of REM sleep correlated with loss of cholinergic neurons.
	Acute brain stem encephalitis with isolated inflammatory lesion in dorsomedial pontine tegmentum (including DRN, MR, PnO, LC, SubC, LDT, PPT) (810).	Large lesions including the SubC and surrounding areas:
	Pharmacological: tetrodotoxin (1111, 1114).	REM sleep behavior disorder (RBD) in humans, oneiric (dream-like) behavior in animals.
	Idiopathic degeneration in humans (400, 1133).	Smaller discrete lesions (focusing on SLD/SubC area):
		REM without atonia in animals, increased limb movements during sleep.
	GABA or muscimol (183, 1112, 1440, 1441)	Wakefulness ↑, NREM ↓, REM sleep ↓.
	Norepinephrine (262), noradrenergic $\alpha 2$ agonist clonidine (1300), or dopamine acting on $\alpha 2$ receptors (263).	Decreased REM and/or REM without atonia.
	Noradrenergic β antagonist, propanolol (1301).	REM ↑ due to increased number of REM episodes.
	Inhibition of adenylyl cyclase (799).	REM sleep ↑ (increased frequency of episodes).
Peribrachial pons (surrounding brachium conjunctivum): includes PPT/LDT, cuneiform nucleus, subcoeruleus (FTG in cat), medial and lateral parabrachial nucleus.	Cooling, electrolytic or neurotoxic lesion in P-wave generation zone (277, 278, 604, 690, 691, 814, 1100).	Loss of pontine component of PGO waves (P-waves). Reduced expression of learning related genes and proteins following active avoidance training. Reduced frequency of hippocampal theta and reduced synchronization between hippocampus and amygdala.
	M_2 receptor antagonist, methoctramine (283).	Block of enhanced PGO-wave activity and REM-sleep like state induced by carbachol in the cat.

Table 1.—*Continued*

Brain Area/System Targeted	Inactivation Technique	Effect on Sleep-Wake and EEG
	Serotonin (279)	Inhibition of P-waves when injected into P-wave generator in dorsal subcoeruleus.
Medial parabrachial nucleus	Neurotoxic: ibotenic acid (758).	Wake 21% ↓
Precoeruleus	Neurotoxic: ibotenic acid (758).	Loss of theta rhythm during REM
Ventral medulla (gigantocellular and magnocellular tegmental fields)	Neurotoxic: quisqualic acid in cat (514) or neonatal rat (606).	Muscle tone ↑ during NREM and REM sleep. Increased movements during REM sleep. Reduction in REM sleep and atonia duration during first postlesion week followed by recovery in weeks 2 and 3. Amount of remaining REM sleep correlated positively with ratio of remaining cholinergic or GABA neurons to serotonergic neurons.
	Transection at ponto-medullary junction in decerebrate cat (1179) or injection of lidocaine into pontine reticular formation (652).	Abolition of muscle atonia produced by electrical stimulation of medial medulla.
Brain stem cholinergic (PPT)	Ibotenic acid (758).	Wake 30% ↓
	Scopolamine, minipump perfusion (1168).	REM sleep ↓ during the daytime (inactive period) in the rat.
	GABA$_A$ agonist muscimol (959, 1303);	Increased REM sleep with muscimol (due to increase in number of REM bouts) Possibly due to preferential inhibition of local GABAergic neurons.
	GABA$_B$ receptor agonist baclofen into PPT/DpMe (370).	Decreased REM sleep and memory consolidation with baclofen.
	α2 Agonist, clonidine, α1 antagonist prazosin or β antagonist (958).	REM sleep ↑.
	Adenylyl cyclase or protein kinase A inhibition (67, 282).	REM sleep ↓ (due to decrease in number of episodes).
	Serotonin (279, 1113).	No effect on PGO waves.
Brain stem cholinergic (LDT)	Ibotenic acid (758).	LDT: increased fragmentation but no effect on amount of sleep.
Locus coeruleus (LC)	Electrolytic lesion (576).	No effect on REM sleep generation.
	Neurotoxic lesion: kainic acid (1394), ibotenic acid (758), dopamine-β-hydroxylase saporin (100).	
	Cooling (201)	REM sleep ↑
	RNAi knockdown of orexin 1 receptor (219).	REM sleep during dark period ↑
	Microdialysis of α2 agonist clonidine (1096).	Decreased activity of LC neurons. Waking ↓, NREM sleep ↑.
	DSP-4 lesion (238, 244, 881).	Reduced immediate-early and synaptic plasticity related gene expression.
		Either no change in baseline sleep-wake (238, 244) or increase in REM (881).
Dorsal raphe nucleus (DRN)	Electrolytic lesion (1451).	No effect.
	Neurotoxic lesion: ibotenic acid (758), 5,7-dihydroxytryptamine (757).	No effect on amounts of sleep-wake.
	GABA$_A$ receptor agonist, muscimol (926).	REM sleep ↑.
Median raphe (MR)	Electrolytic:(1451)	Hippocampal theta rhythm ↑.
	Pharmacological: glutamatergic antagonists (629); GABA$_A$ agonist, muscimol (630), 5-HT$_{1A}$ receptor agonists (1364).	
Dopamine- vPAG/DRN	6-OHDA or ibotenic acid (757).	Marked decrease in waking (>20%), concomitant increase in sleep.

Table 1.—Continued

Brain Area/System Targeted	Inactivation Technique	Effect on Sleep-Wake and EEG
Ventrolateral periaqueductal gray (vlPAG)	Electrolytic lesion in encephale isole cats (730).	Cortical activation preserved.
	Neurotoxic lesion: orexin 2-Saporin (612, 758)	REM sleep ↑ in both normal and orexin KO animals.
	Pharmacological: muscimol in the cat (1120), rat (1118), and guinea pig (1336).	Increased REM bouts and REM bout duration during dark period.
Lateral pontine tegmentum (LPT) = deep mesencephalic nucleus (DpMe)	Electrolytic lesion in encephale isole cats (730).	Cortical activation preserved.
	Neurotoxic lesion: orexin 2-saporin in the rat (758) and mouse (612).	REM sleep ↑. Increased REM bouts during light period and occasional bouts of cataplexy.
	Pharmacological: muscimol in the cat (1120), rat (1118), and guniea pig (1336).	
Superior colliculus/pretectum	Aspiration (857)	Abolition of lights off-induced increase in REM sleep.
Hypothalamus		
Preoptic area/anterior hypothalamus	Viral insult in humans (1378).	Prolonged (>3 wk) and large suppression of sleep (both NREM and REM).
	Electrolytic lesions in the cat (761, 840, 911) and neonatal rat (873).	
	Neurotoxic lesions in the cat: ibotenic (1105) or kainic acid (1255).	
Lateral preoptic area/bed nucleus of the stria terminalis (BNST)	Neurotoxic lesions in the rat. Ibotenic acid (1138) or NMDA (1201).	Reduction in number of erections during REM sleep (1138). NREM sleep ↓ (1201).
Ventrolateral preoptic area (VLPO, core)	Neurotoxic (rats). ibotenic acid (756).	NREM 50-60% ↓, REM sleep 59% ↓, EEG delta power 60-70% ↓ lasting at least 3 wk. Extent of lesion correlated with loss of NREM sleep. Sleep-wake fragmentation.
GABA/galanin-positive neurons		
Extended VLPO (dorsomedial)	Neurotoxic (rat). ibotenic acid (756).	REM sleep 35% ↓, NREM sleep,15% ↓, 25% loss of delta mainly during light period. Extent of lesion correlated with loss of REM sleep.
Ventromedial preoptic area	Neurotoxic (rat). ibotenic acid (756), NMDA (563, 1201).	No effect on sleep-wake (756). Reduced NREM and REM sleep (563, 1201). Disrupted body temperature regulation.
Median preoptic area	Pharmacological: muscimol perfusion (1251)	Prolonged waking state
Suprachiasmatic nucleus (SCN)	Electrolytic: rat (1439).	Loss of circadian rhythms. Reduced REM sleep during the rest (light) phase.
Dorsomedial hypothalamus (DMH)	Neurotoxic: ibotenic acid (52, 224).	Loss of circadian rhythms of sleep-wakefulness.
Posterior/lateral hypothalamus (PH/LH)	Viral insult (1378)	Hypersomnolence in human patients following influenza pandemic.
Orexin/hypocretin (perifornical hypothalamus; PFH)	Damage to PH/LH including perifornical hypothalamus due to tumor (43) or stroke (1129).	Narcolepsy.
	Electrolytic/transection: (730, 840, 911, 1046)	Reduction or abolition of cortical activa-tion. Hypersomnolence for several days followed by recovery (cat).
	Neurotoxic:	PH/LH: no long-term effects (cat)
	PH/LH: ibotenic acid (302, 1106).	LH: wake 30% ↓ (rat).
	LH: hypocretin 2-saporin (411, 413)	TMN area: minor changes.

Table 1.—*Continued*

Brain Area/System Targeted	Inactivation Technique	Effect on Sleep-Wake and EEG
	Orexin KO or orexin receptor double-knockouts (29, 214, 598, 640).	Narcolepsy with cataplexy in mice. Unchanged 24 h wake amount but sleep-wake fragmentation, cataplexy, loss of circadian control of REM sleep. Reduced voluntary motor activity (wheel running).
	Orexin receptor 2 mutations (727).	Inherited narcolepsy in dogs.
	Loss (degeneration) of >90% of orexin neurons and reduced CSF orexin (999, 1284).	Idiopathic narcolepsy-cataplexy in humans.
	Partial (33%) loss of orexin neurons (1285).	Idiopathic narcolepsy without cataplexy in humans.
	Mutation in preproorexin (999).	Early onset narcolepsy in humans.
	Orexin postnatal genetic (ataxin-3) lesion (96, 479).	Narcolepsy with cataplexy in mice and rats.
	Knockdown of orexin in PFH with siRNA (221).	REM sleep during dark period in rats ↑.
	Orexin receptor 1 KO mice (640).	Mild effects on sleep-wake. No cataplexy or sleep-onset REM episodes.
	Orexin receptor 2 KO mice (1415).	Milder form of narcolepsy-cataplexy (less cataplexy or sleep onset REM episodes).
	Orexin receptor (1 and 2) antagonist (140).	Increased sleep, especially REM sleep in rat, dogs, and humans. No cataplexy.
Melanin concentrating hormone (MCH)	MCH knockout mice (5).	NREM and REM sleep ↓.
Perifornical hypothalamus	MCH 1 receptor antagonist (12)	
Histamine (tuberomammillary nucleus)	Reduced CSF histamine in narcolepsy and idiopathic hypersomnia (597).	Excessive daytime sleepiness in humans.
	HDC (synthetic enzyme) knockout mice (29, 978).	No change in 24 h wake amount. Increased fragmentation. Decreased θ-power during waking increased δ during sleep. Increased REM during light period. Decreased sleep latency in novel environment.
	α-FMH (histamine decarboxylase inhibitor) in cat (724), mice (978), and rat (551, 1152).	Wake ↓ (cat, mice). No effect on 24 h values (rat).
	Systemic H1R antagonists crossing the blood-brain barrier: human (1402), cat (724), mice (528).	Reduced wakefulness and alertness ↓ (human, cat). No change (mice), decreased fragmentation.
	H_1R knockout mice (528)	No change in 24 h wake amount or diurnal rhythms of sleep-wake. Decreased fragmentation.
	Systemic H_3R (autoreceptor) agonist in cat (725), rat (686, 885)	Cat: wake ↓ NREM sleep ↑
		Rat: no effect.
Mammillary body (MB)	Pharmacological inhibition: local anesthetic procaine (639).	Abolition of hippocampal theta in urethane-anesthetized animals. Reduced frequency (1 Hz less) of hippocampal theta in awake animals.
Supramammillary nucleus (SuM)/posterior hypothalamus	Pharmacological inhibition: local anesthetic procaine (639).	Abolition of hippocampal theta in urethane-anesthetized rats. Reduced frequency (1 Hz less) of hippocampal theta in awake rats.
Basal forebrain		
Rostral basal forebrain (MS, vDB)	Electrolytic lesions: rabbits (30, 1090).	Hippocampal theta rhythm reduced (neurotoxic) or abolished (electrolytic).

Table 1.—*Continued*

Brain Area/System Targeted	Inactivation Technique	Effect on Sleep-Wake and EEG
	Neurotoxic lesions: rat: kainic acid (preferential loss of noncholinergic neurons) (1463), Orexin-saporin (415).	No other change in sleep-wake.
Rostral BF cholinergic	Pharmacological: AP5 (NMDA receptor antagonist) (104); muscimol (106); procaine(945).	Reduced power of hippocampal theta.
	Neurotoxic lesion: IgG^{192} saporin or orexin-saporin (80, 415, 600, 697, 1463).	Reduced amplitude of hippocampal theta rhythm and theta-gamma coupling. No change in sleep-wake.
Rostral BF GABAergic (mainly PV-Pos)	Pharmacological: inhibition of H-current with ZD7288 in rat (1343, 1446).	Reduced hippocampal theta (1446) or minor effects (1343).
Caudal basal forebrain (SI, HDB, MCPO)	Neurotoxic: ibotenic acid or quisqualate (177, 611, 1064).	No effect on 24 h sleep-wake. Increased delta power in all states. Reduced recovery sleep and delta power after ±SD.
Caudal BF cholinergic	Pharmacological: procaine (190), adenosine (1247).	Increased sleep, delta wave activity.
	IgG^{192}-saporin (94, 102, 103, 592, 611).	No or minor effects on baseline sleep-wake. Reduced EEG gamma. Reduced recovery sleep and delta power after sleep deprivation (611).
Caudal BF, TMN, LC	Triple lesions using saporin-conjugated neurotoxins (101).	No changes in daily amounts of wake. More sleep during light-to dark transition period. More stable sleep architecture.
Forebrain		
Thalamus	Electrolytic: monkey (1046).	No effect on sleep-wake or EEG except abolition of high-voltage spindles (sharp-wave/ripples).
	Neurotoxic: ibotenic acid in rat (177, 397).	
Basal ganglia	Ibotenic acid lesion (1029).	Rostral striatum:
		Wake 15 %↓
		Sleep fragmentation, slowing of EEG during waking (theta→delta).
		Globus pall.: wake 46 %↑ Increased fragmentation.
		Slowing of EEG.
		NAcc core: wake 27 % ↑ NREM bout duration ↓.
		Slowing of EEG.
		STN: minor changes.
		SNr: minor changes.
Substantia nigra	Hypocretin-2 saporin (412).	Insomnia.
SN/VTA	NMDA lesion (683).	No decrease in wakefulness.
Neurotransmitters/neuromodulators (Systemic or icv effects)		
Acetylcholine	Systemic muscarinic antagonists (177, 555, 744).	Increase in EEG delta waves. Increased high-voltage spindles (sharp waves/ripples). Block of PGO waves.
	M2/M4 double knockouts (434).	No effect on sleep-wake
	M3 receptor knockouts (434).	REM 22%↓
	Rats reared on a diet lacking choline (1256).	Reduced NREM and REM sleep
Serotonin	Depletion of serotonin (363, 555, 582, 1080).	Increased PGO waves in all states of sleep-wake.
Norepinephrine	Dopamine-β-hydroxylase knockout mice (539, 956).	Either no change in baseline sleep-wake or decrease in REM. Shorter sleep latency after mild stress.

sociated with substantial impairments in cognitive function. The mechanisms underlying these impairments are discussed in Section V.

D. Sleep Ontogeny

Sleep is the predominant behavioral state in developing animals (645, 1070), and REM sleep is proportionally more abundant in young mammals (1070). As such, sleep, in particular REM sleep, has been suggested to play an important role in the elaboration of neuronal circuitry during development (1070). The circuitry controlling sleep and wakefulness appears to mature early in development (606), although cycling between states is more frequent in younger animals (111, 645). EEG signs of sleep and wakefulness do not become "adultlike" until the later full development of the cortex (110, 377, 585, 1144). In fact, in humans, the development of fast EEG synchrony typical of wakefulness continues through adolescence, reflecting the prolonged maturation of the cortex in higher primates (1318).

E. Sleep Phylogeny

A form of NREM sleep appears to be present in most animals investigated to date (185, 1478), which is one of the arguments in favor of sleep performing a vital function (1174). A distinct REM sleep state only appears in mammals, although a primitive form is evident in reptiles and birds (1175). Sleep physiology is adapted to the particular features of different animals. For example, dolphins and other cetaceans exhibit unihemispheric sleep (1174). The distribution of the durations of sleep bouts in mammals is exponential with time scales that vary across species from mice to humans that are proportional to body mass and metabolic rate, indicating a connection with energy metabolism (742, 1174; discussed more fully in sect. III). Whereas most early animal studies of sleep used cats, dogs, and rats as experimental subjects, more recently there has been an explosion of interest in using more genetically tractable organisms to identify and study the genes and proteins in-

volved in controlling sleep (1478). This work is reviewed in section VI. Interestingly, this work suggests that even organisms such as the fly *Drosophila melanogaster* (492, 1159) and the worm *Caenorhabditis elegans* (1042) have a "rest state" with similarities to mammalian sleep. Furthermore, several homologs of genes controlling rest in these species play a role in the control of mammalian sleep (230).

F. Sleep Disorders

Polysomnographic recordings are used not only in experimental studies but also in clinical sleep laboratories to identify sleep disorders such as sleep apnea and narcolepsy which involve a dissociation and fragmentation of waking, NREM, and REM (780). Disorders of sleep and the brain mechanisms that underlie them are discussed in section VII.

II. WAKEFULNESS

A. Electrographic Signs of Wakefulness

Synchronized electrical activity in large numbers of cortical neurons provides the basis for observable extracellular field potential changes in the EEG. Summed synaptic currents from the apical dendrites of pyramidal neurons are the main contributors to these EEG waves, although intrinsic membrane properties and neuronal firing also contribute (178). Faster frequency EEG rhythms (LVFA) typical of wakefulness and REM sleep are of low amplitude and involve synchronized activity in small, functionally interrelated areas. Lower frequency rhythms such as the theta rhythm occur over more widespread areas and synchronize faster, locally generated fast rhythms (beta/gamma). These EEG rhythms are thought to provide a temporal framework for higher-order brain functions such as attention, memory formation, and conscious awareness by binding together the firing of neurons within cortical areas and by synchronizing cortical and subcortical sites (178, 1238). During quiet or drowsy wakefulness, the slower EEG frequencies become more

FIGURE 2. Location of brain nuclei controlling the sleep-wake cycle (see sects. II–IV) in sagittal (*A*) and coronal (*B*) schematics of the rat brain. Location of sections in *B* are represented as vertical dashed lines in *A*. Medulla oblongata: DPGi, dorsal aspect of the paragigantocellular reticular nucleus; GiV, ventral gigantocellular nucleus. Pons/midbrain: DR, dorsal raphe nucleus; LC, locus coeruleus; LDT, laterodorsal tegmental nucleus; LPB, lateral parabrachial nucleus; LPT, lateral pontine tegmental region; MPB, medial parabrachial nucleus; MR, median raphe nucleus; PB, parabrachial nucleus; PnC, nucleus pontine caudalis; PnO, nucleus pontine oralis; PPT, pedunculopontine tegmental nucleus; SubCA, subcoeruleus nucleus, alpha; SubCD, subcoeruleus nucleus, dorsal; SubCV, subcoeruleus nucleus, ventral; SN, substantia nigra; vlPAG, ventrolateral aspect of the periaqueductal gray; VTA, ventral tegmental area; VTG, ventral tegmental nucleus of Gudden. Hypothalamus: DMH, dorsomedial nucleus of the hypothalamus; LH, lateral hypothalamus; MM, medial mammillary nucleus; MnPO, median preoptic nucleus; MPO, medial preoptic nucleus; PeF, perifornical region of the hypothalamus; PH, posterior hypothalamus; PO, preoptic region (including VLPO); SCN, suprachiasmatic nucleus; SUM, supramammillary nucleus; TMN, tuberomammillary nucleus; VLPO, ventrolateral preoptic nucleus. Forebrain: BF, basal forebrain (including HDB, horizontal limb of the diagonal band; MCPO, magnocellular preoptic nucleus; SI, substantia innominata; VP, ventral pallidum); AMY, amygdala; CPu, caudate putamen; GP, globus pallidus. Thalamus: CM, thalamic centromedial nucleus; LGN, lateral geniculate nucleus; PV, thalamic paraventricular nucleus; RE, nucleus reuniens; RT, thalamic reticular nucleus VL, thalamic ventrolateral nucleus; VM, thalamic ventromedial nucleus; VMPO, ventromedial preoptic nucleus. Hippocampus: CA1, CA1 region of the hippocampus; CA3, CA3 region of the hippocampus; DG, dentate gyrus. Neocortex: AC, anterior cingulate cortex; IL, infralimbic cortex; PrL, prelimbic cortex. [Adapted from Paxinos and Watson (989), with permission from Elsevier.]
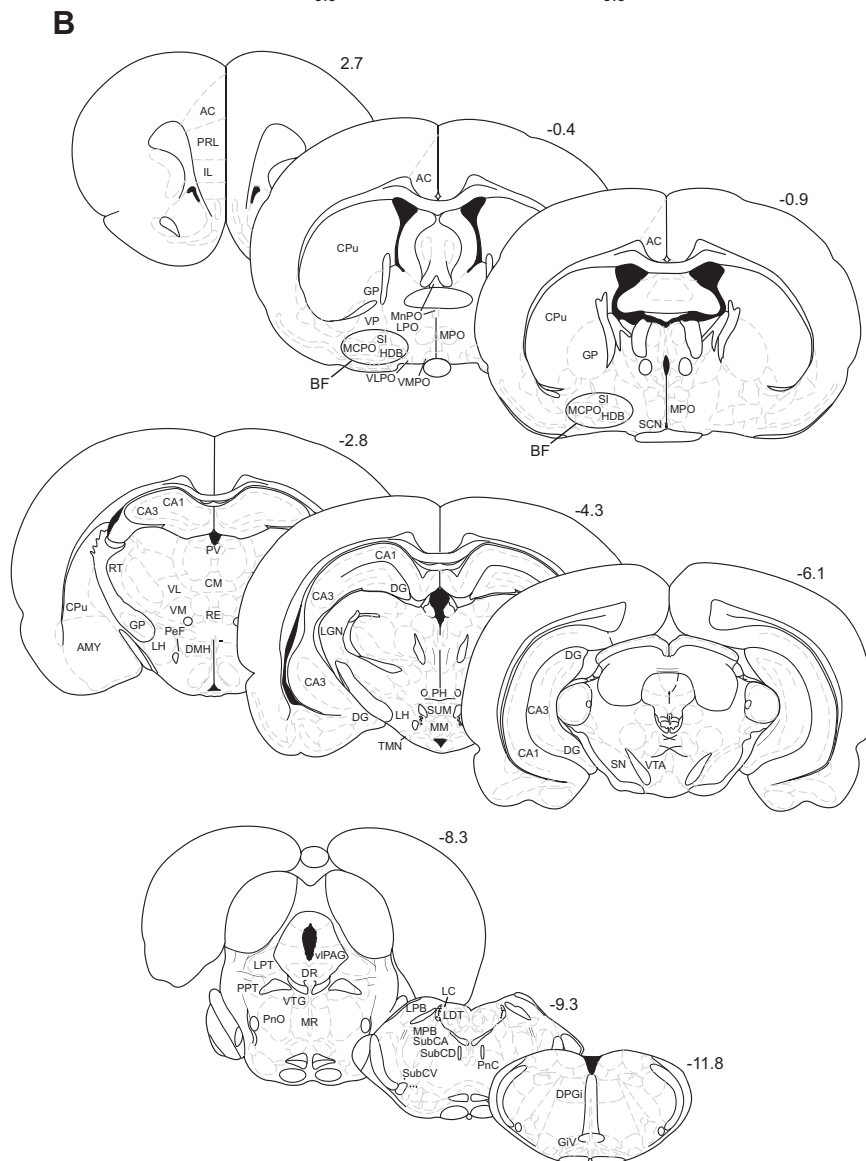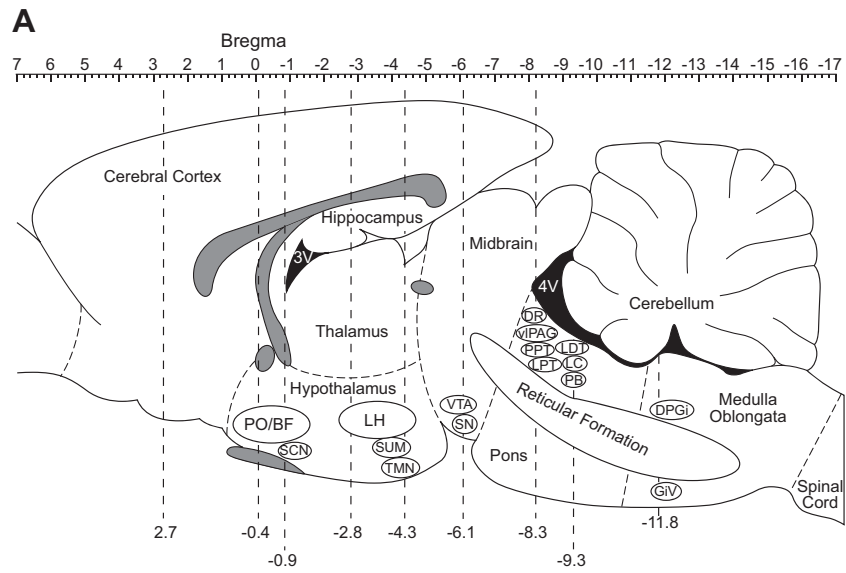
prevalent. Alpha rhythms appear in posterior cortical recordings whilst theta rhythms increase in frontal cortical regions.

1. Gamma/beta rhythms (15–120 Hz)

Low-amplitude gamma (30–120 Hz) and beta (15–30 Hz) frequency rhythms are a prominent feature of the EEG during quiet waking (baseline or spontaneous gamma; **FIGURE 1**) and are enhanced in particular cortical areas following presentation of sensory stimuli (evoked or steady-state gamma). Gamma rhythms often occur concurrently with theta rhythms during active waking and during REM sleep (187, 739, 880), particularly following phasic REM periods with PGO wave activity (26). Gamma rhythms also occur during the brief upstate of the slow oscillation during NREM sleep (see sect. III) (1219). In some studies, gamma rhythms have been subdivided into two frequency bands: low gamma (30–70 Hz) and high gamma (70–120 Hz), which arise in different cortical layers and have different pharmacological modulation properties (35, 950). We here primarily discuss low gamma. Gamma rhythms are generated by cortical networks of fast-spiking [especially parvalbumin (PV)-Pos] interneurons targeting the cell bodies of glutamatergic neurons **(FIGURE 3)**. Rhythmic inhibition and disinhibition of the pyramidal neurons are responsible for the observed field potentials with rate being set by the decay time of the inhibitory synaptic currents. In turn, the interneurons are driven by excitatory input from the pyramidal neurons. Synchrony is enhanced by electrical synapses mediated by gap junctions between interneuronal networks and between the axons of pyramidal neurons as well as by interneuron-interneuron chemical synapses (1405).

Gamma rhythms are generated locally in the neocortex but are modulated by subcortical inputs. The ability to elicit gamma rhythms in isolated brain slices in vitro (163, 366, 1407), together with current-source density and cross-correlational analysis in vivo (26, 1218), suggests that gamma rhythms are generated locally in the cortex. However, their dependence on behavioral state and stimulus presentation indicates that their occurrence is also dependent on subcortical inputs. In fact, gamma rhythms are enhanced by stimulation of the mesencephalic reticular formation, the origin of the ascending reticular activating system (502, 903). Further information on the subcortical control of gamma rhythms is provided in section IIC.

Fast-spiking interneurons containing PV generate gamma rhythms. Evidence supports the conclusion that beta and gamma rhythms are generated by GABAergic interneurons, in particular fast-spiking, PV GABAergic interneurons which synapse on the cell bodies and axon initial segments of pyramidal neurons. *1)* In vivo, fast spiking interneurons discharge at gamma frequency and their firing is phase-locked to the extracellularly recorded oscillation (133, 1026, 1311). *2)* In vitro, gamma and beta rhythms are completely blocked by
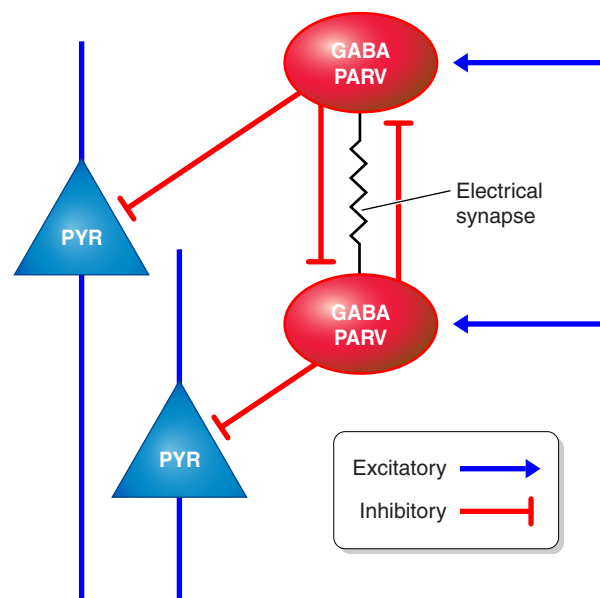

FIGURE 3. Simplified model of cortical circuitry generating gamma oscillations. Cortical circuits consist primarily of excitatory pyramidal neurons and inhibitory GABAergic interneurons. Inhibitory drive generated by interneurons plays an important role in the generation of oscillatory output. Fast spiking interneurons containing parvalbumin (PV) that synapse onto the cell bodies of pyramidal neurons are particularly important in generating gamma oscillations. Recurrent glutamatergic synapses onto GABAergic interneurons provide excitatory drive to the fast spiking interneurons. Both chemical and electrical synapses between PV-positive interneurons enhance synchrony and the coupling of gamma rhythms to theta rhythms.

GABA$_A$ receptor antagonists (366, 1407), and gamma frequency is inversely correlated with the decay time constant of inhibitory synaptic currents (1406). *3)* Optogenetic stimulation of PV neocortical interneurons in vivo (via genetic introduction of bacterial light-activated ion channels) can elicit gamma rhythms, whereas optogenetic inhibition reduces gamma (193, 1194). *4)* Wavelet analysis of local field potentials in the CA3 region of the hippocampus combined with simultaneous intracellular recordings from pyramidal neurons during cholinergically induced gamma rhythms revealed that perisomatic inhibitory currents generated the majority of the field potential (955). *5)* In human visual cortex, GABA concentration measured by magnetic resonance spectroscopy predicts peak gamma frequency and orientation discrimination performance (331, 906). 6) Gene linkage analysis indicates significant linkage between the beta frequencies of the human EEG and GABA$_A$ receptor genes (1015).

PV knockout mice have enhanced gamma oscillations (1379), suggesting PV itself may not be required, although developmental compensation may have taken place. Alterations in PV neurons may be responsible for dysfunctional gamma rhythms in schizophrenia and other disorders that are associated with cognitive abnormalities (1319, 1428).

A) BETA OSCILLATIONS. Beta frequency EEG oscillations (15–30 Hz) are thought to represent one or more of the following: *1*) a slow gamma oscillation, *2*) a subharmonic of ongoing gamma whereby inhibitory neurons fire at gamma frequencies but some excitatory neurons remain refractory for longer periods so that they only fire on a proportion of the gamma cycles, or *3*) a rhythm with its own distinct underlying properties (653). Computational modeling suggests that beta rhythms are more effective than gamma rhythms in synchronizing activity between spatially distant brain loci (653).

2. Alpha rhythms (8–14 Hz)

The two most well-known alpha rhythms in humans are the occipital alpha rhythm which dominates the EEG during relaxed wakefulness **(FIGURE 1)** and the Rolandic mu rhythm observed over somatosensory cortex in the absence of movement (536). Occipital α rhythms were one of the first described EEG rhythms (7, 92). They are commonly observed during relaxed wakefulness in parietal and occipital cortex areas including primary visual cortex and are suppressed by eye opening and visual stimuli (961). Alpha rhythms may play an important role in internally directed thought processes since they are strengthened during tasks requiring mental arithmetic and visual imagery (1052).

A) THALAMOCORTICAL MECHANISMS GENERATING ALPHA RHYTHMS. The mechanisms underlying the generation of alpha rhythms were little understood until recently (536). Alpha rhythms result from an interaction of thalamic and neocortical circuitry, together with a moderate level of brain stem cholinergic input. At the level of the visual cortex, alpha waves are due to a dipole located at the level of the cell bodies of pyramidal neurons in layer V and basal dendrites of pyramidal neurons in layers IV where thalamic input terminates (747, 748). At the level of the thalamus, the firing of two groups of thalamocortical relay neurons in the lateral geniculate nucleus are suppressed at either the positive or negative peak of the alpha rhythm through phasic inhibition. For the occipital alpha rhythm, local lateral geniculate GABAergic interneurons excited by high-threshold bursting thalamocortical neurons are important in periodically silencing thalamocortical neurons, whereas for the mu rhythm the GABAergic reticular nucleus may fulfill this role.

In vitro work in the cat thalamus suggests that alpha rhythms require stimulation of muscarinic cholinergic receptors (mimicking brain stem input) or stimulation of metabotropic glutamate receptor stimulation (mimicking cortical input). Stimulation of these receptors leads to depolarization and the generation of an afterdepolarizing potential (ADP) in the gap junction-coupled network of high-threshold bursting thalamocortical neurons (537, 751, 752), leading to synchronized firing. Concerning these two

mechanisms, in vivo microdialysis experiments suggest that the brain stem muscarinic input is more important (752). Interestingly, the number of spikes in a burst and the inter-burst frequency (2–14 Hz) are dependent on the level of muscarinic receptor activation so that the transition from alpha to the slower theta frequency waves in early (light) sleep or drowsy wakefulness may reflect a gradual withdrawal of brain stem cholinergic input (536, 537).

3. Theta rhythms (4–8 Hz)

Theta-rhythms occur prominently during waking associated with movement in rodents, during tasks requiring attention/memory in humans, and during REM sleep in all mammals **(FIGURE 1)**. They provide a temporal code for pyramidal/granule cell firing important for spatial navigation and episodic memory formation and facilitate synaptic plasticity (178, 587, 1362). In rodents and other lower mammals, very regular theta rhythms, also called rhythmic slow activity, have been studied most closely in the hippocampus and related temporal lobe structures, which in these species are located close to the dorsal surface of the brain **(FIGURE 2)** and strongly influence the EEG signal during movement and REM sleep. In humans, where the temporal lobe is located ventrally, theta rhythms are recorded and studied mainly in frontal and midline cortices that are part of the default network. Interestingly, in both animals and humans, theta-band activity increases strongly in frontal-midline areas during the course of sleep deprivation and is correlated with sleep drive (365, 1386). However, this theta activity is less regular than that generated by the hippocampus and may result from different mechanisms. Here, the mechanisms underlying hippocampal theta are discussed first followed by mechanisms that may be involved in human frontal-midline theta.

The medial septum drives hippocampal theta. A major afferent input to the hippocampus arises in the rostral basal forebrain (medial septum, vertical limb of the diagonal band; MS/vDB, **FIGURE 2**) via the fimbria-fornix. Withdrawal of this input by lesions, pharmacological inactivation or transection completely abolishes hippocampal theta rhythm (30, 106, 445, 1090). MS/vDB neurons fire rhythmically in phase with theta rhythm (997, 998). Thus the MS/vDB is thought to be a pacemaker for hippocampal theta **(FIGURE 4)**. Selective lesion of MS/vDB cholinergic neurons reduce the amplitude but do not change the frequency of hippocampal theta (697). In contrast, kainic acid lesion of the MS/vDB, which largely spares cholinergic neurons but kills PV GABAergic projection neurons, and likely other noncholinergic neurons, eliminated hippocampal theta (1463). In vivo, single-unit recordings from identified PV neurons reported bursts of action potentials at theta frequency which are synchronized with the ongoing hippocampal theta activity (125, 1182). Within the burst, action potential firing rates are at gamma frequencies, providing an explanation of the phase-locking of gamma rhythms
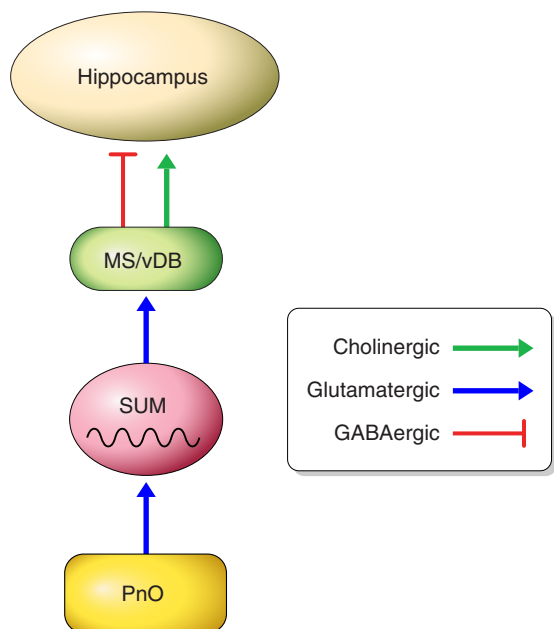
FIGURE 4. A simplified structural model of hippocampal theta rhythm control. Tonic neuronal activity of the reticular formation, largely originating in the nucleus pontine oralis (PnO), excites the supramammillary nucleus (SUM) by means of glutamatergic projections. Pontine tonic activity is converted to rhythmic firing in SUM, indicated by the wave symbol. Glutamatergic SUM output then excites GABAergic and cholinergic neurons of the medial septum/vertical limb of the diagonal band (MS/vDB), which serves as the pacemaker of the hippocampal theta rhythm.

to theta rhythms. Two populations of PV MS/vDB neurons fired anti-phasically, i.e., one population fired at the peak of hippocampal theta, whereas the other fired at the trough (125). In contrast to the GABAergic neurons, slow-firing cholinergic neurons fired only single action potentials in synchrony with theta rhythm (1182). Together these data suggest that PV GABAergic MS neurons are crucial pacemakers for hippocampal theta, whereas cholinergic neurons modulate the amplitude. MS/vDB PV projection neurons selectively innervate the PV hippocampal interneurons (basket and chandelier neurons) responsible for controlling firing of principal neurons (385). Thus hippocampal theta rhythm is (at least partially) generated by rhythmic inhibition and disinhibition of hippocampal pyramidal and dentate granule cells (176). In addition, rhythmic input from the entorhinal cortex plays a large role in the observed variation in extracellular potential (176).

A) BRAIN STEM CONTROL OF THETA RHYTHM. The ascending pathways from the brain stem which generate theta rhythm are still an active area of investigation (1365). Precise mapping studies by Vertes and colleagues (1356, 1365) revealed that the most effective brain stem stimulation sites for theta generation are located within the nucleus pontis oralis (PnO) region of the brain stem reticular formation **(FIGURE 2)**. Extracellular single-unit recordings in the PnO of freely moving rats identified cells that fire in association with states when theta rhythm is present. However, these cells did not fire rhythmically, but

fired tonically at high rates (60–100 Hz) (935, 1355). Thus these neurons are unlikely to be involved in coding the frequency of hippocampal theta rhythm.

Tonic brain stem input is converted into rhythmic firing in the supramammillary nucleus **(FIGURE 4)**. Although it was originally assumed that tonic firing in the reticular formation is translated into rhythmic firing in the MS/vDB, anatomical tracing studies revealed that few neurons in the reticular formation project directly to the MS/vDB (1357, 1359). Thus at least one additional nucleus is likely interposed between these two areas. Anatomical tracing and physiological mapping studies using the local anesthetic procaine suggested that MS/vDB projecting, glutamatergic neurons containing the calcium-binding protein calretinin in the supramammillary nucleus (SuM; **FIGURE 2**) may fulfill this role (638, 710, 1360, 1366) **(FIGURE 4)**. Single-unit SuM recordings in urethane-anesthetized animals reported single spike or rhythmic burst firing phase locked with hippocampal theta (105, 637, 639, 649). Rhythmic SuM firing is not due to descending inputs from the septum or hippocampus since it was not altered by inactivation of the MS/vDB with the local anesthetic procaine (639). However, SuM procaine injection blocked the ability of PnO stimulation to elicit theta (638). Thus it was proposed that the SuM translates tonic firing of the reticular input into phasic bursting at the frequency of hippocampal theta (636). However, in contrast to experiments in urethane-anesthetized animals, in freely moving animals procaine causes only a small reduction in the frequency of hippocampal theta (845, 1286), suggesting that additional pathways are involved. The precoeruleus region of the pons (758), located just rostral to the locus coeruleus, provides the major brain stem glutamatergic input to the MS/vDB. In addition, the nucleus incertus of the medulla (933) projects to the MS/vDB and SuM regions. Although these areas have been implicated in brain stem theta generation, rhythmically firing neurons have not been recorded in these regions. Thus they may relay the activity of the reticular formation (especially PnO) to the MS/vDB and SuM. In contrast, the GABAergic ventral tegmental nucleus of Gudden, located just ventral to the dorsal raphe, contains intrinsically bursting neurons (155) which fire rhythmically at theta frequencies during waking and REM sleep and may generate theta rhythmicity in the limbic Papez circuit through their interconnections with the medial mammillary body (81, 648).

B) THETA RHYTHMS IN HUMANS. In humans, where the hippocampal formation and temporal formation are located ventrally, theta oscillations are most commonly recorded just anterior to the Fz electrode site over frontal and midline cortices (prefrontal and anterior cingulate) (862). Mechanisms that may be responsible for generating this frontal-midline theta (FM-theta) are as follows: *1*) FM-theta may be generated through direct or indirect projections from the hippocampal formation, synchronizing information flow

between hippocampus and neocortex (1184). However, FM-theta is not always coherent with hippocampal theta (862). *2)* FM-theta may represent a slow alpha-rhythm generated by thalamocortical loops during drowsiness (see preceding section). *3)* FM-theta may be generated by pacemaker GABAergic (PV-Pos), cholinergic, and glutamatergic projections from the caudal basal forebrain (BF). GABAergic PV-Pos and cholinergic neurons in the caudal BF show similar firing patterns (321, 481, 698) and projections to interneurons and pyramidal neurons in the neocortex (386) as their counterparts in the rostral BF which project to the hippocampus. Furthermore, the firing of ensembles of noncholinergic BF neurons are correlated with prefrontal cortex field potentials (729). Further research is required to determine the contribution of these three mechanisms to FM-theta. They are not mutually exclusive, and any of them may contribute under different conditions.

B. Brain Stem Reticular and Basal Forebrain Activating Systems

The work of a handful of researchers in the first half of the 20th century allowed the development of current ideas of how LVFA typical of wakefulness and REM sleep is generated. Frederic Bremer (136) found that transection of the brain of cats at the midcollicular level ("cerveau isole" preparation) led to "sleeplike" behavior and slow waves in the cortex. In contrast, transection at the junction of the brain stem and spinal cord ("encephale isole" preparation) did not alter the normal cyclic alternation of sleep-wake states and demonstrated that sensory input from the spinal cord was not necessary for wakefulness to occur. Later work by

Giuseppe Moruzzi and Horace Magoun showed that electrical stimulation of the midbrain reticular formation in anesthetized cats caused the appearance of an "activated" EEG similar to that seen during waking (898). Together these findings led to the important concept of the "ascending reticular activating system (ARAS)," a network (reticulum) of nerve fibers ascending from the brain stem, which through multiple intermediary sites causes activation of the forebrain during waking and REM sleep **(FIGURE 5)**. The activity of brain stem reticular neurons, the origin of both of these pathways, reliably predicts the onset of changes in behavioral state (818, 1228, 1232, 1236).

The ARAS consists of dorsal and ventral pathways **(FIGURE 5)**. Axonal tracing studies coupled with histochemical or immunohistochemical visualization of particular neurotransmitter systems revealed the anatomical pathways transferring brain stem activity to the cerebral cortex (573, 1228). Single-unit recordings and indirect measures of neuronal activity (using immunohistochemical detection of the immediate early gene product Fos) defined the neurons in these areas whose activity is correlated with wakefulness or sleep (575, 1228). Two main pathways have been identified **(FIGURE 5)**.

1. The dorsal pathway of the ARAS (Figure 5)

This comprises midbrain, pontine, and medullary reticular formation glutamate neurons (261, 916, 1227, 1235) and cholinergic neurons in the pedunculopontine and laterodorsal tegmental nuclei (PPT/LDT) (473, 1235) which innervate the midline and intralaminar (nonspecific) thalamocortical projection system (paraventricular,
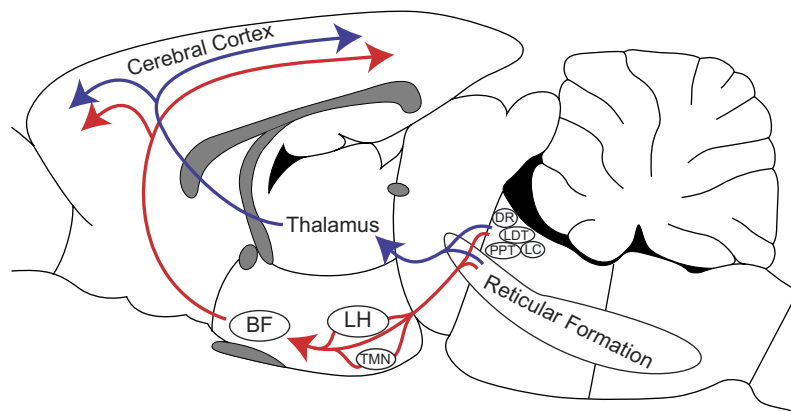

FIGURE 5. Dorsal and ventral pathways of the ascending reticular activating system (ARAS). The dorsal pathway (blue) originates in pontine and midbrain reticular formation, most prominently cholinergic (LDT/PPT) and glutamatergic neurons which project to the "nonspecific" intralaminar and midline thalamic nuclei which diffusely innervate many areas of the cerebral cortex as well as thalamic relay neurons with more selective projections patterns. The ventral pathway also originates in pontine/midbrain regions and projects to the lateral hypothalamic (LH) and tuberomammillary (TMN) nuclei of the hypothalamus, as well as the basal forebrain (BF). Output of LH and TMN also ascend to BF, which in turn projects to the cortex. Noradrenergic neurons of the locus coeruleus (LC) and serotonergic neurons in the dorsal raphe (DR) contribute to both pathways and send direct projections to the cortex as do histamine neurons of the TMN and orexinergic neurons in the LH. LDT, laterodorsal tegmental nucleus; PPT, pedunculopontine nucleus. [Adapted from Paxinos and Watson (989), with permission from Elsevier.]

parataenial, intermediodorsal, centrolateral, paracentral, centromedial, rhomboid, reuniens, centromedian and parafascicular thalamic nuclei). These thalamic nuclei project to widespread and overlapping neocortical areas (559, 578, 750, 970, 1203), although each nucleus has some selectivity in their density of projections to their neocortical targets (1327). Stimulation of the nonspecific nuclei yields widespread cortical responses and elicits fast cortical rhythms (478, 559, 891), while electrical stimulation in sensory relay nuclei elicits short responses in local areas of sensory cortex. In addition to thalamic projections, the brain stem cholinergic (LDT/PPT) neurons also innervate the dopaminergic and GABAergic neurons of the midbrain ventral tegmental area of Tsai (260), which are involved in reward processes and project prominently to the nucleus accumbens and prefrontal cortex. Surprisingly, experiments in rodents (177, 397) and cats (1370) showed that very large lesions of the thalamus appear to have very little effect on cortical activation and the sleep-wake cycle in general, aside from a loss of sleep spindles, suggesting that the dorsal pathway is not absolutely necessary. However, a complete and selective ablation of thalamus is hard to achieve with lesion techniques, and it remains possible that a small thalamic projection remained after these lesions which was sufficient to maintain function. These findings in animals are also seemingly at variance with human studies of coma patients (see sect. VII) and imaging studies of sleep-wake and anesthesia which suggest that changes in reticular and thalamic function precede changes in the cortical EEG (66, 152, 928). At the very least, one can conclude that under normal conditions, the dorsal pathway is involved in and shapes cortical activation.

2. The ventral pathway of the ARAS [Figure 5]

This comprises fibers of the medial forebrain bundle which pass through and make contact with neurons in the midbrain, posterior/lateral hypothalamus, and basal forebrain (BF) on the way to the cortex. The ascending fibers from the brain stem include glutamatergic (parabrachial), noradrenergic (locus coeruleus, LC), serotonergic (dorsal and median raphe), and dopaminergic (periaqueductal gray) neurons. These systems synapse onto glutamatergic, histaminergic, and orexinergic/hypocretin neurons in the posterior/lateral hypothalamus (575). All of these systems converge onto caudal BF cholinergic, GABAergic, and glutamatergic neurons which project to and activate the neocortex (305, 316, 573, 1148, 1228). A branch of this system innervates the rostral BF theta rhythm generator.

In contrast to the thalamic lesions discussed above, a recent study showed that large lesions of the BF, or of the brain stem parabrachial nucleus (PB), which provides the major brain stem glutamatergic input to the BF, led to a comatose state in rats (397), whereas, as discussed above, thalamic lesions had little effect. However, it is important to note that in this study, orexin-saporin was used to lesion the BF and PB, whereas ibotenate was used to lesion the thalamus; thus the two experiments are not directly comparable. Orexin-saporin is a relatively new lesioning tool that requires further study. In particular, it is important to determine if very large lesions, resulting in widespread neuronal death, also affect fibers of passage.

Direct projections to the cortex and the nonspecific thalamic nuclei also arise from brain stem noradrenergic and serotonergic neurons as well as the hypothalamic histaminergic and orexinergic/hypocretin neurons. In section IIC, we discuss the role of the different components of the ARAS, subdivided according to neurotransmitter phenotype.

3. Default network

One novel finding from human imaging studies is the existence of a so-called "default network" of functionally interconnected cortical regions that are active when individuals are left to think to themselves and are not involved in responding to the external environment (1040). Anatomically, the default network consists of regions along the anterior and posterior midline, the lateral parietal cortex, prefrontal cortex, and temporal lobe (33, 1040). Upon presentation of external stimuli requiring a response, the default network regions show a decrease in activity, in contrast to other cortical areas that show increases or no change. Thus, while animal studies have often considered cortical activation as being fairly uniform throughout cortical regions, human imaging studies show that this is not the case. Future studies should distinguish how the ascending systems controlling the default network differ from those affecting other cortical areas.

C. Neurotransmitter Systems Promoting Wakefulness

Multiple neurotransmitter systems contribute to the promotion of wakefulness. However, none of them appears to be absolutely essential. In this section we describe the effects of inactivation or stimulation of these systems, the mechanisms by which they act, and their possible function during wakefulness.

1. Acetylcholine

The cholinergic system promotes high-frequency oscillatory activity typical of wakefulness and REM sleep. The BF cholinergic system has an additional role in the homeostatic sleep response to prolonged waking (discussed more fully in sect. III). The important role of brain stem cholinergic neurons in REM sleep control is discussed in section IV.

Neurons involved in sleep-wake control that release acetylcholine are located in the BF and in the mesopontine tegmentum (LDT/PPT) of the brain stem (44, 849) (Figs. 2 and 6). Identified, cortically-projecting cholinergic neurons in the caudal BF (substantia innominata, horizontal limb of the diagonal band, magnocellular preoptic area, nucleus basalis) fire fastest during both wakefulness and REM sleep (481, 698), and their firing is correlated with cortical activation (321, 698, 789). In particular, caudal BF cholinergic neurons fire bursts of spikes in association with neocortical theta rhythms (698). Rostral BF (MS/vDB) cholinergic neurons projecting to the hippocampus also fire in association with hippocampal theta rhythm but fire only single spikes per cycle (1182). Wake/REM-on neurons have also been recorded in cholinergic brain stem areas although, to date, the firing of identified brain stem cholinergic (LDT/PPT) neurons projecting to the thalamus has not been recorded across the sleep-wake cycle. In urethane-anesthetized animals, identified brain stem cholinergic neurons fire in association with cortical activation produced by tail pinch (126). Consistent with the firing patterns of cortical and thalamic-projecting cholinergic neurons, acetylcholine levels are highest in these areas during wakefulness and REM sleep (200, 560, 1412). Thus increased activity of both brain stem and BF cholinergic systems is associated with states when cortical activation and conscious awareness occur (572, 993, 1429).

BF cholinergic neurons projecting to the neocortex promote LVFA. Caudal BF neurons affect electrographic activity via a direct projection to the cortex (305, 450, 500, 1115, 1148, 1431). Intracellular recordings from cortical neurons in vivo and in vitro have revealed a plethora of cholinergic effects that lead to increased excitability and a facilitation of fast EEG rhythms at the expense of slow oscillations typical of NREM sleep (827, 1216). Prominent muscarinic effects include the following: *1*) a depolarization of pyramidal neurons via block of a leak potassium conductance (M-current) and activation of mixed cation channels; *2*) facilitation of subthreshold oscillations in the beta/gamma range (20–40 Hz), and *3*) blockade of slow afterhyperpolarizations. Nicotinic actions include presynaptic facilitation of glutamate release (443) and depolarization of interneurons (20, 579). In vivo, application of agents which depolarize cholinergic neurons in vitro (22, 334, 375, 619) increases theta and gamma cortical activity, together with waking and REM sleep. In particular, the action of neurotensin is noteworthy, since it appears to be selective for cholinergic neurons (191). Conversely, application of serotonin, which hyperpolarizes BF cholinergic neurons (618), reduces gamma activity (189).

A) CHOLINERGIC ELICITATION OF FAST EEG RHYTHMS IN VITRO AND IN VIVO. In vitro, application of cholinergic agonists causes theta and gamma/beta rhythms in isolated hippocampal (366, 534, 1165) or neocortical areas (107, 163, 950) and promote alpha or theta oscillations in thalamic relay nuclei such as the lateral geniculate nucleus (751, 752). The cholinergic neuromodulatory system is unique in this regard since only cholinergic or glutamatergic agonists have been shown to induce oscillatory activity in vitro. Early, in vivo studies in urethane or ether anaesthetized rats and rabbits established that one form of theta activity (type I theta, 4–7 Hz) was abolished by systemic administration of the muscarinic antagonist atropine sulfate (667). Both brain stem (LDT/PPT) cholinergic neurons projecting to the diencephalon and MS/vDB cholinergic neurons projecting to the hippocampus and neocortex promote theta activity. Infusion of the cholinergic agonist carbachol into the brain stem (PnO) or SuM/posterior hypothalamus increases hippocampal theta (635, 944, 1363) whilst selective lesion of MS/vDB cholinergic neurons reduces the amplitude of hippocampal theta (697). Muscarinic receptor blockade weakens the coupling between gamma and theta rhythms (501), suggesting that the enhanced acetylcholine release that occurs during waking and REM sleep promotes this coupling. Thus acetylcholine promotes the cortical rhythms typical of wakefulness and REM sleep and the coupling of gamma to theta rhythms.

B) BRAIN STEM CHOLINERGIC PROJECTIONS TO THE THALAMUS. While BF cholinergic neurons promote cortical activation via a direct projection to the cortex, brain stem cholinergic neurons do so via their projections to the thalamus, comprising a major component of the dorsal ARAS pathway **(FIGURE 5)**. Anterograde and retrograde tracing studies coupled with choline acetyltransferase immunohistochemistry revealed a massive cholinergic projection to the thalamus (291, 473, 474, 940, 974, 1193, 1235, 1430) which, depending on the thalamic region studied, make up 25–85% of the projection from all neurons in the pontine tegmentum. A minor cholinergic projection to the thalamus, especially the reticular nucleus and anterior nuclei, arises from BF (976).

Similar to BF cholinergic neurons, the firing of brain stem cholinergic neurons correlates with, and anticipates, cortical activation and deactivation (126, 336, 615, 1221). In vivo, electrical stimulation of brain stem areas containing cholinergic neurons enhances beta/gamma frequency firing in thalamocortical neurons and in the EEG (1226). In vitro, cholinergic agonists depolarize relay neurons via a muscarinic (M_1/M_3, $G\alpha_q$ G protein) receptor-mediated block of leak potassium conductance. This depolarization facilitates single-spike firing at the expense of the rhythmic bursting observed during NREM sleep (143, 826, 832). Acetylcholine directly depolarizes ventral tegmental area dopaminergic neurons via nicotinic receptors containing $\alpha4$-$\alpha7$ and $\beta2$ subunits (646, 1002), and by activation of muscarinic M_1-like (probably M_5) receptors (680, 1461), which increases

burst firing (743) and facilitates dopamine release in target regions such as the nucleus accumbens (373).

In addition to acetylcholine, brain stem cholinergic neurons also release the gaseous neurotransmitter NO. In vitro, electrical stimulation of LDT produced NO (707), whereas in vivo studies showed that NO is released in the thalamus (1414) and medial pontine reticular formation (709) in relation to behavioral state. Administration of NO donors enhances neuronal activity in the thalamus and neocortex (265), while NOS inhibitors cause inhibition of thalamic cell activity. NO dampens the oscillatory activity of thalamocortical relay neurons by altering the voltage dependence of the hyperpolarization activated cation current, I_h (967).

C) EFFECTS OF CHOLINERGIC LESIONS. While electrical or pharmacological stimulation of cholinergic neurons is highly effective in stimulating LVFA, lesioning of brain stem or BF cholinergic neurons does not lead to pronounced changes in 24-h amounts of wakefulness. Selective lesioning of BF cholinergic neurons using the toxin ^{192}IgG-saporin led to relatively minor changes in wakefulness (94, 611). However, high-frequency EEG power, especially gamma-activity, was strongly reduced with extensive lesions of caudal cholinergic BF neurons (94, 600) but was unchanged with less complete lesions (611, 1398, 1399). More consistently, IgG^{192}-saporin lesions of MS/vDB cholinergic neurons reduced the amplitude of hippocampal theta rhythm (80, 415, 697, 1463). Lesioning of the cholinergic neurons reduced the homeostatic response to sleep deprivation, but again this required an extensive destruction of cholinergic neurons (102, 592, 611). Thus it appears that there is considerable redundancy in the cholinergic system, and effects are only seen with extensive lesions.

2. Serotonin

Overall, the evidence suggests that serotonin promotes a quiet waking state with reduced cortical activation. Serotonin also plays an important role in suppression of REM sleep (sect. IV) and in the response to stress, which may account for some aspects of stress-related sleep disorders (sect. VII).

Serotonin neurons are clustered in several nuclei along the midline of the brain stem in the raphe nuclei (FIGURE 2) (553). Early experiments where serotonin levels were depleted erroneously suggested that serotonin promotes sleep (581, 899). Recent experiments examining mice in which serotonin neurons are genetically deleted suggest that insomnia resulting from disruption of serotonin signaling was due to a disruption of thermoregulation, leading to an increase in motor activity to generate heat (162). In contrast to the early depletion experiments, recording of the electrical discharge of serotonin neurons (839, 1308) and measurements of serotonin release (1020, 1411) revealed that serotonin neurons are wake-active, suggesting that serotonin is wake-promoting. Neuronal firing decreased during NREM sleep and ceased during REM sleep. Accordingly, systemic application of serotonergic receptor agonists increases waking and reduces NREM and REM sleep (884). Serotonergic suppression of NREM sleep is likely due to a 5-HT$_{1A}$ receptor-mediated postsynaptic inhibition of sleep-active VLPO neurons (403), whereas the inhibition of REM sleep involves a postsynaptic inhibition of REM-on brain stem cholinergic neurons (130, 522).

A) MECHANISMS BY WHICH SEROTONIN PROMOTES WAKEFULNESS. Serotonin promotes waking via depolarization of histaminergic tuberomammillary neurons (344) and BF GABA neurons projecting to the hippocampus (23) and neocortex (154). Serotonin has complex effects on the thalamus. A direct depolarization of lateral geniculate neurons and other first-order thalamic relay neurons via a 5-HT$_7$ receptor-mediated modulation of hyperpolarization-activated cation conductance was initially reported (205, 206, 829, 1342), an action which blocks spindle oscillations (696). However, most higher-order relay and nonspecific nuclei are inhibited by serotonin (877) via a combination of a direct 5-HT$_{1A}$-mediated postsynaptic hyperpolarization and an indirect increase in inhibitory input due to depolarization of GABAergic thalamic reticular nucleus neurons (833). Sensory relay neurons may also be inhibited by serotonin (1071) through a depolarization of local interneurons (877, 969, 1109). However, serotonin also facilitates glutamate release from thalamocortical terminals via 5-HT$_{2A}$ receptors (10, 11), the main target of hallucinogenic drugs such as lysergic acid diethylamine (LSD) which act as partial agonists of this receptor (794). Serotonin blocks the slow afterhyperpolarizations of intralaminar thalamic (430), hippocampal (1302), and neocortical pyramidal neurons (40, 1475) via activation of receptors coupled to stimulation of adenylyl cyclase (5-HT$_4$/5-HT$_7$), allowing the faster firing typical of wakefulness.

B) STATE-DEPENDENT FIRING OF SEROTONIN NEURONS. Most serotonin neurons fire in a slow, tonic fashion across the sleep-wake cycle (839, 1308). However, a subpopulation also fires in bursts (471). In contrast to norepinephrine and histamine neurons, most serotonin neurons recorded in vitro do not fire action potentials spontaneously (1335). Thus afferent input from other wake-active systems is required to maintain their firing (158, 713, 1095, 1335). Serotonin neurons are depolarized by norepinephrine, histamine, and orexins via activation of a long-lasting inward current due to the opening of mixed cation channels (158, 735, 1335), likely of the transient receptor potential family (1151). Unlike the other wake-active neuromodulatory systems discussed here, serotonin neurons promote a state of quiet or relaxed waking; single-unit recordings report highest activity during feeding and decreased firing during active waking (554). Serotonin neurons are also activated by stress (476),

and 5-HT$_{1A}$ knockout mice lack the rebound of REM sleep observed following the stress of immobilization (130).

C) SEROTONIN INHIBITS THETA AND GAMMA RHYTHMS. Serotonin acts in opposition to the cholinergic system **(FIGURE 6)**, inhibiting both BF (618) and brain stem cholinergic neurons (763, 1280), resulting in a blockade of fast rhythms (especially theta and gamma) promoted by activation of the cholinergic system. In particular, median raphe (MR) serotonergic neurons inhibit hippocampal theta rhythm (1365). Electrical or pharmacological stimulation of the MR abolishes theta rhythm in both anesthetized and unanesthetized rats (51, 629, 1356, 1451), whereas lesions or pharmacological inactivation of MR result in continuous theta (630, 1451). An involvement of serotonin in these effects was suggested by the following findings: *1*) treating rats with *p*-chlorophenylalanine, resulting in a 60–80% depletion of forebrain serotonin, blocked the effects of MR electrical stimulation (51); *2*) continuous theta in raphe lesioned animals could be interrupted by administration of the serotonin precursor L-5-hydroxytryptophan (1451); and *3*) inhibition of MR serotonin neurons with 5-HT$_{1A}$ agonists generates theta rhythm in urethane-anesthetized rats (631, 1364). Similarly, serotonin inhibits caudal BF cholinergic neurons (618) and reduces EEG gamma activity (189).

3. Norepinephrine

Norepinephrine neurons are generally thought of as part of the central flight-or-fight response, being particularly im-

portant in waking associated with stressful situations. Norepinephrine also plays an important role in the maintenance of muscle tone during waking and suppression of REM sleep (see sects. IV and VII).

Norepinephrine neurons are located in small clusters throughout the brain stem (194). The most prominent noradrenergic innervation of the forebrain arises from the LC **(FIGURE 2)**. It is this nucleus that has been studied most closely with respect to the sleep-wake cycle. LC neurons fire most rapidly during wakefulness and are activated further by stressful stimuli (1050), but their firing slows during NREM sleep and ceases prior to and during REM sleep (511). Norepinephrine strongly excites many neurons of the ARAS **(FIGURE 6)**, mainly via α_1 receptors, including thalamic relay neurons (829), serotonin dorsal raphe (DRN) neurons (9, 68, 158, 962, 1335), BF cortically-projecting cholinergic (375) and GABAergic neurons (154). Norepinephrine inhibits neurons in the sleep-active ventrolateral (403) and median preoptic nuclei (63), as well as REM-on brain stem cholinergic neurons (706, 1280), by acting on postsynaptic α_2 receptors and activating an inwardly rectifying potassium conductance. β-Receptors inhibit slow calcium-dependent afterhyperpolarizations of cortical pyramidal neurons, allowing the faster firing typical of wakefulness (463) and blocking the slow oscillations typical of NREM sleep (1220).

Studies utilizing neurotoxic or electrolytic lesions of the LC or norepinephrine system reported minor changes in the amount of wakefulness (100, 244, 576, 758, 881). How-
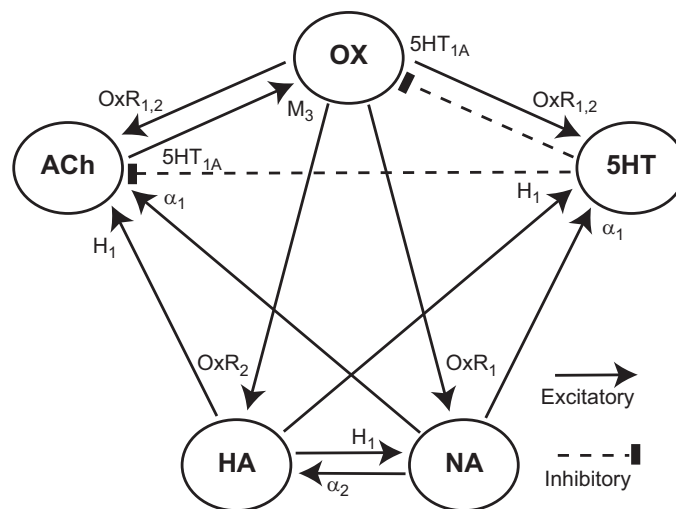

FIGURE 6. Functional interactions between wake-promoting neuromodulatory systems projecting to the cortex. Wake-promoting neuromodulatory systems are interconnected mainly in a mutually excitatory network. Cholinergic (ACh) basal forebrain, orexinergic (OX) lateral hypothalamic, serotonergic (5-HT) raphe, noradrenergic (NA) locus coeruleus, and histaminergic (HA) tuberomammillary neurons all interact to promote wakefulness. Thus, if one region is experimentally lesioned, other systems remain and maintain cortical activation and wakefulness. The main exceptions to this pattern are inhibitory serotonergic and norepinephrine projections to cholinergic and orexin neurons. Cortically projecting glutamatergic and GABAergic systems are also important in cortical activation and wakefulness (see text). Note: adrenergic projections to the histamine neurons act by disinhibition (inhibition of GABAergic synaptic inputs), whereas other effects shown are postsynaptic. Receptors involved are as follows: $\alpha 1$, alpha adrenergic type 1; $\alpha 2$, alpha adrenergic type 2; H1, histaminergic type 1; M3, muscarinic cholinergic; OxR1, orexin receptor type 1; OxR2, orexin receptor type 2.

ever, depletion of norepinephrine using peripheral administration of the toxin DSP-4 reduced the expression of ~20% of waking-related gene transcripts, particularly those involved in synaptic plasticity and cellular stress responses (238, 241, 244). Studies of long-term potentiation implicate noradrenergic β-receptors in promotion of synaptic plasticity (519, 1202). Thus one important function of norepinephrine released during waking appears to be the promotion of synaptic plasticity required for memory formation, in particular emotional memory (1312).

4. Histamine

Histamine neurons were first implicated in wake promotion due to the sedative side effects of first-generation antihistamines (H_1 receptor antagonists) that cross the blood-brain barrier and affect central histaminergic systems (159, 1402). More recent studies have clearly shown that histamine neurons in the tuberomammillary nucleus (TMN; **FIGURE 2**) are slow firing (<10 Hz) and have a wake-on, NREM-slow and REM-off firing pattern (564, 1264, 1338). In vitro, histamine neurons are spontaneously active (464, 1242) due to the activity of a persistent tetrodotoxin-sensitive sodium current (1257). They are excited directly by orexins (342) and serotonin [via $5\text{-}HT_{2C}$ receptors (344)] and indirectly by norepinephrine [through inhibition of GABAergic inputs (1243)]. Histamine has excitatory effects on most nuclei of the ARAS (**FIGURE 6**; Refs. 159, 465) and, accordingly, injection of histamine into many nuclei of the ARAS promotes wakefulness (722). Conversely, histamine inhibits sleep-active projection neurons of the VLPO via excitation of local inhibitory interneurons, leading to a promotion of wakefulness (736).

Modest decreases/increases in waking have been observed following pharmacological suppression or activation, respectively, of the histamine system (159, 722). However, inactivation of the histamine system via lesions (302, 413), knockout of the histamine H_1 receptor (528), administration of an irreversible inhibitor of the histamine synthesizing enzyme histidine decarboxylase (HDC; Refs. 551, 642, 1152) or knockout of HDC (29, 978) have relatively minor effects on 24-h amounts of waking or cortical activation suggesting that, similar to the other aminergic systems, the histamine system is not absolutely essential for wakefulness. Histamine neurons maintain their level of firing during cataplectic attacks in narcoleptic animals (in contrast to norepinephrine and serotonin neurons) implicating them in the preservation of consciousness which accompanies the cataplectic state (564). In addition, increased activation of histamine neurons as measured by Fos activity has been observed during feeding anticipatory behavior (851, 1323). More fine-grained analysis of sleep and wakefulness in HDC knockout animals revealed a deficit in wakefulness when placed in a novel, potentially dangerous environment (29, 978). This is consistent with a role for histamine in stress- or danger-induced arousal (159).

5. Orexins/hypocretins

Orexins/hypocretins were discovered relatively recently by two groups who gave them their two names (290, 1101). We will use the term *orexins* for these peptide neurotransmitters in this review. Orexins consolidate wakefulness (increase the duration of long waking bouts), suppress REM sleep (sect. IV), and enhance wakefulness in periods of starvation (1452). Considerable evidence links them to the sleep disorder narcolepsy (see sect. VII).

A) OREXINS PROMOTE WAKEFULNESS. Early work showed that intracerebroventricular application of orexin A dose-dependently increases wakefulness in rats (1005). More recent work using light-activation of orexin neurons via viral vector-mediated introduction of channelrhodopsins (6) found that excitation of orexin neurons in the lateral hypothalamus at frequencies above 5 Hz increased the probability of a transition from sleep to wakefulness. Conversely, administration of recently developed orexin receptor antagonists increased both NREM and REM sleep in animals and humans at the expense of wakefulness (140).

B) OREXIN NEURONS INCREASE WAKING IN RESPONSE TO LOW FOOD AVAILABILITY. One function of the orexin system may be to integrate nutritional state with arousal (4, 1416, 1452). Orexin neurons respond to a wide variety of peripheral and central signals indicating nutritional state (164, 268, 393, 1048, 1452). Several metabolic signals which increase with feeding, such as glucose, leptin, and neuropeptide Y, inhibit orexin neurons in vitro (164, 393, 1452). In contrast, orexin neurons are activated by fasting in non-human primates (308), and given their wake-promoting effects, they are likely to be primary mediators of the increase in waking and suppression of sleep caused by limited availability of food. In fact, orexin knockout mice fail to respond to fasting with an increase in waking and activity (1452).

C) OREXIN NEURONS ARE WAKE-ACTIVE. Orexin neurons are most active during waking as assessed by Fos immunohistochemistry (351, 872) and measurements of peptide release (641). In the squirrel monkey, which has a sleep-wake cycle similar to that of humans, orexin levels peaked in the latter third of the day and remained elevated during 4 h of extended wakefulness, consistent with a role for orexins in consolidating wakefulness in opposition to accumulating sleep drive (1472). Single-unit recordings in the rat from the area where orexin neurons are located revealed one group of slow-firing neurons that were wake-active and REM-off (13, 666). Later recordings in freely moving rats confirmed that this population corresponds to orexin neurons, determined by electrophysiological criteria (856) or post hoc immunohistochemical staining (699, 1265). Orexin neurons fire fastest during active waking, decrease firing during quiet waking, and cease firing during sleep, except during microarousals or immediately preceding the arousal from sleep.

In vitro, intracellular recordings from identified orexin neurons revealed that they have a depolarized resting membrane potential (333, 715), leading to spontaneous firing in the absence of injected current or application of neurotransmitter agonists. In addition, they are excited by a positive feedback loop involving local orexin release, activation of orexin type 2 receptors (1455), and excitation of local glutamatergic inputs (715). This positive feedback loop may help to synchronize the firing of the whole orexin neuron population. Furthermore, glutamatergic inputs to orexin neurons are potentiated via a cAMP-dependent mechanism during prolonged waking (1047), which is a mechanism suggested to be important in the maintenance of wakefulness in the face of increased sleep pressure (1299). However, recent optogenetic stimulation experiments found that sleep deprivation blocks the ability of orexin to activate its downstream targets and enhance waking (195).

D) CONTROL OF OREXIN NEURONS BY AFFERENT INPUTS. Orexin neurons receive afferent inputs from other nodes of the sleep-wake circuitry (FIGURE 6) as well as from areas involved in emotional regulation such as the amygdala and lateral septum (1102, 1466). They are excited by acetylcholine via M_3 muscarinic receptors (84, 947, 1454) but inhibited by serotonin via a postsynaptic activation of 5-HT_{1A} receptors (715, 905). This inhibitory action is also observed in vivo since intracerebroventricular application of an 5-HT_{1A} antagonist, WAY100635, increased locomotor activity during the dark (active) phase in wild-type mice, but not in orexin/ataxin-3 mice in which orexin neurons are ablated (905). Both inhibitory (715, 716, 1453) and excitatory (84, 1453, 1454) effects of norepinephrine on orexin neurons have been reported in recordings from mouse and rat brain slices. The inhibitory response is mediated by α_2 receptors activating inwardly rectifying potassium conductance (716, 1453), whereas the excitatory action is due to activation of α_1 receptors and activation of a nonselective cationic current (1453). In the rat, it has been suggested that the response to norepinephrine shifts from an excitation to an inhibition during a short period (2 h) of sleep deprivation (452). In addition, norepinephrine increases the frequency of inhibitory postsynaptic currents (IPSCs) via an effect on presynaptic GABAergic terminals (716, 1453). In vitro, dopamine inhibits orexin neurons via D_2 receptors (716), whereas in vivo, systemic dopaminergic agonists increase their activity as assessed by Fos immunohistochemistry, likely by an indirect action (161). Orexin neurons are unaffected by histamine, which is somewhat surprising, considering the close proximity of histamine and orexin neurons in the hypothalamus (342).

E) INHIBITION OF OREXIN NEURONS DURING SLEEP. The spontaneous activity of orexin neurons in vitro suggests that they must be actively inhibited during NREM and REM sleep when their activity level slows markedly. This inhibition likely arises from GABAergic neurons in the preoptic area

and BF. Orexin neurons are postsynaptically inhibited by both $GABA_A$ and $GABA_B$ receptors (15, 715, 1150, 1445), and $GABA_B$ receptors also mediate a presynaptic inhibition of glutamatergic and GABAergic inputs (1445). In vivo, antagonism of $GABA_A$ receptors increases the firing rate of wake-on (presumed orexinergic) neurons in the perifornical hypothalamus during NREM sleep, indicating an inhibitory GABA receptor-mediated tone during this state (15). Mutant mice with a constitutive loss of $GABA_B$ receptors in orexin neurons (via knockout of the GABA-B1 gene) have fragmented sleep-wake cycles, due to an upregulation of inhibitory tone which shunts (short-circuits) excitatory and inhibitory inputs (811). Feedback control of orexin neurons may occur through the release of coexpressed dynorphin peptides (223), which cause a hyperpolarization, inhibition of calcium channels, and reduction of excitatory synaptic inputs (717), although direct evidence for feedback control by this mechanism is lacking at present. In addition, orexin neurons are inhibited by the sleep homeostatic factor adenosine via A_1 receptors (14, 1277) (see sect. III).

F) DOWNSTREAM EFFECTORS OF OREXIN PROMOTION OF WAKEFULNESS. How do the orexins consolidate wakefulness? Anatomical studies demonstrated a strong innervation of sleep-wake circuitry by the orexin neurons, particularly the aminergic nuclei (273, 524, 1000). The strongest projection was found to the LC which expresses exclusively the type I receptor, whereas most other sleep-wake nuclei express the type II receptor or both type I and II (249, 506, 793, 853, 1307). In vivo, injections of orexin A into the LC enhanced wakefulness at the expense of REM sleep (128, 467), whereas in vitro recordings revealed a postsynaptic excitation mediated by activation of nonselective cation channels and blockade of leak potassium channels (524, 552, 904, 1326). Similarly, in vitro studies showed that orexins had excitatory effects on serotonergic DRN neurons (157, 158, 651, 735), histaminergic tuberomammillary neurons (85, 342, 1456), BF (47, 334), and brain stem cholinergic neurons (169, 651) and ventral tegmental area dopamine and GABA neurons (660). Furthermore, orexins target neurons in the dorsal ARAS pathway, exciting neurons in the reticular formation (160), nonspecific thalamic nuclei (83, 312, 436, 527), thalamocortical terminals (685), and deep layer VI cortical neurons (86). In addition to the LC, in vivo studies showed wake-promoting effects of orexins in the BF (348, 1279), tuberomammillary nucleus (530), laterodorsal tegmentum (1442), and reticular formation (1392). Orexins also directly increase muscle tone via excitation of spinal cord motoneurons (1457).

It was proposed that orexins exert their wake-promoting action through stimulation of the histamine system since orexins excite histamine neurons in vitro (342), and the wake-promoting effect of intracerebroventricular orexin A is reduced/lost in HDC knockouts and histamine H_1 receptor knockouts (530) or with application of a histamine H_1

receptor antagonist (1163). Furthermore, low histamine levels have been reported in the brains of narcoleptic dogs (922) and in the cerebrospinal fluid (CSF) of human narcoleptics, particularly in unmedicated patients (597, 925). However, the dependence of the intracerebroventricular effect of orexin A application on the histamine system may simply reflect the close proximity of histamine neurons to the ventricular system, compared with other postsynaptic targets. In contrast to orexin knockout animals, HDC or histamine H_1 receptor knockout animals do not have reduced duration of sleep-wake states (29), and optogenetic stimulation of orexin neurons is still able to increase the probability of awakening in HDC knockout animals. However, expression of the orexin type II receptor in histamine neurons and other areas surrounding the TMN in mice lacking type II receptors was sufficient to consolidate wakefulness, although sleep was still fragmented (869). Orexins actions at other sites are likely to be similarly important. For instance, optogenetic inhibition of LC norepinephrine neurons inhibited the wake-promoting effect resulting from optogenetic excitation of orexin neurons (196).

6. Neuropeptide S

Like the orexins, neuropeptide S (NPS) is a recently discovered peptide activating a previously "orphan" G protein-coupled receptor activating phospholipase C (1449). NPS is coexpressed in glutamate-producing neurons located just rostral to the LC (precoeruleus region) which project to widespread areas of the brain, including sleep-wake regulatory regions such as the midline thalamic nuclei, lateral hypothalamus, and preoptic area (1448, 1449). Intracerebroventricular application of NPS increased locomotor activity and decreased sleep in rats (1449), whereas NPS receptor knockout mice had reduced exploratory activity in a novel environment (317). In addition to its role in promoting wakefulness, recent experiments suggest a role for the peptide in controlling fear and anxiety (586, 1449).

7. Dopamine

Pharmacological agents increasing dopaminergic tone such as amphetamines and modafinil (Provigil) are the most potent wake-promoting substances currently known. As such, they are commonly prescribed to treat sleep disorders involving excessive daytime sleepiness (see sect. VII). Although these substances can enhance the release of other neuromodulators such as serotonin and norepinephrine, their effects are abolished in dopamine transporter (DAT) knockout animals (1425), confirming that their main effect is on dopaminergic systems (129). Additional evidence supporting a role for dopaminergic systems in promotion of wakefulness comes from analysis of D_2 receptor knockout mice that exhibit a significant decrease in waking amounts due to a shorter wake bout duration and a concomitant increase in sleep (1032). One possible mechanism explaining this effect is a disinhibition of intralaminar thalamic neurons via indirect basal ganglia-thalamic pathways (1135). In Parkinson's disease, where dopamine neurons in the substantia nigra degenerate, waking is interrupted by sleep episodes (1087). However, dopamine neurons are not the only neurons to be affected by this disease.

A) VENTRAL TEGMENTAL AREA DOPAMINE NEURONS. While the average firing rate of dopamine neurons in the ventral tegmental area (VTA) and substantia nigra does not vary across sleep-wake states (858), VTA dopamine neurons fire more bursts during waking and REM sleep, resulting in increased release of dopamine in target areas such as the nucleus accumbens and prefrontal cortex (271). In particular, increased bursting is observed in the presence of rewarding or aversive stimuli requiring an alerting response (1209). VTA neurons are excited in vitro by several neuromodulators that promote arousal such as orexins, substance P, and corticotrophin releasing hormone (658, 660).

B) VENTRAL PERIAQUEDUCTAL GRAY DOPAMINE NEURONS. Dopaminergic neurons in the ventral periaqueductal gray (vPAG)/DRN **(FIGURE 2)** show Fos activity during waking but not during sleep (757). Selective lesioning of these neurons by injections of 6-hydroxydopamine (63% loss) or nonselective lesions with ibotenic acid (80% loss) resulted in a marked (>20%) reduction in 24-h amounts of wakefulness, one of the most pronounced effects of lesions on wakefulness reported to date (757). In contrast, lesions of the serotonergic neurons in this area were without effect on 24-h amounts of sleep and waking. Retrograde tracing studies showed that dopaminergic vPAG neurons project to other parts of the ARAS such as the BF and midline thalamus, and receive input from sleep-active VLPO neurons (757). These data all support a role for these neurons in control of wakefulness, but electrophysiological recordings from these neurons across behavioral state are lacking at present.

8. GABA

GABAergic neurons and glutamatergic neurons (reviewed below) are very abundant and widely distributed in the brain. Hence, it is not surprising that some populations of the neurons utilizing these two neurotransmitters are involved in promoting wakefulness, whereas others are associated with sleep. Thus, although pharmacological agents potentiating the activity of GABAergic systems have been most closely linked with sleep (see sects. III and IV), select GABAergic subpopulations in the cortex (especially PV interneurons, sect. IIA) and in subcortical sites, are thought to be critical in the production of cortical LVFA. Cortically-projecting GABA neurons are located in the BF (386, 450, 500), hypothalamus [colocalized in histamine (1371), and melanin-concentrating hormone neurons (60)] and in the VTA (1206). Hypothalamic melanin-concentrating hormone neurons fire predominantly during sleep (482) and so

are unlikely to contribute to wakefulness. While the activity of histamine neurons is correlated with wakefulness, the function of GABA in histamine neurons is unclear, especially since it would be expected to counteract excitatory actions of histamine on target neurons. GABAergic neurons in the thalamic reticular nucleus play a crucial role in thalamocortical rhythms during sleep and wakefulness (see sect. III).

A) BF AND VTA GABA NEURONS. GABAergic neurons in the BF and VTA **(FIGURE 2)** in particular appear to be important for cortical LVFA since a fast-firing subpopulation of these neurons increases their activity during waking and REM sleep (481, 700). Many GABAergic BF neurons projecting to the cortex contain PV (451). Preliminary studies (154) showed that identified cortically-projecting BF GABA neurons are excited by neurotransmitters promoting cortical activation (acetylcholine, norepinephrine, histamine, orexins), likely accounting for their faster firing rate during waking and REM sleep (481). Rostral and caudal PV GABAergic projection neurons synapse onto hippocampal (385) and neocortical PV-positive neurons (386) which control hippocampal and cortical gamma rhythms, respectively (see sect. II*A*). Other subpopulations of BF GABA neurons that are likely sleep related project to the thalamic reticular nucleus (49) and lateral hypothalamus (449). The firing of cortically projecting GABA neurons in the BF (481) but not VTA (700) was correlated with gamma activity in the EEG. However, VTA GABA neurons increased their firing prior to intracranial self-stimulation of the medial forebrain bundle, indicating that they may be involved in the attentive processes related to brain reward (1205). VTA GABA neurons are excited by the wake-promoting orexins (660) and by histamine (659). Ibotenic acid lesions of the rostral BF (MS/vDB), which preferentially affect noncholinergic neurons, abolish theta and gamma rhythms in the hippocampus (see sect. II*A*). Similarly, chemical lesions of the caudal BF have dramatic effects on cortical LVFA and attention that are correlated with the loss of PV-positive GABA neurons (166, 397, 611).

B) STRIATAL MEDIUM SPINY NEURONS. GABAergic medium spiny neurons in the striatum receive a massive glutamatergic cortical input and control the activity of thalamocortical neurons. Transitions from NREM sleep to wakefulness convert the firing of striatal neurons from fast cyclic firing, synchronized with cortical field potentials, to an irregular pattern of action potentials triggered by disorganized depolarizing synaptic events of variable amplitude (777). Cell body specific lesions of the rostral striatum reduce waking by ~15% and produce cortical slowing of the EEG (1029). Conversely, lesions of the globus pallidus, the main recipient of inhibitory striatal projections, increase waking by 46%. Improved function in minimally conscious patients produced by stimulation of the nonspecific thalamic nuclei (1136) may be mediated by increased cortico-striatal-thalamic interplay (1135).

9. Glutamate

The vast majority (>90%) of glutamatergic projections to the cortex arise from the thalamic relay nuclei innervating cortical layers III and IV, and from nonspecific thalamic nuclei innervating layers I and VI (540, 750). In addition, the BF (500), claustrum, amygdala, VTA, laterodorsal tegmentum, and hypothalamus (540) provide minor glutamatergic projections to the cortex. Vesicular glutamate transporters are expressed in cortically projecting orexin neurons in the perifornical hypothalamus (1077) and serotonergic DRN neurons (439), suggesting that glutamate is a cotransmitter in these neurons. Furthermore, glutamate is the major neurotransmitter released from rostral midbrain brain stem reticular formation neurons projecting to the thalamus. Dissociative anesthetic agents such as ketamine inhibit glutamatergic NMDA receptors, whereas pharmacological agents that prolong the decay of AMPA receptor currents (AMPAkines) are proposed to enhance attention and cognition.

A) THALAMIC INTRALAMINAR AND RELAY NEURONS. The thalamus is an important component of the dorsal branch of the ARAS involving the nonspecific thalamic nuclei **(FIGURE 5)**, as well as the specific relay nuclei which convey external sensory information to the cortex. EEG rhythms typical of wakefulness are sculpted through interactions between the thalamocortical relay neurons, corticothalamic pyramidal neurons, and GABAergic neurons in the thalamic reticular nucleus. At the onset of conscious states (i.e., wakefulness and REM sleep), thalamic relay neurons are excited by the action of acetylcholine, norepinephrine, and histamine, leading to a switch in firing pattern from synchronized burst firing (typical of NREM sleep) to tonic firing able to faithfully transmit sensory information to the cortex (826, 828, 1228). This switch in firing pattern is due to a depolarization mediated by a block of leak potassium conductance by G_q-coupled receptors (muscarinic $M_{1/3}$, norepinephrine α_1, histamine H_1) and a block of the pacemaker current I_h by G_s/adenylyl cyclase-coupled receptors (muscarinic M_2/M_4, norepinephrine β, serotonin 5-$HT_{4,6}$, histamine H_2). In a thalamocortical slice preparation, coincident stimulation of nonspecific thalamic nuclei (centrolateral intralaminar nucleus) or direct stimulation of layer I together with relay nucleus stimulation induced supralinear summation of the two inputs in cortical output layer V, providing a possible mechanism by which the nonspecific nuclei promote arousal (741).

10. Effector systems of neurotransmitters promoting wakefulness

The effector systems used by the neurotransmitter systems involved in generation of wakefulness have been

studied by in vitro electrophysiology, pharmacology, and genetic methods (see sect. VI). The majority of the receptors implicated in cortical LVFA and wakefulness are either ionotropic (glutamatergic AMPA, kainate and NMDA receptors, $GABA_A$ receptors, nicotinic acetylcholine and serotonin 5-HT_3 receptors) or metabotropic receptors coupled to G_q G proteins and the beta form of the enzyme phospholipase C (glutamatergic $mGluR_1$ and $mGluR_5$, cholinergic muscarinic M_1, M_3, M_5, norepinephrine α_1, histamine H_1, serotonin 5-HT_2, orexin type I and type II receptors). Phospholipase C (PLC)-β occurs in four isoforms. Mice lacking the $\beta1$ or $\beta4$ subunits of PLC have disrupted theta rhythms and other EEG abnormalities (595, 1166). Activation of these metabotropic receptors causes a depolarization in target neurons mediated by one or a combination of three mechanisms: *1*) blockade of leak potassium conductances (two-pore potassium channels) (1348); similar to deletion of PLC-β isoforms, mice lacking the TASK3 two-pore potassium channel have deficient theta oscillations and altered sleep behavior (965); *2*) activation of mixed cation channels [likely of the transient receptor potential (TRP) family] (1151); and *3*) activation of electrogenic sodium-calcium exchangers (343, 1434). In addition, effects on other intrinsic membrane currents contribute to the activation of thalamocortical and limbic neurons (828, 918). For the most part, the role of individual subunits of these channels/transporters in the control of sleep-wake behavior remains to be determined.

D. Synthesis

Studies involving stimulation of the brain areas and neurotransmitter systems comprising the ARAS consistently report EEG activation and wakefulness as a result. These studies include both older techniques of electrical stimulation or infusion of pharmacological agents as well as state-of-the-art optogenetic techniques where light-activated ion channels are introduced into the desired neuronal population by genetic engineering techniques (6, 1473). In contrast to the stimulation experiments, studies where localized inactivation of individual neurotransmitter systems or nuclei of the ARAS have been performed (summarized in **TABLE 1**) generally produce relatively minor changes in cortical EEG or the amount of wakefulness in a 24-h period (see sect. II*C*), with the possible exception of the parabrachial nucleus (see sect. II*B*). There are several possible explanations for this dichotomy between stimulation and inactivation experiments. First, the ARAS systems are strongly interconnected, mutually excitatory to each other **(FIGURE 6)** and converge onto common effector systems at the level of thalamic and cortical neurons (826, 918). Thus there is considerable redundancy in the system, and inactivation of any individual component of the system is compensated for by the other systems. This is perhaps not surprising considering the enormous adaptive advantage of wakefulness! A second possibility for the mild effects of loss-of-function experiments is that the systems so far targeted are not absolutely required for wakefulness. The majority of studies have focused on neuromodulatory systems, whereas selective inactivation of glutamatergic and GABAergic systems projecting to the neocortex have not been tested due to technical difficulties in targeting these systems. The neuromodulatory systems are clearly able to generate cortical activation when stimulated but may only be required for specific aspects of wakefulness. Specific roles for these systems could be *1*) facilitation of LVFA (acetylcholine); *2*) inhibition of sleep-active neurons (norepinephrine, serotonin, acetylcholine; see sect. III); *3*) maintenance of high muscle tone (norepinephrine) during waking (see sect. IV*A*); *4*) consolidation of wake periods (orexins); *5*) maintenance of waking in a novel environment (histamine); *6*) enhanced arousal in the presence of rewarding stimuli (dopamine, acetylcholine); *7*) enhanced arousal in the presence of aversive stimuli (norepinephrine, serotonin, histamine); and *8*) consolidation of memories through enhancement of synaptic plasticity (acetylcholine, norepinephrine, serotonin, histamine, dopamine, orexins). Methods to selectively stimulate these systems (e.g., using optogenetic techniques) together with whole brain imaging will be helpful in further delineating their function.

III. NREM SLEEP

Subjectively experienced as a loss of conscious awareness, the onset of sleep is heralded in the EEG by the replacement of LVFA by large-amplitude, slow (<4 Hz) waves and the appearance of thalamocortical spindles **(FIGURE 1)**. These EEG changes are due to the progressive reduction in firing of neurons in the ARAS. This section describes the mechanisms underlying the EEG signs of NREM sleep (also called slow-wave sleep) and the mechanisms that cause the circadian and homeostatic inhibition of wake-promoting ARAS neurons.

A. Electrographic Signs of NREM Sleep

In humans, the different stages of NREM sleep are classified according to the criteria established by Rechtschaffen and Kales (1053) **(FIGURE 1)**. Stage 1 NREM sleep exhibits theta activity at frontal sites and alpha activity posteriorly, similar to drowsy waking (sect. II). Stage 2 NREM sleep is characterized by the appearance of sleep spindles (7–15 Hz) and K-complexes in the EEG. Stages 3 and 4 of NREM sleep (deep sleep) exhibit prominent, high-amplitude slow, delta waves (1–4 Hz). The cortical slow oscillation (0.5–1 Hz) discovered by Steriade and colleagues synchronizes the activity of cortical and thalamic neurons that generate spindle and delta waves throughout NREM sleep (1217). In animals, NREM sleep is not usually subdivided into these four

stages, but deep (delta) sleep may be distinguished from light NREM sleep. NREM sleep is also characterized by low skeletal muscle tone and slow, rolling eye movements. Here we first describe phasic events occurring during NREM sleep in the thalamocortical system (spindles) and hippocampal formation (sharp wave-ripple complexes) and then discuss the delta and slow oscillations typical of deep NREM sleep.

1. Thalamocortical spindles

Spindles and K-complexes are the defining features of stage 2 NREM sleep in humans (FIGURE 1). K-complexes represent a combination of one cycle of the neocortical slow oscillation followed by a spindle in thalamocortical neurons (27, 28, 197). Several lines of evidence support the contention that spindles are generated in the thalamic GABAergic reticular and perigeniculate nuclei (394, 1228): *1*) spindles occur even in the absence of the cerebral cortex (1215); *2*) large thalamic lesions (177, 397, 1370) or specific lesions/deafferentation of the thalamic reticular nucleus abolish spindles in thalamocortical neurons (1223); *3*) spindle activity can be recorded in the deafferented reticular nucleus (1224); *4*) spindles are absent in the anterior part of the thalamus, which does not receive afferents from the thalamic reticular nucleus (i.e., the anterodorsal, anteromedial, and anteroventral nuclei; Ref. 975), and in their projection areas (cingulate cortex, habenular nucleus). Although the thalamic reticular nucleus is the generator of spindles, in intact animals spindles are initiated and terminated in concert with delta and slow oscillations in corticothalamic and thalamocortical neurons due to the extensive interconnections of these cells (828).

A) CELLULAR MECHANISMS UNDERLYING SPINDLES. As aminergic inputs are slowly withdrawn during early NREM sleep, long-lasting (50 ms) bursts of action potentials are generated in reticular nucleus neurons due to activation of low-threshold (T-type) calcium channels. These channels are of the $Ca_v3.2$ and $Ca_v3.3$ subtype (1269), which allow bursting at the resting membrane potential. Bursts at spindle frequencies lead to large and long-lasting inhibitory synaptic potentials (IPSPs) in thalamocortical neurons which remove the inactivation of T-type ($Ca_v3.1$) (1269) calcium channels. Thus, at the offset of the IPSPs, when the cell becomes more depolarized, the low-threshold calcium channels are activated, calcium enters the cell, resulting in a low-threshold calcium spike crowned by a short (5–15 ms) burst of sodium-dependent action potentials in the thalamocortical neurons. This burst in thalamocortical neurons leads to EPSPs in cortical neurons and to action potentials which together make up the spindle recorded in the EEG. Synchronization of spindles is achieved via recurrent inhibitory and electrical synaptic connections between thalamic reticular neurons (828). Spindles can also be recorded in cortical projection sites such as the basal ganglia (298),

possibly providing a substrate for procedural learning during sleep. Spindles decline during deep sleep due to the increased hyperpolarization of thalamocortical relay neurons but may reappear just prior to the transition to REM sleep when thalamocortical relay neurons become more depolarized again (due to increased ascending brain stem excitation).

B) INHIBITION OF SPINDLES DURING WAKEFULNESS AND REM. In vivo, extracellular and intracellular recording studies revealed that thalamic reticular neurons fire tonically during waking and switch to burst firing during NREM sleep, similar to thalamocortical relay neurons (802, 1222). Tonic firing and inhibition of bursts/spindles during waking is likely due to excitation of these thalamic reticular neurons by norepinephrine and serotonin (833) released from ascending projections arising in the LC and DRN. Norepinephrine, acting via α_1 receptors and serotonin, acting via $5\text{-}HT_2$ receptors, causes a depolarization by block of a leak potassium conductance leading to an inactivation of low-threshold calcium channels responsible for bursting (833). Spindles can also be inhibited by input from other ARAS systems, in particular brain stem cholinergic (974) and BF cholinergic and GABAergic inputs (49, 976). The mechanism underlying inhibition of spindle activity during REM sleep is less clear but has been proposed to be due to input from REM-on cholinergic neurons which hyperpolarize thalamic reticular neurons via a muscarinic M_2 receptor mediated inhibition of leak potassium conductance (192, 831).

2. Hippocampal sharp waves and high-frequency ripples

High-frequency (100–400 Hz) field potentials termed sharp wave-ripple complexes can be recorded in the hippocampus and associated areas during quiet wakefulness and NREM sleep in rodents (174, 180, 181) and in humans (132). Sharp-waves occur in the CA3 region of the hippocampus when the highly interconnected CA3 pyramidal network is released from the control exerted by subcortical inputs, especially the MS/vDB. Sharp-wave like epileptiform waves occur in the hippocampus following transection of the fimbria-fornix, the main fiber bundle carrying ascending fibers from the MS/vDB and other ARAS systems (182). Ripple occurrence is also increased by pharmacological blockade of histamine H_1 receptors, which mediate histaminergic excitation of MS/vDB neurons (647, 1012) or blockade of serotonin $5\text{-}HT_3$ receptors (1012), which excite inhibitory hippocampal/dentate interneurons. When released from inhibition, the synchronized firing of CA3 pyramidal neurons leads to a concerted activation of Schaffer-collateral synapses in the CA1 region and subsequently of subicular and downstream retrohippocampal cortical structures (227). Feed-forward and feedback activation of hippocampal GABAergic interneurons leads to a high-frequency oscillation in the membrane potential of pyramidal

neurons due to IPSPs, reflected as a high-frequency ripple in the extracellular potential (1462). Phase-locked interneurons fire at high frequencies on every cycle of the extracellularly recorded oscillation and entrain the firing of pyramidal neurons, which fire at lower frequencies (643, 1462). Accordingly, ripple frequency is reduced by pharmacological prolongation of GABA$_A$ receptor-mediated currents (1013). Surprisingly, ripple amplitude and entrainment of pyramidal neurons were increased in mice lacking the GluR1 subunit of AMPA-type glutamatergic receptors specifically on PV-positive interneurons, possibly as a result of developmental compensation (1035). Although many pyramidal neurons contribute to each sharp wave/ripple, each wave of a ripple reflects the firing of a discrete subpopulation of these neurons (228, 1462). Modeling studies suggest that electrical coupling between the axons of pyramidal neurons is required to synchronize their activity (1306). In support of this idea, the occurrence of ripples in vitro was reduced in mice lacking one type of gap junction protein (connexin 36), and the intraripple frequency was reduced (781). However, in another report, the occurrence of in vitro kainate-induced sharp waves was actually increased in these mice (957).

3. Delta (1–4 Hz) and slow (<1 Hz) oscillations

Delta and slow oscillations in the cortex and thalamus are typical of the deeper stages of NREM sleep (FIGURE 1). They result from increased withdrawal of excitatory neuromodulatory inputs (primarily cholinergic and aminergic), resulting in a more hyperpolarized membrane potential of the pyramidal/thalamic relay neurons. Delta oscillations are best understood at the thalamic level. Recordings in vivo from thalamocortical neurons revealed that stereotyped high-frequency bursts of action potentials occur at delta frequencies interspersed with silent periods (25, 314, 817, 932, 1225), a pattern which can be abolished by brain stem cholinergic stimulation or by increases in ambient light (25, 932, 1225). The ability of thalamocortical neurons to generate burst firing in the delta frequency range is due to their intrinsic membrane properties (556, 557, 711, 830, 1199). Hyperpolarization resulting from the activation of calcium-dependent potassium conductances after a burst of action potentials or from inhibitory synaptic inputs leads to the opening of hyperpolarization-activated, cAMP-modulated cation (HCN) channels causing the so-called H-current (I_h). This slowly activating current provides a depolarizing drive towards the threshold for action potentials and is a major contributor to the duration of the interburst interval (830, 968). I_h is modulated during waking by activation of neurotransmitter receptors coupled to stimulation of cAMP (e.g., norepinephrine β, histamine H$_2$) and by release of NO from cholinergic projections (967, 968) resulting in a shift in the activation curve to more positive membrane potentials and reducing the ability of the cells to generate intrinsic oscillations (828, 829). As well as activating I_h, hyperpolarizations result in deinactivation of low-threshold calcium

channels, allowing their subsequent activation once the membrane potential reaches less negative potentials (828). Opening of these calcium channels leads to a low-threshold spike (LTS) and a burst of action potentials (556–558). Bursts of action potentials in thalamocortical neurons lead to a prominent burst in large numbers of cortical pyramidal neurons. Bursting of corticothalamic neurons potentiates intrinsic rhythms in thalamocortical neurons and entrains their firing through excitation of thalamic reticular neurons leading to rhythmic hyperpolarizations in thalamocortical neurons, creating increased network synchronization (25, 1225). Calcium influx through the low-threshold channels allows activation of calcium-dependent potassium conductances, restarting the cycle. Ascending influences during waking or REM sleep block this cycle by acting on PLC-coupled receptors that block a leak potassium conductance causing inactivation of the low-threshold calcium channels and bringing the membrane potential out of the range of the H-current (826, 828).

A) ROLE OF LOW-THRESHOLD CALCIUM CHANNELS IN DELTA WAVES. Low-threshold bursts in thalamocortical neurons were abolished in mice constitutively lacking the Ca$_v$3.1 calcium-channel gene (695) or in mice with a targeted deletion of Ca$_v$3.1 in rostral-midline thalamus (32). Delta waves were abolished in these mice with knockouts in the whole brain or thalamus, whereas deletions of Ca$_v$3.1 channels in cortical neurons did not affect delta waves (32). Loss of delta waves was associated with fragmented sleep with a higher incidence of brief arousals. Similar to thalamocortical neurons, bursting in thalamic reticular neurons is regulated by calcium dynamics involving low-threshold calcium channels, endoplasmic reticulum calcium ATPases which sequester intracellular calcium, and small-conductance calcium-dependent potassium (SK) channels (266). Like Ca$_v$3.1 knockouts, mice lacking the SK2 channels responsible for slow afterhyperpolarizations in thalamic reticular nucleus neurons had disrupted sleep and a threefold reduction of low-frequency rhythms during NREM sleep (266).

B) THE NEOCORTICAL SLOW OSCILLATION (0.5–1 HZ). This phenomenon, discovered by Steriade in anesthetized cats (1230), was subsequently observed in naturally sleeping animals (28, 1237, 1289) and in humans (27, 272). Somewhat confusingly, despite its name, the so-called slow oscillation does not necessarily imply rhythmicity. High-density EEG recordings in humans revealed that each cycle of the slow oscillation represents a traveling wave originating most frequently in prefrontal-orbitofrontal regions and propagating towards more posterior cortical areas (809). The slow oscillation occurs throughout all NREM sleep stages and serves to bind together the other EEG phenomena of NREM sleep such as spindles and delta waves (1217, 1228, 1229). Slow-wave activity (SWA; 0.5–4 Hz), a combination of EEG power in the frequency bands reflecting the slow

oscillation and delta oscillations, is widely considered to be a measure of sleep need and/or intensity (3, 1292). Periods of sleep deprivation cause increases of SWA in the subsequent sleep period in both animals and in humans. SWA is highest at the beginning of the sleep period and progressively decreases during sleep. Naps during the day also reduce SWA in the subsequent night (1292). The hypothesized relationship between SWA and synaptic strength is discussed in section III*D*. The slow oscillation is generated within the cortex since it is abolished in thalamic neurons following removal of the cortex (1290), and it persists following disconnection of subcortical inputs (1231) and can occur in vitro in cortical slices, following manipulation of the ionic milieu bathing the slices (269, 1110). However, in intact animals, the slow oscillation strongly influences the activity of the thalamus through corticothalamic projections and conversely the thalamus influences the cortex through thalamocortical projections (264, 535, 1229, 1231).

C) CELLULAR MECHANISM CAUSING UP AND DOWN STATES. Intracellular recordings from cortical neurons in vivo (259, 1374) and in vitro (1110) revealed that the slow oscillation consists of prolonged depolarizations associated with extracellular gamma frequency activity (UP states) separated by prolonged hyperpolarizations (DOWN states) when most cortical neurons are silent (255, 256). These states are well-synchronized over widespread areas of cortex (1374). The UP states are due to a barrage of excitatory synaptic inputs mediated by glutamatergic AMPA/kainate and NMDA receptors and activation of a persistent sodium current and usually begin in deeper cortical layers, possibly due to an increased frequency of excitatory spontaneous synaptic potentials (211). Consistent with this idea, the frequency and amplitude of miniature excitatory postsynaptic currents in pyramidal neurons of frontal cortex was enhanced following waking and decreased following sleep (737). Fast inhibitory $GABA_A$ receptor-mediated potentials also occur during the UP state due to input from GABAergic interneurons activated by the firing of principal glutamatergic neurons. The hyperpolarizing phase is due to withdrawal of excitatory input.

B. Generation and Maintenance of NREM Sleep

An involvement of the preoptic area (PO)/BF **(FIGURE 2)** in the control of sleep has been inferred since the observations by Constantin von Economo of damage to this area in the brains of patients with persistent insomnia following the influenza pandemic in the early years of the 20th century (1377). Extensive lesions of the PO/BF led to long-lasting insomnia in the cat (840, 1105), whereas warming caused increases in sleep (1068). Whereas most brain neurons exhibit a wake-On, a wake/REM-on or state-indifferent firing patterns across the sleep-wake cycle, the PO/BF is unusual

in that it contains a large number of neurons utilizing the neurotransmitter GABA which have sleep-on, wake-off firing patterns. Many of the sleep-active neurons in the medial and lateral preoptic area are also temperature sensitive, likely explaining the coupling of body temperature and sleep (16). In the BF, caudally projecting, possibly sleep-active, GABA neurons (449) are intermingled with cortically projecting cholinergic, GABAergic, and glutamatergic neurons (451) which increase firing in association with cortical activation (481).

1. Ventrolateral preoptic nucleus

With the use of Fos immunohistochemistry to identify neurons that had been recently active, a cluster of sleep-active neurons was identified in the ventrolateral preoptic nucleus (VLPO) **(FIGURE 2)** of the rat (1162). These neurons contained the inhibitory neurotransmitters GABA and galanin and projected heavily to nuclei of the ARAS, especially the histaminergic tuberomammillary nucleus (406, 1161, 1162, 1210). Single-unit recordings targeting this area confirmed that it contains sleep-active neurons (1254). Extensive neurotoxic lesions of the central cluster of the VLPO in the rat led to a large decrease in delta power and NREM sleep time and a fragmentation of the sleep-wake cycle (756), effects which persisted for at least 3 wk postlesion. Furthermore, the number of remaining Fos-immunoreactive neurons was linearly related to NREM sleep time and EEG delta power.

In vitro recordings in the rat determined that many VLPO neurons are multipolar, triangular-shaped neurons, which exhibit a LTS. All of these were inhibited by norepinephrine and acetylcholine, and the majority were also inhibited by serotonin ($5-HT_{1A}$) (403). Activation of non-$\alpha 7$ containing nicotinic receptors enhances the release of norepinephrine onto VLPO neurons, indicating a synergistic inhibitory action of acetylcholine and norepinephrine (1091). Other VLPO neurons, possibly local interneurons, had a fusiform/bipolar shape, lacked an LTS, and were excited by serotonin and an adenosine A2a receptor agonist (403, 404). Initial experiments suggested that histamine and orexin did not affect the firing rate of VLPO neurons, but more recent experiments have revealed an indirect histaminergic inhibition due to excitation of local inhibitory interneurons (736). Retrograde tracing revealed surprisingly few cholinergic projections to VLPO but prominent projections from the histaminergic tuberomammillary nucleus, norepinephrine neurons in the LC and ventrolateral medulla, and serotonergic neurons in the dorsal median and central linear raphe nuclei (222). However, somatodendritic release of acetylcholine from nearby cholinergic neurons in the HDB and MCPO is a possibility. Interestingly, VLPO neurons also receive direct inputs from the retina (759) and indirect projections from the suprachiasmatic nucleus via the dorsomedial hypothalamus (222, 306, 1250), one pathway by which light exposure could affect sleep. In vitro studies also re-

vealed that VLPO neurons are excited by adenosine through an indirect mechanism: A_1 receptor-mediated presynaptic inhibition of inhibitory synaptic inputs (203, 888). In addition, activation of adenosine A_{2a} receptors by infusion of an A_{2a} agonist in the subarachnoid space underlying the VLPO area increases the activity of VLPO neurons in vivo (1128).

2. Median preoptic area

Single-unit recordings and Fos studies have defined another preoptic nucleus containing a large population of GABAergic sleep-active neurons, the median preoptic nucleus (MnPO), located just dorsal to the third ventricle **(FIGURE 2)** (432, 1094, 1252). Like VLPO neurons, MnPO neurons project to and inhibit wake-promoting neurons of the ARAS in the perifornical lateral hypothalamus, DRN, and LC (1251, 1321). Inactivation of the MnPO by infusion of the $GABA_A$ receptor agonist muscimol led to a prolonged waking state in rats (1251). On the other hand, high-frequency electrical stimulation or perfusion with glutamate or the $GABA_A$ receptor antagonist bicuculline enhanced NREM sleep and inhibited the activity of wake-active neurons in the perifornical hypothalamus (1251). MnPO neurons recorded in vitro were dose-dependently inhibited by norepinephrine via α_2 receptor-mediated activation of inwardly rectifying potassium channels (63), possibly explaining their silence during waking. Experiments comparing the extent of Fos during spontaneous sleep, sleep deprivation, and recovery from sleep deprivation suggest that MnPO neurons are active during sleep deprivation, whereas VLPO neurons are mainly active during sleep (462, 871, 994). Thus MnPO neurons increase their activity in response to increased homeostatic sleep pressure, whereas VLPO neurons may function to consolidate and maintain sleep and regulate sleep depth (462).

3. Wake-NREM transitions and the flip-flop model

Von Economo (1378) was the first to propose the existence of an anterior hypothalamic sleep-promoting area and a posterior hypothalamic waking center. More recent anatomical tracing experiments revealed that neurons in the core of the VLPO project heavily to wake-promoting histamine neurons in the tuberomammillary nucleus (TMN) of the posterior hypothalamus and also to wake-promoting serotonin DRN neurons and norepinephrine LC neurons in the brain stem (1161). Around the same time, pharmacological and electrophysiological experiments showed that GABA and galanin inhibit TMN, DR, and LC neurons (420, 421, 726, 1003, 1141), whereas serotonin and norepinephrine inhibit most VLPO neurons (403). Similarly, histamine excites a subpopulation of inhibitory interneurons in the VLPO via H_1 and H_2 receptors and thereby causes an indirect inhibition of VLPO projection neurons (736). In addition, histamine neurons appear to utilize

GABA as a cotransmitter (677); thus TMN neurons can potentially also inhibit VLPO neurons through release of GABA. These mutually inhibitory interactions between VLPO neurons and TMN/DRN/LC neurons were conceptualized in the form of a flip-flop switch (838, 1117) such that activation of VLPO leads to inactivity of TMN/DRN/LC neurons and promotes sleep, whereas activation of TMN/DRN/LC leads to inactivity of VLPO neurons and promotes wakefulness **(FIGURE 7)**. A crucial aspect of this model is that the two halves of the switch, by strongly inhibiting each other, create a feedback loop that is stable in only two states such that intermediate states of sleep and wakefulness are very brief. A further component to the model was the proposal that orexins stabilize behavioral state via their strong excitatory actions on wake-promoting neurons. Analysis of orexin knockout mice revealed that they have many more transitions between wake, NREM, and REM states than do wild-type mice, supporting this model (870). Although intuitively appealing, this model has a few weaknesses. First, the model does not well represent the changes in firing of all the neuronal subpopulations involved. While sleep-active preoptic neurons have fast transitions around state-transitions (1266), the firing rate of wake-active BF neurons changes more slowly (1266) and thus more closely resembles a latch than a switch. Furthermore, recordings of histamine neurons showed that they begin firing after the onset of EEG activation during NREM→Wake transitions (1264), which would seem inconsistent with them being involved in causing the state change. Second, the mechanism responsible for turning the switch on and off is unclear since a switch remains in one state unless a third mechanism causes a transition. Possible candidates for facilitators of the wake-sleep transition are sleep homeostatic factors that slowly build up during wakefulness and are discussed in the following section.

C. NREM Sleep Homeostasis

Homeostatic control of sleep refers to the increased propensity for sleep during prolonged waking and the prolonged sleep time and depth of sleep (reflected as increased EEG slow wave activity) following a period of sleep deprivation (123, 311). Sleep homeostasis is considered to reflect the accumulation of sleep homeostatic factors during waking, particularly in the BF and cortex, in a manner related to brain energy usage (see sect. III*D*). Sleep homeostatic factors inhibit the activity of ARAS neurons as well as cortical neurons and thereby facilitate the slow oscillations typical of NREM sleep.

1. Sleep factors

The search for sleep-promoting factors dates back 100 years when Ishimori (548) and Legendre and Pieron (701) reported that injection of CSF from a sleep-deprived dog into the cisterna magna of a normal animal induced sleep.
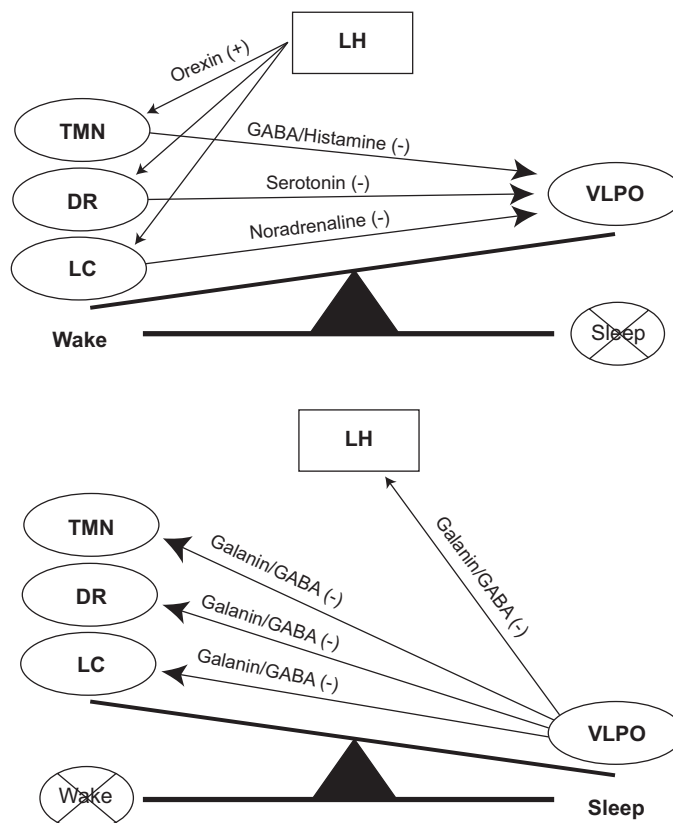
FIGURE 7. The "flip-flop" switch model of transitions between sleep and wakefulness (1117). The wake state is stabilized by lateral hypothalamic (LH) excitatory orexinergic input to wake-related nuclei, including GABAergic/ histaminergic neurons of the tuberomammillary nucleus (TMN), serotonergic neurons of the dorsal raphe nucleus (DR), and noradrenergic neurons of the locus coeruleus (LC). During sleep, GABAergic/galaninergic ventrolateral preoptic (VLPO) neurons inhibit wake-promoting nuclei, including LH. Transitions between wake and sleep are due to mutual inhibition between these sleep- and wake-related nuclei. (Adapted from Saper et al. *Nature* 437: 1257–1263, 2005, with permission from MacMillan Publishers Ltd.)

Later in 1967, Pappenheimer et al. (972) performed similar experiments where CSF from the cisterna magna of goats deprived of sleep for 72 h induced sleep in cats and rats following intraventricular application. These pioneering studies suggested that endogenous humoral factors are induced and accumulate during waking and generate a homeostatic sleep response. This led to a series of investigations in search of humoral sleep-promoting substances (545), leading to the identification of several substances including *1*) delta sleep inducing peptide (438); *2*) uridine (517); *3*) oxidized glutathione, originally designated as SPS-B (516); *4*) muramyl dipeptide (*N*-acetylmuramyl-L-alanyl-D-isoglutamine), originally described as Factor S (971); and *5*) prostaglandin D_2 (1317). In the following years, a variety of additional endogenous sleep-inducing substances were identified including peptides, growth factors, and cytokines as well as neuromodulators such as adenosine and NO. Homeostatic sleep factors should fulfill the following criteria: *1*) administration of the substance induces sleep; *2*) the levels of the substance in the brain should increase with increasing sleep propensity; and *3*) the substance should act on brain regions and neurons involved in the regulation of sleep or wakefulness. Recent studies

have focused extensively on the role of adenosine, nitric oxide, prostaglandin D_2, and cytokines in sleep regulation and the following sections will review the latest research on these factors.

A) ADENOSINE. The neuromodulator adenosine links energy metabolism, neuronal activity, and sleep (79, 91, 319, 446). The hypnogenic effects of adenosine were first described in cats by Feldberg and Sherwood (359) and later in dogs by Haulica et al. (483). Systemic and central administrations of adenosine or adenosine A_1 receptor agonists induced sleepiness and impaired vigilance (91, 226, 320, 1022, 1037, 1038, 1373) by inhibition of wake-active neurons. Adenosine A_{2A} receptors are also implicated in mediating the somnogenic effects of adenosine by excitation of sleep active neurons (485, 531, 1123). Stimulants such as caffeine and theophylline counteract the sleep-inducing effects of adenosine by serving as antagonists at both A_1 and A_{2A} adenosine receptors (384, 1192).

Adenosine levels correlate with time spent awake. Endogenous, extracellular adenosine levels in the BF (102, 591, 843, 1017, 1018) and cortex (591, 1017) increase in pro-

portion with time spent awake **(FIGURE 8)**. Thus adenosine induces sleep and adenosine levels track sleep need, fulfilling the criteria for adenosine being a homeostatic sleep factor. Measurements of extracellular adenosine levels across the sleep-wake cycle and in response to sleep deprivation revealed that adenosine levels rise only in select regions of the brain (1017, 1247). In particular, adenosine levels correlate with time awake in the region of the caudal BF containing cortically projecting wake-active neurons, and in the cortex itself. In contrast, adenosine levels did not follow this pattern in other brain areas such as the preoptic area of the hypothalamus, ventral thalamus, DRN, or pedunculopontine tegmentum. BF adenosine levels also rise when rats are exposed to a sleep fragmentation protocol (844), possibly explaining excessive daytime sleepiness in sleep disorders where sleep is fragmented (see sect. VII).

I) Mechanisms underlying adenosine increases during wakefulness. Increased levels of extracellular adenosine during prolonged wakefulness are caused by interactions between neuronal and glial mechanisms. Glutamatergic stimulation of the BF elevates extracellular adenosine and increases sleep (1409). Selective activation of glutamatergic NMDA receptors on hippocampal pyramidal (790) or on brain stem cholinergic neurons (134) also leads to slow adenosine release and inhibition of neuronal activity. In the BF, cell-specific lesion of cholinergic neurons attenuates the sleep deprivation-induced increase of adenosine (102, 592), suggesting either that increases in extracellular adenosine are derived from these neurons or that they release an essential signal for extracellular adenosine accumulation. Such a signal may be NO (see next section). There is also strong recent evidence in support of an astrocytic origin of adenosine via so-called "gliotransmission." Neurotransmitter release, especially glutamate release, triggers a rise in astrocytic calcium which triggers gliotransmision of ATP along with other neurotransmitters such as glutamate and D-serine (360, 979). In turn, breakdown of the extracellular ATP released by glia yields adenosine, which depresses neuronal activity (981, 1474). Blockade of vesicular release via transgenic expression of a dominant-negative SNARE domain specifically in astrocytes (dn-SNARE mice) blocked the accumulation of homeostatic sleep pressure following sleep deprivation as reflected by slow-wave activity and prevented the sleep-suppressing effects of an adenosine A_1 receptor antagonist (360, 472), suggesting that blocking gliotransmission affected sleep by reducing the accumulation of extracellular adenosine.

II) Adenosine mediates its sleep-promoting effects through activation of both A_1 and A_{2A} receptors. Electrophysiological, behavioral, and molecular evidence suggest that in wake-active areas, the effects of adenosine are primarily mediated via A_1 receptors. In vitro studies have demonstrated inhibitory postsynaptic effects mediated by activation of inwardly rectifying potassium channels on brain stem (48, 1041) and BF cholinergic neurons (45), orexin neurons (738), and hippocampal/neocortical pyramidal neurons (417, 834). A weaker postsynaptic inhibitory effect mediated via an A_1 receptor-mediated shift of the activation threshold of the hyperpolarization-activated current I_h is observed in thalamic relay neurons (826) and BF noncholinergic neurons (45). Adenosine further dampens neuronal activity and promotes sleep via presynaptic inhibitory effects on excitatory glutamatergic inputs to cortical glutamatergic neurons (446) and wake-active cholinergic (48, 134, 897, 1332) and orexin (1444) neurons, as well as on inhibitory GABAergic inputs to sleep-active VLPO neurons (203, 888). Infusion of A_1 receptor agonists in the BF, laterodorsal tegmentum, lateral hypothalamus, and prefrontal cortex increases sleep, whereas infusion of A_1 receptor antagonists in the same areas increases waking (14, 1022, 1039, 1247, 1277, 1332). Although adenosine A_1 receptors have effects in multiple regions of the brain controlling sleep-wakefulness, as mentioned above, to date adenosine levels have only been shown to increase with prolonged wakefulness in the BF and neocortex. Consistent with the BF being a crucial site mediating adenosine effects, local perfusion of an A_1 receptor antagonist in this region activated wake-active neurons (17, 1276), and localized suppression of A_1 receptor expression using antisense oligonucleotides signif-

FIGURE 8. Investigations of the role of adenosine (AD) as a neuromodulatory sleep factor. *A*: extracellular AD concentrations in the feline basal forebrain (BF) for 10-min consecutive samples from an individual animal, showing elevated levels during wakefulness. Labels indicate behavioral state: W, wakefulness; S, slow wave (NREM) sleep; R, REM sleep. [Adapted from Porkka-Heiskanen et al. (1018). Reprinted with permission from AAAS.] *B*: AD concentrations in the feline BF rise during 6 h of sleep deprivation (SD) and decrease towards baseline levels during 3 h of spontaneous recovery sleep. [Adapted from Porkka-Heiskanen et al. (1018). Reprinted with permission from AAAS.] *C*: AD and nitric oxide (NOx, red) concentrations in the rat BF rise during 11 h of SD. The rise of NOx during SD precedes the rise of AD. AD levels are significantly elevated by hour 2 of SD and remain elevated until recovery sleep, when levels fall towards baseline levels. Levels are normalized to baseline levels in the 2 h preceding SD. [Adapted from Kalinchuk et al. (591), with permission from John Wiley and Sons.] *D*: AD and NOx levels in the rat frontal cortex also rise during SD. Again, the rise of NOx during SD precedes the rise of AD. The rise of AD is significant by hour 6 of SD and is delayed compared with the rise seen in BF, as shown in *C*. Levels are normalized to baseline levels in the 2 h preceding SD. [Adapted from Kalinchuk et al. (591), with permission from John Wiley and Sons.] *E*: graphic depiction of the intracellular signaling pathway of the AD A1 receptor in BF observed following sleep deprivation in rats. Steps of the pathway: *1*) AD binds to the A1 receptor; *2*) activation of PLC pathway, releasing inositol 1,4,5-trisphosphate (IP$_3$); *3*) IP$_3$ receptor-mediated intracellular calcium mobilization and activation of protein kinase C; *4*) phosphorylation of Iκ-B and release of nuclear factor-κB (NF-κB) dimer; *5*) nuclear translocation of NF-κB dimer; *6*) promoter DNA binding of NF-κB and transcriptional activation of target genes including A1 receptor; *7*) protein synthesis (A$_1$ receptor synthesis). This signaling cascade appears to be confined to cholinergic neurons of BF. [Adapted from Basheer et al. *Neuroscience* 104: 731–739, 2001, with permission from Elsevier.]
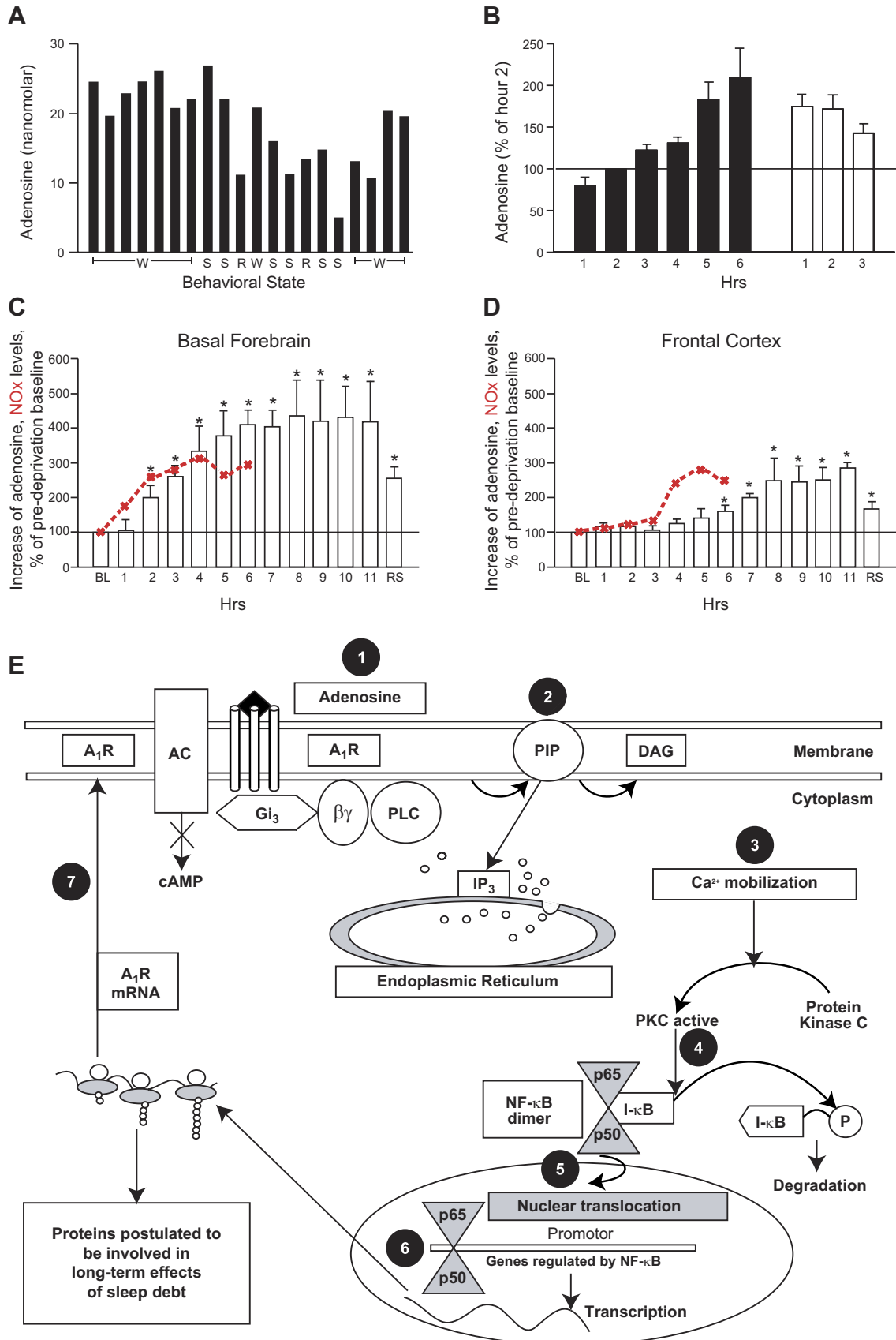
icantly reduced spontaneous sleep time as well as the homeostatic sleep response (1282). In contrast, adenosine A_1 receptor blockade in the lateral hypothalamus did not block the homeostatic sleep response (1277). While sleep homeostasis was intact in constitutive A_1 receptor knockout mice (1214), conditional deletion of A_1 receptor in forebrain and brain stem after 6–8 wk of age, circumventing developmental compensation, not only resulted in a decreased homeostatic sleep response after sleep restriction but also led to a failure in working memory consolidation (sect. V) (99).

Prolonged sleep deprivation upregulates A_1 receptor mRNA and protein in BF and cortex in both rats and humans (74, 76, 340, 341). Upregulation of adenosine receptors provides an additional level of homeostatic control beyond rises in extracellular adenosine levels. The intracellular signaling pathway leading to this positive feedback regulation was revealed in experiments in rat BF (79) **(FIGURE 8)**. The A_1 adenosine receptor, coupled to the inhibitory G_{i-3} G protein, is capable of "dual signaling," i.e., inhibition of adenylyl cyclase and stimulation of PLC (422). Increased stimulation of the A_1 receptor during sleep deprivation activates the PLC pathway, mobilizing intracellular calcium which in turn activates the transcription factor NF-kB and upregulates A_1 receptor expression (73, 74).

What is the involvement of the adenosine A_{2A} receptor in the homeostatic sleep response of adenosine? A_{2A} receptors are coupled to the stimulatory G_s subunit and activate adenylyl cyclase. In contrast to the A_1 receptor with its wide distribution in brain, the distribution of A_{2A} receptor is more restricted to basal ganglia structures such as striatum, nucleus accumbens, and olfactory tubercle with much lower abundance in other areas such as the hippocampus, neocortex, BF, and other sleep-wake regulatory structures (1076). In rats, selective A_{2A} receptor agonists such as CGS21680 administered to the subarachnoid space adjacent to BF and ventrolateral preoptic area (VLPO) induce NREM sleep (485, 1123, 1124, 1320). The local application of the A_{2A} receptor selective agonist CGS21680 increases Fos expression in the VLPO (1128). Consistent with this are the observations that adenosine excites one subpopulation of sleep-promoting VLPO neurons via A_{2A} receptors (404), and administration of CGS21680 into the lateral preoptic area close to the VLPO induces sleep (850). In A_{2A} receptor knockout mice, the homeostatic sleep response following sleep deprivation (1320) and the wake-promoting effects of caffeine were blocked (529), although given the strong expression of this receptor in the basal ganglia, effects on motivation or motor behavior may confound these results. Accordingly, the locomotor stimulatory effects of caffeine mediated via A_{2A} receptor blockade were shown to require the presence of A_{2A} receptors in the nucleus accumbens (694).

The importance of adenosine as a sleep factor is supported by studies of enzymes involved in adenosine metabolism. Adenosine deaminase is involved in clearance of adenosine from the extracellular space. Blocking its activity using coformycin increased extracellular adenosine and sleep (949). The enzyme adenosine kinase phosphorylates adenosine to adenosine monophosphate, and blocking adenosine kinase activity with ABT-702 increased sleep in rat (1036). These data from rats are consistent with findings in mice that a genomic region encoding adenosine deaminase influences the rate at which NREM sleep need accumulates during wakefulness (sect. VI) (378). In humans, a genetic variation of the adenosine deaminase gene resulting in an amino acid substitution (asparagine for aspartic acid) results in decreased enzyme activity and is associated with increased sleep time and sleep intensity (687, 1059).

B) NO. NO is a small gaseous molecule with multiple roles in the control of sleep and wakefulness (407) (see also sects. II and IV). In the brain, it is predominantly synthesized under basal conditions by neuronal NO synthase (nNOS) and endothelial NO synthase (eNOS) in blood vessels. nNOS is highly expressed in brain stem cholinergic neurons and participates in their control of cortical activation and REM sleep. In this section we focus on the role of NO in the homeostatic regulation of NREM sleep.

I) NO promotes NREM sleep. The enzymatic activity of NOS is highest in the rat brain when animals are awake (57), and NO itself is detected in higher quantities in the cortex during waking (167). Systemic or intracerebroventricular (icv) administration of NOS inhibitors at light onset reduced NREM sleep within the first few hours in rats (199, 324, 325, 599, 882, 883, 1062) and in rabbits (601). Thus, although some studies (1347) provided contradictory evidence, most evidence suggests that NO promotes NREM sleep. Recent studies suggest that NO produced by the inducible isoform of NOS (iNOS), is responsible for this effect. Microdialysis infusion of an iNOS selective inhibitor, during sleep deprivation prevented NREM sleep rebound (593), while an inhibitor of nNOS decreased REM recovery but did not affect NREM recovery (593). Consistent with these findings, iNOS knockout mice had less NREM sleep during the dark period (218). The induction of sleep deprivation-induced iNOS occurs in neurons within the BF (590). The iNOS expressing neurons also express Fos during sleep deprivation, suggesting they are wake active and the number of iNOS/Fos double-labeled neurons positively correlates with the sleep pressure following prolonged sleep deprivation (590). Furthermore, NO itself also rises during the early stages of sleep deprivation as assessed by the dye 4,5-diaminofluorescein diacetate (DAF-2/DA), which fluoresces upon binding NO. Currently, the cellular signaling pathway by which sleep deprivation leads to the induction of iNOS is unknown.

II) How does NO produced by iNOS cause sleep in the BF? NO has multiple cellular effectors, but one which may be particularly important in the context of the homeostatic sleep drive is release of adenosine (FIGURE 8). In vitro studies in culture and brain slices have shown that NO donors cause release of adenosine, which in turn inhibits neuronal activity (149, 352, 1075). Multiple pathways for NO-stimulated adenosine release may exist including inhibition of adenosine kinase (1075), inhibition of glycolysis and the mitochondrial electron-transport chain with a subsequent decrease in ATP/ADP ratio (150), and stimulation of neurotransmitter release leading to corelease of ATP which is subsequently degraded to adenosine (142). In vivo, NO production and adenosine increased concurrently in the BF during sleep deprivation (589, 593). Furthermore, under nondeprived conditions, microdialysis perfusion of an NO donor, DETA/NO, mimicked the ability of sleep deprivation to increase adenosine and NREM sleep (589). Recent in vitro electrophysiological evidence suggests that NO causes an initial excitation of cholinergic and cortically projecting GABAergic BF neurons which is followed by a long-lasting inhibition that can be reversed with an adenosine A_1 receptor antagonist, suggesting mediation by adenosine (154). Similarly, in vivo, the effects of NO donors on BF neurons were found to be dose-dependent, with lower doses favoring excitation and higher doses leading to more inhibition (662, 663). Similar mechanisms may also be active in the perifornical lateral hypothalamus (661).

III) Sleep-active cortical interneurons contain nNOS. The presence of nNOS has been recently described in a small subset of cortical interneurons which are sleep active as determined by Fos immunohistochemistry (416, 620). In rats, mice, or hamsters, a majority of cortical GABAergic interneurons that express nNOS also express Fos during the recovery sleep that follows sleep deprivation. Fos expression in these sleep-active, nNOS-immunoreactive neurons parallels changes in the intensity of slow-wave activity in the EEG, and thus these neurons are suggested to be part of the neurobiological substrate that underlies homeostatic sleep regulation (416, 620, 984).

C) PROSTAGLANDIN D_2. Prostaglandins are lipid signaling molecules produced from arachidonic acid through the cyclooxygenase pathway. The most abundant prostanoid in the brain, prostaglandin D_2 (PGD_2), meets all the criteria of a potent sleep-factor (485, 531, 943). Infusion of PGD_2 into the third ventricle or preoptic area of rats (546, 1316, 1317) or the third ventricle of monkeys (953) increased sleep in a dose-dependent manner. Further investigations in rats showed that the levels of PGD_2 in CSF increase with increasing time awake and propensity to sleep (963, 1043). The effects of PDG_2 are mediated via the prostaglandin receptor 1 ($DP_1 R$) as shown by the absence of sleep-inducing effects of PGD_2 infusions in DP_1R knockout mice (867). Blocking the PGD_2 receptor with a selective antagonist,

ONO-412, reduces sleep time (485). Lipocalin-type prostaglandin synthase (L-PGDS) is expressed in the brain and has been associated with sleep-wake regulation (1031). Animals that overexpress human L-PGDS show a significant increase in NREM sleep that is positively correlated with the increases in PGD_2 produced in the brain (1004). Inhibitors of L-PGDS, such as selenium-based compounds, inhibit sleep, an effect that is reversed by subsequent administration of PGD_2 (812). In L-PGDS knockout mice, the PDG_2 levels do not increase following sleep deprivation (485).

The somnogenic effects of PGD_2 are predominantly mediated via the membranes surrounding the brain in the leptomeninges/arachnoid space (485). The expression of both L-PGDS and DP_1R is mainly observed in the rostroventral area of the subarachnoid space near the BF which is the most potent site for the sleep promoting effects of PGD_2; in this area, L-PGDS and DP_1R expression is colocalized in arachnoid trabecular cells (95, 867) along with the synthesizing and degradation enzymes for adenosine (949). PGD_2 infusion induces Fos expression in the sleep active neurons of the VLPO area (1126). Furthermore, the sleep-promoting effects of PGD_2 have been shown to be mediated by A_{2A} receptors in the VLPO. Subarachnoid administration of an A_{2A} agonist induces Fos expression in the VLPO and increases NREM sleep (1128). The activation of DP_1R by PGD_2 in the meninges is followed by an increase in adenosine that acts on the A_{2A} receptor in the sleep promoting preoptic area (867). Blocking the A_{2A} receptor with the selective antagonist KF17837 also blocks the sleep-inducing effects of PGD_2. The role of adenosine in the leptomeninges has been demonstrated by infusion of A_{2A} selective agonist CGS 21680, leading to increased Fos expression in VLPO and increased sleep (518, 1128). Like adenosine, PGD_2 is implicated in the homeostatic sleep response as animals that lack L-PDGS or PGD2 receptors fail to exhibit a sleep rebound in response to sleep deprivation (484, 485) and infusion of PGD_2 mimics the effects of prolonged wakefulness in promoting sleep (1125).

Clinical data suggest that the PGD_2-A_{2A} sleep inducing system may be particularly important in mediating enhanced sleep in pathological states. For instance, synthesis of PGD_2 was massively upregulated in the CSF of patients with African sleeping sickness (991). L-PGDS was also upregulated in sleep apnea patients exhibiting excessive daytime sleepiness (EDS) compared with controls or patients without EDS (70).

D) CYTOKINES. Cytokines are best known for their role in the immune system response to infection which includes enhanced sleep (543). Several cytokines and their receptors are present in the brain, and even in the absence of immune challenge, they are involved in sleep regulation (543, 669). Among the different cytokines, the most convincing evidence for a sleep-regulatory role is available for interleu-

kin-1 (IL-1) and tumor necrosis factor-α (TNF-α). Administration of either of these cytokines increases NREM sleep in mice, rats, rabbits, cats, and sheep (603, 669, 670, 943). In humans, IL-1 administration results in fatigue and sleepiness (603, 669, 670, 943). Consistent with their somnogenic role, the endogenous brain and plasma levels of IL-1 and TNF-α increase with increased propensity to sleep. For example, in rat, the mRNA and protein expression of IL-1 and TNF-α in brain shows diurnal variation with changes paralleling the amount of NREM sleep (135, 368, 1262). In cat cerebrospinal fluid, the changes in IL-1-like activity correspond to sleep-wake behavior (762). In humans, plasma concentrations of IL-1 peak at sleep onset (874). The mRNA levels of these cytokines increase during sleep deprivation (1262).

The somnogenic effects of IL-1 and TNF-α are mediated through the IL-1 type 1 receptor and the TNF 55-kDa receptor. Mice lacking these receptors showed reduced sleep and failed to respond to IL-1 and TNF-α (353, 354). Antagonists against IL-1 and TNF-α receptors reduce sleep (954, 1267, 1368). Reduction of sleep in IL-1 receptor knockout mice was predominantly observed during the dark period, whereas TNF receptor knockout mice showed decreased sleep during the transition from the dark to the light period, suggesting involvement in the circadian component of sleep regulation. Accordingly, TNF-α has been shown to inhibit the expression of clock genes by interfering with the interaction of CLOCK-BMAL1 with the E-box regulatory element (198).

I) Mechanisms underlying cytokine-induced sleep. It has been suggested that the release of extracellular ATP associated with neurotransmitter release during waking promotes astrocytic production of IL-1 and TNF-α via activation of P2 purinergic receptors (97, 1253). In addition to effects on cortical synapses (see next section), cytokines may act to induce sleep by affecting monoaminergic neurons that express the IL-1 receptor. Administration of IL-1 into the DRN or LC (293) induces sleep (409, 788), and blocking the 5-HT$_2$ receptor attenuates the sleep-inducing effects of IL-1 (542).

2. Local regulation of sleep homeostasis

Sleep is normally a global, coordinated phenomenon affecting the whole organism and nervous system. However, recent evidence suggests that slow waves and spindles can be induced or modulated locally in cortical areas (532, 671, 921, 1383). The most striking example of local sleep is the unihemispheric sleep exhibited by cetaceans (766). In rodents, multiunit recordings showed that groups of cortical neurons display coordinated off-states, associated with local slow waves as the duration of wakefulness increases, even while the scalp EEG shows a LVFA pattern typical of wakefulness (1383). Dissociation of different sleep/wake phenomena is also a feature of several sleep disorders (778).

A number of cortically produced neuromodulators could be involved in local modulation of sleep intensity. These include *1*) adenosine and NO (discussed above); *2*) TNF-α, which is a regulator of sleep and sleep intensity and also regulates synaptic homeostasis (1213); *3*) brain-derived neurotrophic factor (BDNF), which is involved in the establishment of neuronal circuitry during development and promotes synaptic plasticity in the adult. Cortical infusion of BDNF locally enhances NREM slow-wave activity, whereas infusion of a BDNF antibody or an inhibitor of trkB receptors causes the reverse effect (355). *4*) Cortistatin is a recently discovered peptide neuromodulator structurally related to somatostatin which is expressed in cortical and hippocampal interneurons and hyperpolarizes hippocampal pyramidal neurons (289). Intraventricular administration of cortistatin increased cortical slow waves (127, 289). Furthermore, the cortistatin transcript was upregulated following sleep deprivation (127, 232). *5*) Growth hormone releasing hormone (GHRH): local administration of a GHRH antagonist or siRNA targeting GHRH to the somatosensory cortex increased EEG delta power during NREM sleep but not during waking (718). Use-dependent alterations in the release of these neuromodulators may account for local cortical changes in synaptic weights and/or cortical region-dependent alterations in NREM delta activity (532, 609, 865, 1381).

D. Functional Aspects of NREM Sleep

1. Brain energy metabolism

The brain constitutes only 2% of the body mass. However, brain oxygen and glucose utilization account for ~20% of those of the whole organism (775), consistent with the high energetic costs incurred by neural tissue, both whilst processing information and at rest (54). Compared with wakefulness, sleep reduces brain energy demands, as suggested by the 44% reduction in the cerebral metabolic rate (CMR) of glucose (791) and a 25% reduction in the CMR of O$_2$ (774) during sleep.

A) LOCAL CHANGES IN ATP USAGE DURING THE SLEEP-WAKE CYCLE. Under normal physiological conditions, use-dependent variations in the CMR of glucose and O$_2$ maintain a balance in brain energetics at all times to maintain a stable level of the high-energy molecule ATP. At the molecular level, this is achieved due to tightly coupled ATP biosynthesis/usage and an efficient buffering of ATP energy via paired creatine kinase reactions to conserve ATP energy in the form of phosphocreatine and its release, as needed, in the cell (1477). However, recent studies indicate that transient changes in brain ATP levels can occur in a brain region specific- and treatment-dependent manner. For example, altered ATP levels have been observed in response to localized electrical stimulation, glucose deprivation, or manipulations of Na$^+$-K$^+$-ATPase activity (56, 225, 764, 773). In a

recent rat study, ATP tissue levels showed a surge in the initial hours of spontaneous sleep in wake-active but not in sleep-active brain regions of rat (323). The surge was dependent on sleep but not on time of day, since preventing sleep by gentle handling of rats for 3 or 6 h delayed the surge in ATP. A significant positive correlation was observed between the surge in ATP and EEG NREM delta activity (0.5–4.5 Hz) during spontaneous sleep. Inducing sleep and delta activity by adenosine infusion into the BF during the normally active dark period also increased tissue levels of ATP. Taken together, these observations suggest that a surge in ATP occurs when the neuronal activity is reduced, as occurs during sleep. The levels of the cellular energy sensor, phosphorylated AMP-activated protein kinase (P-AMPK), show reciprocal changes to ATP levels. Thus P-AMPK levels are lower during the sleep-induced ATP surge than during periods of wakefulness or sleep deprivation. Together, these results suggest that the sleep-induced surge in ATP and the decrease in P-AMPK levels set the stage for increased anabolic processes during sleep and provide insight into the molecular events leading to the restorative biosynthetic processes occurring during sleep (323) **(FIGURE 9)**.

B) ADENOSINE AS A REGULATOR OF BRAIN ENERGY. One of the proposed functional theories for adenosine's role in sleep-wake behavior suggests that adenosine, a byproduct of energy metabolism, may serve as a homeostatic regulator of brain energy during sleep (91, 1130). Extracellular adeno-sine concentrations rise with increased metabolism and neural activity (1027). Wakefulness has a greater metabolic rate than NREM sleep (774, 791), and accordingly, extracellular adenosine levels in neostriatum and hippocampus were higher during the circadian active period and lower during the circadian inactive period in rats (541). Differential pulse voltammetry using a glucose sensor in cortex reveal that extracellular glucose levels are higher during NREM sleep compared with waking, an observation consistent with the idea that energy metabolism and glucose utilization/breakdown decrease during NREM sleep compared with waking (915). Thus changes in adenosine levels during spontaneous sleep-wake and sleep deprivation conditions may be direct reflections of ATP breakdown.

C) HYPOTHALAMIC NEUROMODULATORS LINKING METABOLISM AND THE SLEEP-WAKE CYCLE. Several hypothalamic neurotransmitter systems link energy usage and arousal (658). The role of the orexins was discussed in section II. Several recent studies have suggested that the GABAergic/MCH neurons may be involved in connecting metabolism and sleep (1353). Mice lacking MCH or the MCH 1 receptor eat less, are lean, and have a higher metabolic rate (804, 1164). Recordings from identified MCH neurons across the sleep-wake cycle revealed that they are silent during wake and fire occasionally during NREM sleep but maximally during REM sleep (482). This silence during waking is likely due to direct inhibition by norepinephrine, serotonin, and acetylcholine
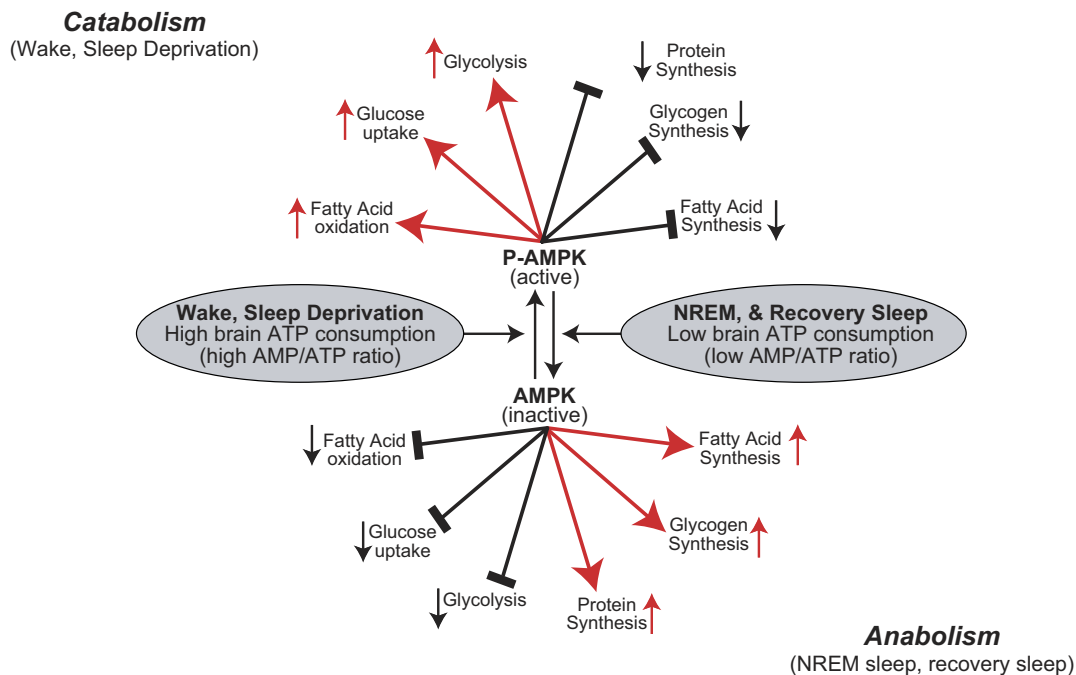

FIGURE 9. Sleep and energy metabolism. The interaction between state-dependent changes in ATP, AMPK, and AMPK-regulated anabolic and catabolic pathways is shown. Wakefulness and sleep deprivation are both characterized by increased neuronal activity and increased consumption of ATP. A higher AMP/ATP ratio results in and leads to increased phosphorylated-AMPK [P-AMPK], promoting catabolic processes. Sleep states are characterized by increased NREM delta activity, low neuronal activity, and a rise in ATP levels. The resulting lower AMP/ATP ratio leads to decreased phosphorylated AMPK, promoting anabolic processes, such as synthesis of proteins, glycogen, and fatty acids. [Adapted from Dworak et al. [323].]

(1325). Intracerebroventricular injections of MCH increased REM sleep via an increase in the number of REM episodes and increased NREM sleep to a lesser extent (1353), while an MCH1 receptor antagonist decreased NREM and REM sleep (12). The mechanisms connecting the energy conservation and sleep promoting functions of this peptide remain to be established.

2. Synaptic homeostasis

Together, the slow oscillation and cortical delta waves are termed SWA. Recent evidence suggests that sleep intensity, as measured by SWA, can be modulated locally in the cortex in a use-dependent fashion (532, 671, 1298). What might be the function of such a local regulation? Learning and synaptic plasticity studies, together with the results of experiments investigating genomic and proteomic changes during sleep (see sect. V), led Cirelli and Tononi to propose the synaptic homeostasis theory of sleep (1298). This theory proposes the following:

1) Wakefulness is associated with net synaptic potentiation. Gene and protein studies showed that animals killed following prolonged periods of wakefulness have upregulated levels of genes/proteins implicated in long-term potentiation, whereas genes/proteins implicated in long-term depression were increased following periods of sleep (241, 242). A recent ex vivo slice study showed that the frequency and amplitude of miniature excitatory postsynaptic currents (EPSCs) recorded from pyramidal neurons in the prefrontal cortex were higher following a prolonged period of waking and decreased after sleep, independent of time of day (737). Although consistent with the hypothesis, it should be noted that changes in miniature EPSCs may not accurately reflect action potential-dependent changes in synaptic strength. Several other theories of sleep and memory are based on the premise that long-term potentiation is induced during sleep (53, 175, 1417), especially during the sharp-wave/ripple complexes and spindles of NREM sleep (175, 179) or in association with the theta rhythm during REM sleep (534) (sect. V). More direct evidence of synaptic potentiation was found in *Drosophila* (172), where synapse size and number increased with waking and decreased during sleep.

2) Synaptic potentiation is coupled with the homeostatic regulation of cortical slow-wave activity. This idea is supported by large-scale computational models of the thalamocortical system (350, 507). It is further bolstered by experiments in which application of neuromodulators previously shown to enhance LTP, locally enhanced SWA in subsequent sleep periods (see sect. IIIC above) and learning experiments showing local increases in SWA in cortical areas following learning of a particular task (532). For instance, in an experiment pairing transcranial magnetic stimulation of the motor cortex with median nerve stimulation, subjects showing a potentiation of local field potentials also had a local increase in slow-wave activity during subsequent sleep (533).

3) SWA leads to synaptic downscaling, allowing improved cognitive performance following NREM sleep. Local neocortical field potential recordings in rats (1385) and high-density EEG recordings in humans (1063) showed that the slope and amplitude of slow waves were lower at the end of the sleep phase compared with those during sleep at the beginning of the sleep phase, findings which are consistent with synaptic downscaling if, as suggested by modeling studies, slow wave slope and amplitude reflect synaptic strength. Furthermore, single and multiunit recordings showed that the firing rate of neocortical neurons was higher following a period of sustained wakefulness, whereas firing rates and synchrony decreased following a period of sustained sleep (1384). These findings are also consistent with the increased energetic cost of wakefulness discussed in the previous section.

Although the synaptic homeostasis theory is an attractive hypothesis supported by a large amount of evidence, several questions remain. *1*) Many different forms of NMDA receptor-dependent and NMDA receptor-independent synaptic plasticity have been described. Which of these are involved in sleep-dependent changes? *2*) Are homeostatic changes restricted to synapses between glutamatergic neurons? So far experiments have targeted cortical regions and not investigated other brain areas such as the striatum and cerebellum where GABA neurons predominate and homosynaptic long-term depression of glutamatergic synapses is the predominant form of synaptic modification associated with learning. Furthermore, how inhibitory synapses change across the sleep-wake cycle remains unclear. Experiments in zebrafish revealed circadian and homeostatic changes in synapses from orexin neurons (36), suggesting that neuromodulatory synapses also change according to the sleep-wake cycle. *3*) What happens to synapses during REM sleep?

E. Synthesis

The induction of sleep is mediated by the build-up of homeostatic sleep factors such as adenosine and NO in the BF and cortex and by increased activity of median preoptic nucleus GABA neurons that inhibit the wake-promoting neurons of the ARAS. Circadian influences are mediated by retinal and indirect SCN projections to GABAergic sleep-promoting neurons in the VLPO and other regions of the preoptic area and BF. Once initiated, sleep and the silence of cortically projecting wake-active neurons is maintained by increased firing of VLPO and other preoptic/BF GABA neurons and subsequent postsynaptic inhibition of ARAS neurons via activation of GABA and galanin receptors. As ascending excitatory influences are progressively withdrawn, cortical and thalamic neurons become increasingly hyperpolarized entering into the range of membrane potentials

conducive to rhythmic bursting due to activation of I_h and I_t currents and leading to the characteristic EEG phenomena of NREM sleep. During early NREM sleep, effective cortical connectivity (assessed by transcranial magnetic stimulation) begins to break down (808), and in deep sleep, the activity of the brain regions comprising the default network becomes decoupled, in particular the frontal cortex (523). Local cortical differences in delta power during NREM sleep reflect the extent to which that cortical area was active during the prior waking period and the duration of prior waking, possibly reflective of increased synaptic potentiation during waking with respect to sleep. Energy usage is high during waking and during sleep deprivation, due to increased neuronal firing, synaptic activity, and synaptic potentiation. This increased energy usage of waking is reflected in increased release of sleep homeostatic factors such as adenosine during waking and a surge of ATP production which occurs during the early NREM sleep that follows waking. Synaptic activity and plasticity are major components of brain energy usage (775), potentially tying together the proposed energetic and synaptic plasticity functions of NREM sleep. Under normal conditions, wakefulness transitions first into NREM sleep and then later transitions into REM sleep. The mechanisms underlying REM sleep and the cyclic oscillation of NREM and REM sleep during the night are described next.

IV. REM SLEEP

Dreaming, which occurs most frequently in REM sleep, has inspired and fascinated artists, writers, and scientists for centuries. However, REM sleep was only defined as a separate brain state relatively recently. Experiments by Aserinsky, Dement, and Kleitmann in humans (50, 299) and Jouvet in animals (580) showed that REM sleep is defined by a distinct constellation of tonic and phasic features of the EEG and EMG. The association of an activated cortical EEG reminiscent of waking, together with paralysis of antigravity muscles **(FIGURE 1)**, led Jouvet to term this state *Le sommeil paradoxal* (paradoxical sleep). In young animals, where REM is the predominant sleep state (585, 1070), it is also known as active sleep (NREM sleep is called quiet sleep in this terminology). Awakening human subjects during REM sleep commonly led to reports of dreaming (300); thus REM sleep has also been called dream sleep, although some dreaming also occurs in NREM sleep (509). Since the discovery of REM sleep, research on REM sleep can be subdivided into three main areas: *1*) delineation of the neurons, circuits, and neurotransmitter effector systems responsible for the individual signs of REM sleep; *2*) control of when and for how long REM sleep is expressed (REM sleep master control mechanisms); and *3*) investigation of the relation of REM sleep to learning and memory. In this section we focus on the first two of these areas and the relation of REM sleep to dreaming; studies of REM sleep and learning and memory are covered in section V.

The terminology used to describe the reticular formation regions involved in REM-sleep control **(FIGURE 2)** differs between brain atlases, between species, and between different investigators. In the cat, the REM control area was defined as a region immediately ventral to the main cluster of noradrenergic neurons in the LC and dorsal to the gigantocellular tegmental field (FTG). This region was termed subcoeruleus (SubC) which is the term used in this review. A subset of this area, containing caudally projecting neurons involved in REM muscle atonia, and with tonic firing patterns very specific to REM sleep (1093) was termed the peri-LC alpha. Slightly lateral to this area, neurons with burst firing patterns correlated with PGO waves were found in the parabrachial area (276, 824, 1092), which at its most rostral extent also includes the cholinergic PPT area. In the rat and mouse brain atlases of Paxinos and colleagues (988, 989) the REM control region is also termed SubC (dorsal or alpha parts); however, in these species the region immediately ventral to the LC is cell-poor and the REM-control neurons (particularly those involved in muscle atonia) appear to be located slightly more rostrally, ventral to the cholinergic neurons of the laterodorsal tegmental nucleus (LDT). Hence, the functionally equivalent region in the rat or mouse has been termed the sublaterodorsal nucleus (SLD). This area corresponds to the rostral part of the subcoeruleus area as defined by Paxinos and Watson in the rat (160). REM-on neurons in this area are primarily glutamatergic, as indicated by vGLUT2 in situ hybridization and Fos immunohistochemistry (248). Other nearby reticular formation areas containing glutamatergic neurons such as the nucleus pontis oralis (PnO) and nucleus pontis caudalis (PnC) play a role in particular aspects of REM sleep such as theta rhythm generation or rapid eye movements.

I) Spike discharge characteristics of neurons in regions of the brain stem involved in REM control (see also sect. IV*B*). Intracellular recordings from medullary and pontine reticular formation neurons in naturally sleeping cats revealed that the excitability of these neurons was greater during REM than during NREM sleep or waking, i.e., there is a tonic depolarization during REM (209, 549) **(FIGURE 10)**. Phasic depolarizations associated with action potential firing were superimposed upon this tonic depolarization (549). In contrast, the membrane potential was more hyperpolarized during waking and NREM sleep with phasic depolarizations occurring with motor activity during waking. When recorded in vitro, SubC "reticular" neurons fire tonically at high rates with little adaptation when depolarized (160), as in other reticular areas (418, 934). Identified GABAergic neurons in this area show similar properties (156), making it difficult to distinguish GABAergic from glutamatergic neurons solely on the basis of intrinsic membrane properties. A subset of the reticular formation neurons fire stereotyped high-frequency bursts of action potentials due to the presence of low-threshold calcium channels
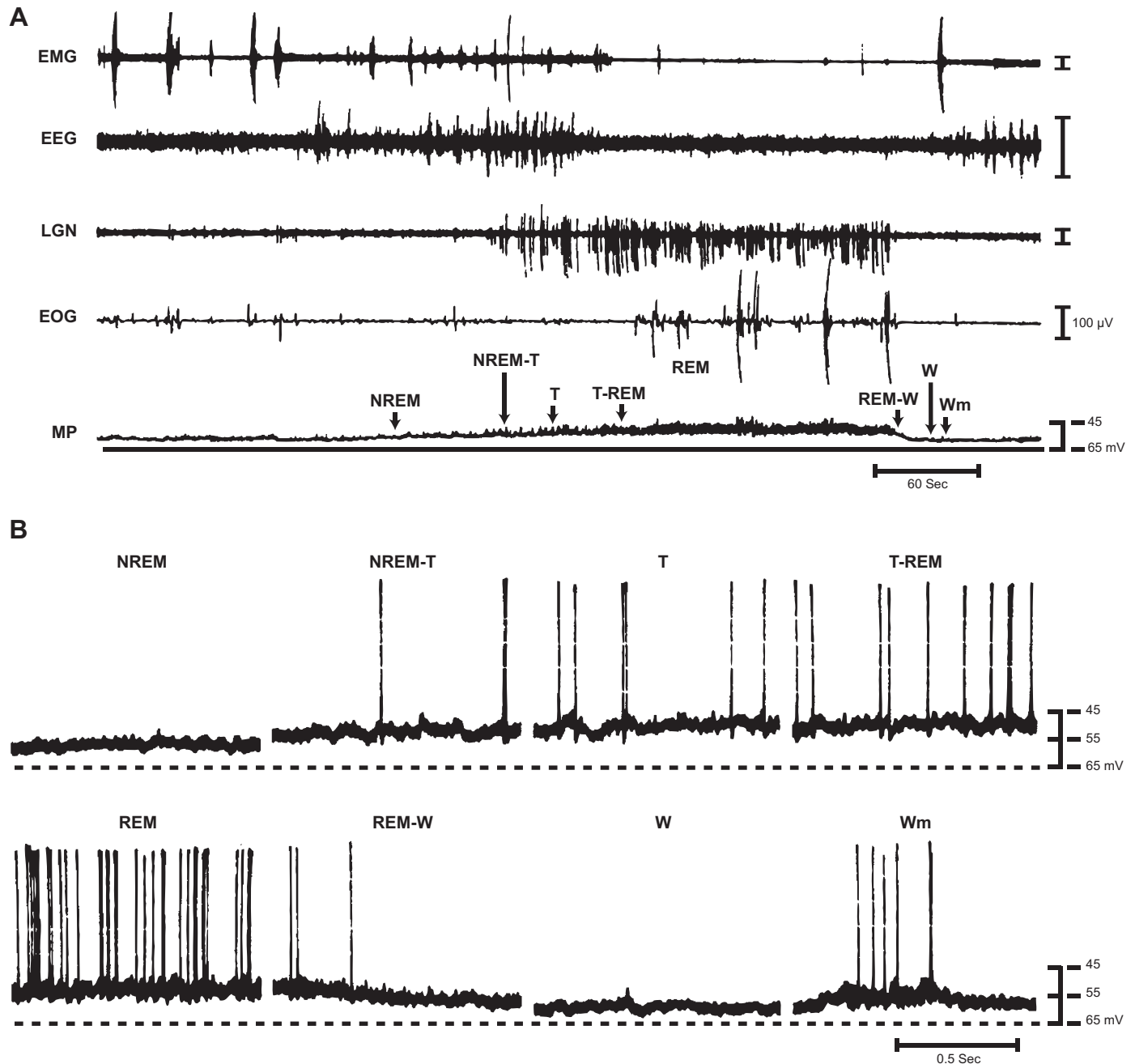
FIGURE 10. Pontine tegmental membrane depolarization and action potential activity increases prior to and during REM sleep. *A*: first trace is nuchal (neck) EMG in the cat, showing a lack of muscle tone during REM sleep; second trace is frontal cortex EEG, showing low-amplitude activity during REM sleep; third trace is lateral geniculate nucleus (LGN) neuronal activity, revealing PGO waves immediately preceding and during REM sleep; fourth trace is extraocular muscle EOG, showing eye movement during REM sleep; and fifth trace is the membrane potential record for one pontine tegmental neuron (MP). *B*: oscilloscope photographs depict the changes of action potential frequency that accompany MP depolarization. Arrows in the MP trace of *A* correspond to the eight oscilloscope photographs of *B*, showing tonic neuronal firing during transition into REM sleep, the REM sleep episode, and transition out of REM sleep. REM, REM sleep; NREM, NREM sleep; T, transition; W, wake; Wm, wake with movement. [Adapted from Ito et al. (550).]

that are deinactivated by hyperpolarization (160, 448). Cholinergic neurons also exhibit this property (whereas most aminergic brain stem neurons do not). These neurons may be involved in phasic phenomena of REM sleep such as PGO waves. Interestingly, many presumed REM-on neurons in the SubC exhibit "spikelets" (small alterations in membrane potential resembling low-pass filtered action potentials), indicating that they are likely to be electrically coupled (489) and suggesting a possible mechanism by which their firing may be synchronized.

A. REM Sleep Signs

1. Electrographic signs of REM sleep

Ascending pathways from the brain stem areas that control activation of the neocortex during waking and REM sleep were covered in section II. We focus here on REM specific aspects of hippocampal theta rhythms and PGO waves, which appear prior to the REM state and define the transitional REM period (t-REM) in between NREM and REM sleep.

A) THETA ACTIVITY. Theta rhythmic activity is a prominent feature of the EEG during REM sleep in rodents (FIGURE 1) and other lower mammals (1069). Early studies in rats and rabbits established that there are two forms of theta activity. Type I (4–7 Hz) was observed when the animals were under urethane or ether anesthesia and during behavioral immobility and was abolished by systemic administration of the muscarinic antagonist atropine sulfate (667). A higher frequency form of theta (type II theta, 7–12 Hz) was observed during waking associated with movement and was abolished by urethane anesthesia. Theta occurring during REM sleep appears to represent a combination of type I and type II, since atropine sulfate abolished continuous lower-frequency theta during tonic REM periods whilst leaving intact intermittent, higher frequency hippocampal theta during periods with muscle twitches (1069, 1166). Similarly, mice with a knockout of phospholipase $\beta 1$ (an effector for M_1-type muscarinic receptors) lacked type I theta activity and had only intermittent theta activity during REM sleep (1166). A recent genetic study suggests that theta generation during REM is different from theta during waking. A deficiency in short-chain fatty acid β-oxidation (affecting the enzyme short-chain acylcoenzyme A dehydrogenase, Acads) caused a slowing (by ~1 Hz) of peak theta frequency during REM sleep in mice but did not affect waking theta (1260).

I) Theta rhythm during REM sleep in humans. Low-frequency (4–7 Hz) theta activity has also been observed in the human hippocampus (of epileptic patients) during sleep but, in contrast to rodents, theta rhythm was not observed continuously but rather was limited to short (1 s) epochs (188). The occurrence of these short theta epochs in humans was not correlated with the occurrence of rapid eye movements. A further contrast to rodents was the finding that theta activity was not observed in the basal temporal lobe or frontal cortex during REM (188). Another study has demonstrated a type of rhythmic slow activity in the hippocampus during REM sleep with a slightly lower peak frequency (1.5–3 Hz; delta), leaving open the possibility that these EEG signals in humans are equivalent to the type I and type II theta but that the peak frequencies for the two types are shifted to lower values (113).

II) Brain stem generation of theta rhythm during REM sleep. The ascending pathways controlling forebrain theta rhythm are discussed in section IIA. One recent study (758) suggested that a region just dorsal to the LC termed precoeruleus is necessary for theta activity during REM sleep. This region was found to provide the major glutamatergic input to the MS/vDB and contained cells that were active during REM sleep (contained Fos immunoreactivity). Ibotenic acid lesions of this area abolished theta rhythm during REM sleep (758). However, this part of the study was based on a small number of animals, and no quantification of damage to surrounding regions containing cholinergic neurons (known to be important for control of theta rhythm) was reported. Therefore, the precise role of the precoeruleus in theta rhythm generation during REM sleep awaits further confirmation with more targeted lesions (i.e., lesions affecting only glutamatergic neurons).

B) PGO WAVES. Synchronized electrical field potentials in the pons, lateral geniculate nucleus, and occipital cortex (PGO waves) occur singly at high amplitude in the period immediately preceding the onset of REM sleep (transitional REM period; 30–90 s) and in bursts of lower amplitude during REM sleep itself (98, 146, 274, 580, 584, 1228). They are considered the source of dreaming episodes and visual imagery during REM sleep (1228) since they occur simultaneously with rapid eye movements associated with gaze direction in dream imagery (300, 825) and are prominent in visual thalamocortical circuits (144, 145, 901). PGO waves have been studied most intensively in cats, where the largest potentials can be recorded in the LGN and occipital cortex. However, more recent studies in both animals and humans describe a widespread activation of limbic, parahippocampal and many thalamocortical systems during these phasic REM events (26, 274, 1395). The pontine component of PGO waves has been recorded in rats (286, 356, 610, 1113), but the thalamic (dLGN) component is difficult or impossible to record in rodents, likely due to the smaller size of this region and the fact that rodents are not very visual animals. However, phasic potentials during REM sleep can be recorded in several other forebrain areas in this species (274). In non-human primates, PGO wavelike phasic field potentials have been recorded from the LGN and pons of macaques (251) and the LGN of baboons (1380). In humans, two recent studies recorded phasic field potentials during REM sleep in the pons (720) and subthalamic nucleus (364), respectively. Furthermore, event-related fMRI showed activation of the thalamus and occipital cortex, as well as limbic regions such as the hippocampus and amygdala phase-locked to rapid eye movements (866, 1395). Thus phasic activations of thalamocortical and limbic brain regions generated by synchronized activation in the pons appear to be typical of both animals and humans, although the pattern of forebrain activation may vary according to the species studied.

I) The thalamocortical component of PGO waves. Thalamic PGO waves are biphasic field potentials with an initial negative-going component (1228). Although the thalamic component can be recorded most easily in the lateral geniculate nucleus (LGN) due to its laminated structure (and resulting summation of extracellular field potentials), they also occur in other thalamic nuclei such as the pulvinar, rostral intralaminar, and anterior nuclei. In humans, PGO waves have also been observed with depth recordings from the subthalamic nucleus (364). The cellular mechanisms underlying the thalamic component of PGO waves were investigated by Hu, Steriade and Deschenes using intracellular recordings in urethane-anesthetized and reserpine-treated cats (526). In these animals, each PGO wave was accompanied by a depolarization of relay neurons lasting 200–300 ms, interrupted by a short-lasting (50–60 ms) hyperpolarization occurring 40–80 ms after the onset of the depolarization due to the coactivation of GABAergic geniculate interneurons. Action potential firing may precede or follow the brief hyperpolarization. The negative-going component of the field component correlates with the early depolarization recorded intracellularly, whereas the subsequent positive-going component reflects the subsequent hyperpolarization. In recordings from naturally sleeping animals, single PGO waves of high amplitude can be recorded during the period of NREM immediately preceding REM when thalamic relay neurons are still hyperpolarized (1233). The firing of relay cells causes the depolarization of pyramidal neurons in the primary visual cortex (occipital cortex), the cortical component of PGO waves.

II) PGO waves require cholinergic input to the thalamus. The following evidence suggests that the induction of PGO waves in the thalamus is due to a strong cholinergic input from the brain stem, acting on ionotropic nicotinic receptors (274, 277, 1228): *1)* brain stem cholinergic neurons send a massive projection to the LGN and other thalamic nuclei (291, 974, 1235). *2)* Electrical stimulation of the brain stem in the region of cholinergic neurons elicits PGO-like waves in the LGN (1100). *3)* Lesions in the region of brain stem cholinergic neurons abolish PGO waves (1394). *4)* Neurons of the cholinergic LDT/PPT area fire in bursts that are correlated with thalamic PGO waves (336, 615, 665, 1099, 1234). These PGO burst neurons are inhibited by the cholinergic agonist carbachol, suggesting activation of inhibitory muscarinic autoreceptors (337, 665, 1097). *5)* Systemic (1081) or iontophoretic (525) application of nicotinic antagonists into the lateral geniculate nucleus blocks the thalamic component of PGO waves. 6) Nicotinic receptor agonists depolarize LGN neurons (1476) and also presynaptically facilitate glutamatergic synaptic inputs (457). Together these pieces of evidence strongly support the idea that bursting of cholinergic brain stem neurons leads to a nicotinic receptor-mediated depolarization of LGN and other thalamic neurons which underlies the negative-going component of the field potential at the thalamic level.

III) Noncholinergic brain stem neurons generate the pontine component of PGO waves. The initial study of the pontine component of PGO field potentials (so-called P-waves) found that they can be recorded in a large swathe of the brain stem reticular formation, most prominently the part of the reticular formation close to the abducens nucleus (146). More recent studies in rats have focused on the SubC/parabrachial (PB) area (356, 610, 801) where there are relatively few cholinergic neurons (160) and on the equivalent caudolateral peribrachial region of the cat. This site is the most sensitive site for carbachol to enhance P-wave frequency (1033) and a concomitant facilitation of learning and memory formation (280, 286, 813). Conversely, neurotoxic lesions of this area abolish PGO waves (277). Neurons in the SubC/PB area fire synchronized bursts of action potentials preceding and phase-locked to PGO waves (274, 824, 1098, 1234). PGO-burst neurons in this region exhibit a longer latency (50–150 ms) to thalamic PGO waves than those in the regions with high concentration of cholinergic neurons projecting to the thalamus (10–25 ms). The stereotyped nature of the bursts in PGO burst neurons led Steriade and colleagues (973) to conclude that the bursts were mediated by a low-threshold calcium spike. Low-threshold bursts are present in brain stem cholinergic neurons (596, 763, 1410) and in noncholinergic neurons in the SubC region (160). Neurons with low-threshold calcium spikes in the SubC are hyperpolarized by carbachol (160). The inhibition of SubC neurons by acetylcholine during REM sleep will deinactivate their low-threshold calcium current and allow them to fire bursts of action potentials. This would also be consistent with the block of carbachol-induced PGO waves in the cat by a M_2 receptor antagonist (283), since activation of M_2 receptors usually causes a hyperpolarizing response (332, 419). Low-threshold bursts in brain stem cholinergic neurons are inhibited by serotonin (763), likely explaining the inhibitory action of serotonin on PGO-wave generation (sect. IV*B*). Together, the data suggest that P-waves are initiated in the SubC/PB area and trigger bursts in cholinergic neurons projecting to the thalamus (274).

2. Muscle atonia and twitches

Atonia of skeletal muscles is one of the cardinal, defining features of REM sleep. The dramatic consequences of a malfunction in the brain mechanisms controlling atonia can be observed in the sleep disorders narcolepsy and REM sleep behavior disorder (RBD) (sect. VII). In narcolepsy, atonia is activated at inappropriate times, resulting in cataplexy (atonia triggered by emotional arousal) during waking, and sleep paralysis at the transition from sleep to wakefulness (923). Conversely, in RBD, atonia fails and patients act out their dreams, resulting in injury to themselves and their bed partners (1131).

A) INHIBITION OF MOTONEURONS DURING REM SLEEP. Intracellular recordings by Chase and colleagues in somatic (trigeminal) and spinal (lumbar) motoneurons of unanesthetized cats

showed that REM atonia is accompanied by a hyperpolarization caused by a barrage of IPSPs, as well as a decrease in input resistance, making the motoneurons relatively insensitive to excitatory inputs (210, 889, 910). The IPSPs were completely blocked by local iontophoretic application of strychnine, an antagonist of glycine receptors but not by antagonists of $GABA_A$ receptors (picrotoxin or bicuculline methiodide), suggesting that glycine is the neurotransmitter involved (889, 1196). Opening of these chloride-permeable channels is likely responsible for the observed decrease in input resistance and reduced responsivity to synaptic inputs. Overall, the evidence that glycinergic inhibition is necessary for REM atonia remains strong (208, 1195). Nevertheless, although Chase and colleagues showed that local application of strychnine blocked all the effects observed during REM in the motoneurons they recorded, they did not show that an antagonism of glycine receptors blocks muscle atonia.

Recently, the well-accepted role of glycine in generating atonia has been challenged by Brooks and Peever (147), although their conclusions have been disputed (208, 398, 767, 1195). Brooks and Peever monitored the activity of masseter motoneurons extracellularly whilst using reverse microdialysis to apply pharmacological agents at the trigeminal motor pool (which innervates the masseter muscle). Antagonism of glycine receptors with strychnine or $GABA_A$ receptors with bicuculline increased masseter muscle tone during waking and non-REM sleep but not during the tonic periods of REM sleep. Thus they concluded that glycine and $GABA_A$ receptors are not involved in REM atonia (at least for somatic motoneurons). Similar results were described by others for respiratory hypoglossal motoneurons and associated genioglossus muscle activity (894, 895). Kubin and co-workers showed in the carbachol model of REM sleep that coantagonism of norepinephrine, serotonin, and GABA receptors abolished REM-sleep like depression of hypoglossal motor neuronal activity (361). However, Horner and colleagues (894) report contrasting results suggesting that $GABA_A$ receptors are important in control of hypoglossal muscle tone during NREM but not during REM sleep.

I) Disfacilitation of excitatory inputs during REM. Using the same methodology described above, Peever and colleagues (165) showed that trigeminal motoneurons receive a glutamatergic input during waking which helps maintain muscle tone. Motoneurons also receive excitatory input from brain stem norepinephrine and serotonin neurons during waking which depolarize them and increase their response to excitatory input (1403, 1404). During REM sleep, these neurons are silent so this excitatory influence is lost (disfacilitation). Indeed, antagonism of both norepinephrine and serotonin receptors at the hypoglossal motor nucleus abolished the REM-sleep like reduction of muscle tone induced by pontine carbachol in anesthetized rats

(362). The shut-off of norepinephrine LC neurons (564, 1435) and reduced firing of DRN neurons (564) during REM-like cataplectic attacks in dogs support the importance of this mechanism.

Disfacilitation and active inhibition contribute to atonia. Although glycinergic inhibition may be the most important mechanism producing decreased firing of motoneurons during NREM and their silence during REM sleep, a combination of mechanisms including disfacilitation (reduced norepinephrine, serotonin, glutamate release) and active inhibition (increased glycine, GABA) is likely to be involved. In addition to these direct effects on motoneurons, a presynaptic inhibition of excitatory inputs could be important. In fact, in vitro evidence for a presynaptic inhibition mediated by muscarinic M_2 receptors has been demonstrated for hypoglossal motoneurons (90). It is also worth recognizing the possibility that mechanisms controlling atonia and muscle twitches may differ between somatic (particularly respiratory) and spinal motoneuron pools (376, 398).

II) Muscle twitches are caused by phasic glutamatergic input. During REM, occasional bursts of muscle activity occur (muscle twitches). These twitches, particularly in developing animals, have been suggested to be important in the refinement of spinal cord connectivity (996). In intracellular recordings from lumbar motoneurons, twitches are accompanied by brief depolarizing events that can be blocked by the non-NMDA glutamate receptor antagonist kynurenate, but not the selective NMDA receptor antagonist APV (1197). Similarly, muscle twitches in masseter muscles were blocked by an AMPA/kainate receptor antagonist (CNQX) into the trigeminal motoneurons pool (165). Thus twitches during REM sleep are due to bursts of excitatory, glutamatergic AMPA/kainate receptor-mediated synaptic potentials.

B) BRAIN STEM CONTROL OF ATONIA AND MUSCLE TWITCHES. Increased activity of neurons in the SubC region of the pons causes muscle atonia. Lesions of several areas of the brain stem reticular formation cause a loss of muscle atonia during REM sleep and may lead to expression of motor behaviors during sleep (569, 893). Similarly, injections of carbachol at a variety of dorsal and ventral brain stem sites can lead to atonia (504, 798, 1057). However, the area most consistently implicated in atonia in both adult (119, 580, 758, 893, 1358) and neonatal animals (606) is the SubC/SLD of the dorsolateral pons (FIGURE 11): *1*) small electrolytic lesions of the SubC abolish REM muscle atonia in the cat and in the rat, whilst larger lesions encompassing more widespread areas of the reticular formation are required for the expression of dreamlike ("oneiric") behavior (606, 893, 900, 1111) typical of RBD (sect. VII). *2*) Selective inactivation of glutamatergic neurotransmission of neurons in the SubC and neighboring LDT region in mice strongly reduced atonia and led to motor behaviors during REM sleep (668).
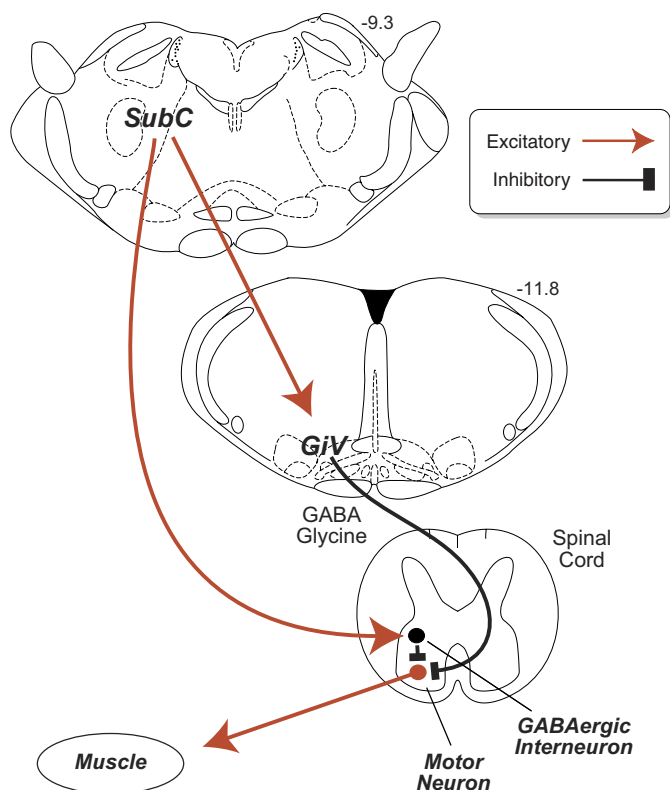
FIGURE 11. Descending circuitry responsible for muscle atonia during REM sleep. During REM sleep, descending pontine subcoeruleus (SubC) glutamatergic projections excite diffusely organized glycinergic neurons of the bulbar reticular formation, including the medullary ventral gigantocellular nucleus (GiV). GABAergic/glycinergic output from the GiV inhibits spinal motoneurons, producing muscle atonia. An alternative pathway consists of a direct SubC glutamatergic projection to the spinal cord, directly synapsing on inhibitory interneurons of the ventral horn. When activated, these interneurons inhibit the spinal cord motor neurons, again producing muscle atonia. Red lines denote excitation; black, inhibition. [Adapted from Pakinos and Watson (989), with permission from Elsevier.]

3) Rats receiving infusions of the fiber-sparing neurotoxin orexin-2-saporin into the SubC in the rat have increased limb movements during REM sleep (100), whereas injections of antisense oligonucleotides directed against the type II orexin receptor in the pontine reticular formation near the SubC cause cataplexy and increased REM sleep (1278). 4) Neurons have been recorded in the SubC in the cat (1099) and neonatal rat (606) which fire tonically at increased rates just prior to and during the muscle atonia of REM sleep. 5) Electrical stimulation of the SubC in rats which have had the forebrain removed (470) (i.e., decerebrate) elicits bilateral muscle atonia. 6) Application of the cholinergic agonist carbachol to this area in the cat causes, at short latency, a pharmacologically induced state virtually indistinguishable from REM sleep, including the muscle atonia component (62, 863, 1340, 1450). In the rat, carbachol does not consistently cause a REM-like state when injected into the SubC (119, 675), but a state similar to REM can be induced by SubC application of the $GABA_A$

receptor antagonists bicuculline and GABAzine (119, 1009).

I) Descending projections of the SubC mediate atonia. Earlier work (119, 210, 681, 684, 776, 1458) suggested that the SubC region causes glycinergic inhibition of motoneurons via a glutamatergic activation of glycine neurons in the ventral medulla (1045) which project to the spinal cord (515) **(FIGURE 11)**. Indeed, glycine-containing neurons in the nucleus reticularis gigantocellularis (NRGc)/nucleus magnocellularis (NMC) and nucleus paramedianus reticularis (nPR) express REM-sleep related Fos immunoreactivity (890), and electrical stimulation of the NRGc leads to IPSPs in spinal α-motoneurons (466, 1268). Glutamatergic stimulation of the NMC or cholinergic stimulation of the nPR in decerebrate cats is effective in eliciting muscle atonia (684). However, this pathway does not appear to be essential for REM atonia. In fact, transection at the pontomedullary junction abolishes inhibition of muscle tone produced by stimulation of the ventromedial medulla (1179), suggesting that stimulation of the medulla may in fact cause atonia via ascending activation of the SubC. Furthermore, recent experiments by Lu and colleagues found that functional lesions of GABA and glycine containing neurons in the medulla (through genetic inactivation of the gene for the vesicular GABA/glycine transporter, vGAT) did not abolish muscle atonia (758, 1367). Instead, these authors proposed that REM-on glutamatergic [vesicular glutamate transporter 2 (vGluT2) mRNA positive] neurons in the dorsal SubC project directly to glycinergic neurons in the spinal cord (758), which, in turn, inhibit spinal motoneurons during REM **(FIGURE 11)**. Consistent with this interpretation, inactivation of glycinergic/GABAergic neurotransmission from local neurons in the ventral horn in the mouse reduced atonia (668). Inactivation of supraolivary medulla glutamatergic (VGluT2-positive) neurons caused exaggerated muscle twitches during REM sleep (1367), suggesting that glutamatergic projections from the medulla may participate in control of motoneuron excitability.

3. Rapid eye movements

The observation of rapid eye movements during sleep led to the discovery of this distinct brain state (50). Eye movements during REM sleep are characterized by both tonic and phasic components (347, 803, 1339). The tonic component consists of a strong downward and convergent movement of the two eyes due to a relaxation of the lateral recti muscles and a tonic contraction of the medial muscles. The relaxation of the lateral recti is due to a tonic inhibition and reduction of firing of the abducens motoneurons similar to that seen in other motoneurons during this phase of sleep (347). The phasic component consists of rapid eye movements that are either isolated or in bursts occurring simultaneously with PGO waves (347, 803, 1339). Lesion, stimulation, and recording experiments have identified the paramedian reticular formation regions immediately rostral

and caudal to the abducens motor nucleus as being responsible for REMs. These fast movements are due to a burst of action potentials in abducens motoneurons as a result of inputs from excitatory and inhibitory burst neurons that are also responsible for saccades during alertness (1245, 1246). The mechanisms responsible for long-lasting bursts of action potentials in these "short-lead burst neurons" remain to be determined, but it is noteworthy they are much longer (1245, 1246) (4–24 action potentials) than the bursts typically produced by low-threshold calcium channel activation (typically 1–4 action potentials) seen in P-wave related neurons. The activity of burst neurons is normally inhibited by omnipause neurons (OPNs), which are characterized by pauses in firing that begin ~13–16 ms before saccades. These neurons are located on either side of the midline in the caudal pons (nucleus raphe interpositus in the monkey) at the same level as the descending fibers of the sixth nerve.

4. Other REM phenomena

Sleep-related penile erections (SRE) are a prominent feature of REM sleep in sexually potent males and can be a useful diagnostic tool to differentiate between psychogenic and organic erectile dysfunction (508). In healthy adult males the erection begins near the onset of REM sleep, persists throughout the REM episode, and then ends rapidly at the exit from REM sleep. Similarly, in females, increased blood pressure is observed in the vagina during REM sleep (1, 1072). The development of methods to measure erections in rats (1140) has allowed some delineation of the brain circuits involved, although research in this area is sparse. In contrast to most other REM sleep signs, SREs require the activation of the forebrain, in particular the lateral preoptic area (LPOA)/ventral bed nucleus of the stria terminalis since lesions of this area abolished SREs whilst leaving waking erections unchanged (1139). Current models (508) suggest two output pathways from the LPOA: one from the LPOA to serotonergic paragigantocellularis neurons in the ventral medulla, which in turn excite thoracolumbar (T11-L2) sympathetic preganglionic neurons innervating the penis, and another via the paraventricular nucleus of the hypothalamus which send oxytocinergic projections to parasympathetic preganglionic neurons in the sacral (S2-S4) spinal cord. Recent evidence also suggests a role for another forebrain site, the lateral septum, presumably acting through projections to the hypothalamic sites described above. Electrical stimulation in dorsal and intermediate aspects of the lateral septum was effective in triggering SRE during REM (456).

REM sleep is also associated with increased rate and variability of heart rate, breathing, and autonomic nervous system function as well as with altered body temperature regulation. These alterations are likely to be important in the context of cardiovascular disease, sleep apnea, and other disorders (see sect. VII).

B. REM Sleep Master Control Mechanisms

1. Location and neurotransmitter content of REM sleep controlling neurons in the brain stem

Seminal work by Jouvet (580) in cats revealed that a knife cut placed at the junction of the brain stem and midbrain eliminated forebrain signs of REM sleep (cortical LVFA, hippocampal theta) whereas muscle atonia and REMs were preserved, suggesting that the REM sleep generating neurons are located in the brain stem. Further work using electrolytic lesions or cell body selective neurotoxins showed that the most important region is the dorsolateral pons (570) **(TABLE 1)**; in particular, the region surrounding and including the LC and laterodorsal tegmental nucleus as well as the reticular formation immediately ventral to these areas. Large lesions of this area led to substantial reductions in the amount of REM sleep (570), whereas smaller, more discrete lesions could abolish particular features of REM sleep such as muscle atonia (893, 1358). The development of histochemical techniques in the 1960s and immunohistochemical techniques in the 1970s/80s revealed the presence of norepinephrine, serotonin, and cholinergic neurons in the REM-sleep control area (570). The ability to visualize these neurons, together with their large size and clustering into distinct nuclei, led to an explosion of interest in their role in REM sleep control. Only relatively recently have improved immunohistochemical, in situ hybridization, and transgenic techniques allowed the visualization of GABAergic and glutamatergic neurons in the REM control area (118, 156, 248, 248, 372, 758, 784, 785). Thus less is understood of these GABAergic and glutamatergic systems, although recent studies suggest that they are likely to be of comparable importance.

2. Mechanisms controlling NREM-REM transitions

One of the most consistent features of human sleep is the alternation between NREM and REM sleep during the night. Early sleep is characterized by a progression from light NREM to deeper stages of NREM sleep with the first REM episode occurring ~90 min into sleep. The 90-min cycles of NREM and REM sleep continue through the night with the proportion of REM sleep steadily increasing and the proportion of deep NREM declining over the course of a night's sleep. Lower mammals, including rats, mice, and cats, do not have such long consolidated periods of sleep as humans; each of the behavioral states is much shorter and more transitions occur between states. However, the general sleep architecture is similar in that, with the exception of disease states (especially narcolepsy), sleep following a period of prolonged wakefulness is initially NREM sleep. REM sleep follows a period of NREM and is not entered into directly from wakefulness.

A) RECIPROCAL INTERACTION MODEL (CHOLINERGIC AND AMINERGIC MECHANISMS). Based on extracellular recordings of neu-

ronal activity from the REM sleep zone in the dorsolateral pons, McCarley and Hobson proposed a mechanistic explanation for the alternation of NREM and REM during the night - the reciprocal interaction model (511, 819), involving two populations of neurons (**FIGURE 12***A*). REM-on neurons increased their firing just prior to and during REM, whereas REM-off neurons showed the reverse pattern. REM-off neurons were proposed to be norepinephrine neurons (serotonin neurons show a similar pattern of firing), whereas REM-on reticular neurons were proposed (erroneously) to be cholinergic neurons. Subsequently, the REM-on cholinergic neurons were localized to the LDT and

FIGURE 12. The original (*A*) and modified (*B*) reciprocal interaction models of REM sleep control, originally proposed by McCarley and Hobson (819). *A*: the original reciprocal interaction model demonstrates increased REM activity as positive feedback of REM-on neuronal populations occurs. This activity leads to excitation of REM-off neuronal populations, which then inhibit REM-on activity. REM-off activity is self-inhibiting, and eventually wanes, releasing REM-on neurons as REM sleep again occurs. [Adapted from McCarley and Hobson (819). Reprinted with permission from AAAS.] *B*: LDT/PPT REM-on activity excites pontine reticular formation (PRF) glutamatergic REM-on cells, promoting REM sleep. LDT/PPT REM-on neurons also excite GABAergic interneurons adjacent to REM-off neurons, inhibiting REM-off neuronal activity. REM-on output also inhibits GABAergic REM-off interneurons, which in turn inhibit REM-on PRF neurons. As REM sleep progresses, REM-on cells begin to excite REM-off cells, leading to REM sleep cessation. Dorsal raphe (DR) and locus coeruleus (LC) REM-off neurons inhibit laterodorsal/pedunculopontine tegmental nuclei (LDT/PPT) REM-on neurons during waking and NREM sleep. Self-inhibition of these REM-off neurons leads to disinhibition of REM-on neurons, again allowing REM sleep. [Adapted from McCarley. *Sleep Med* 8: 302–330, 2007, with permission from Elsevier.]

PPT regions and were proposed to direct the firing of glutamatergic effector neurons in the reticular formation responsible for the different aspects of REM sleep (e.g., muscle atonia) **(FIGURE 13)**. A mathematical model using Lotka-Volterra equations (derived from population models of predator/prey interactions) was able to capture the basic structure of the oscillation between NREM and REM sleep (819) **(FIGURE 12***A***)**. The essence of this model is that REM-off neurons (norepinephrine and serotonin neurons) inhibit REM-on neurons (cholinergic neurons) during waking and NREM sleep, but as these neurons reduce their firing during NREM, REM-on neurons are disinhibited and REM sleep is generated. Positive feedback between REM-on neurons (cholinergic and glutamatergic reticular neurons) stabilizes the REM state (Figs. 12 and 13). A key feature of this model, not reproduced in other more recent models of REM-sleep control [e.g., REM sleep flip-flop model of Lu et al. (758)] is that REM-on neurons are proposed to be excitatory to REM-off neurons so that as the REM state continues, REM-off neurons gradually become more active, terminating the REM bout and giving a mechanistic explanation for changes in state. A more sophisticated version of this model has been produced by McCarley and Massaquoi (821) (the limit cycle model) which incorporates circadian influences on the REM oscillator (these may be mediated by the orexins; see below) as well as local GABAergic neurons (next section, **FIGURE 12***B*), which are likely to be important in shutting off REM-off neurons as well as in controlling the activity of REM-on neurons (807, 816, 821–823).
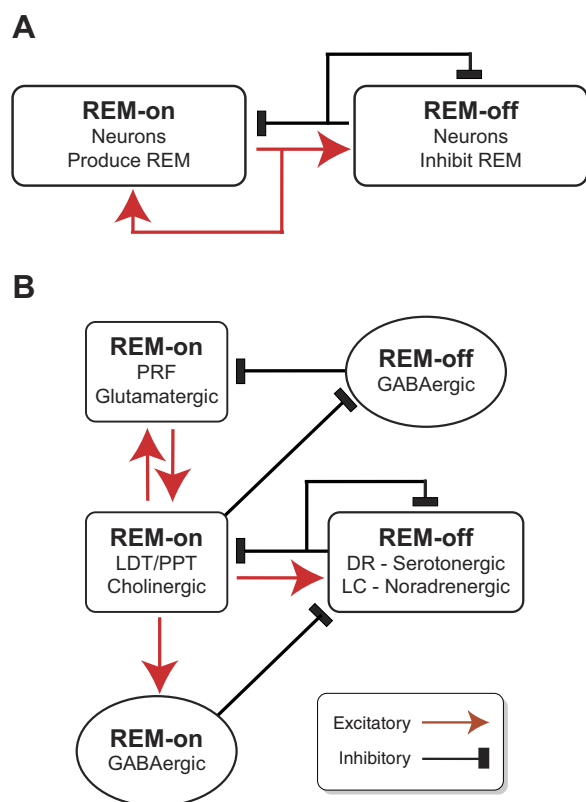
I) Evidence supporting the reciprocal interaction model: state-dependent firing patterns and neurotransmitter release. A large body of evidence supports the reciprocal interaction model of REM sleep (816) and is summarized here (contrary evidence is discussed subsequently). Confirming the initial recording data, multiple studies support the contention that the discharge of presumed cholinergic and aminergic neurons shows an activity profile consistent with causality, i.e., these neurons show an increase or decrease in firing rate, respectively, prior to the beginning of REM sleep (336, 511, 615, 768, 1280). In these studies, neurons were identified based on location, extracellular action potential characteristics, and antidromic activation. In the future it will be important to confirm the neurotransmitter phenotype of the cell recorded using juxtacellular labeling/post hoc immunohistochemistry techniques together with recordings of activity across sleep-wake cycles. So far, this has only been achieved in anesthetized preparations (126), which do not show the full range of sleep-wake behaviors. Confirming the single-unit recording data, measurements of extracellular neurotransmitter levels show that the firing pattern of the cholinergic and aminergic neurons are translated into the predicted pattern of release across the sleep-wake cycle (560, 704, 709, 1020, 1172, 1411, 1412). In contrast to the single-unit recording data, these measure-
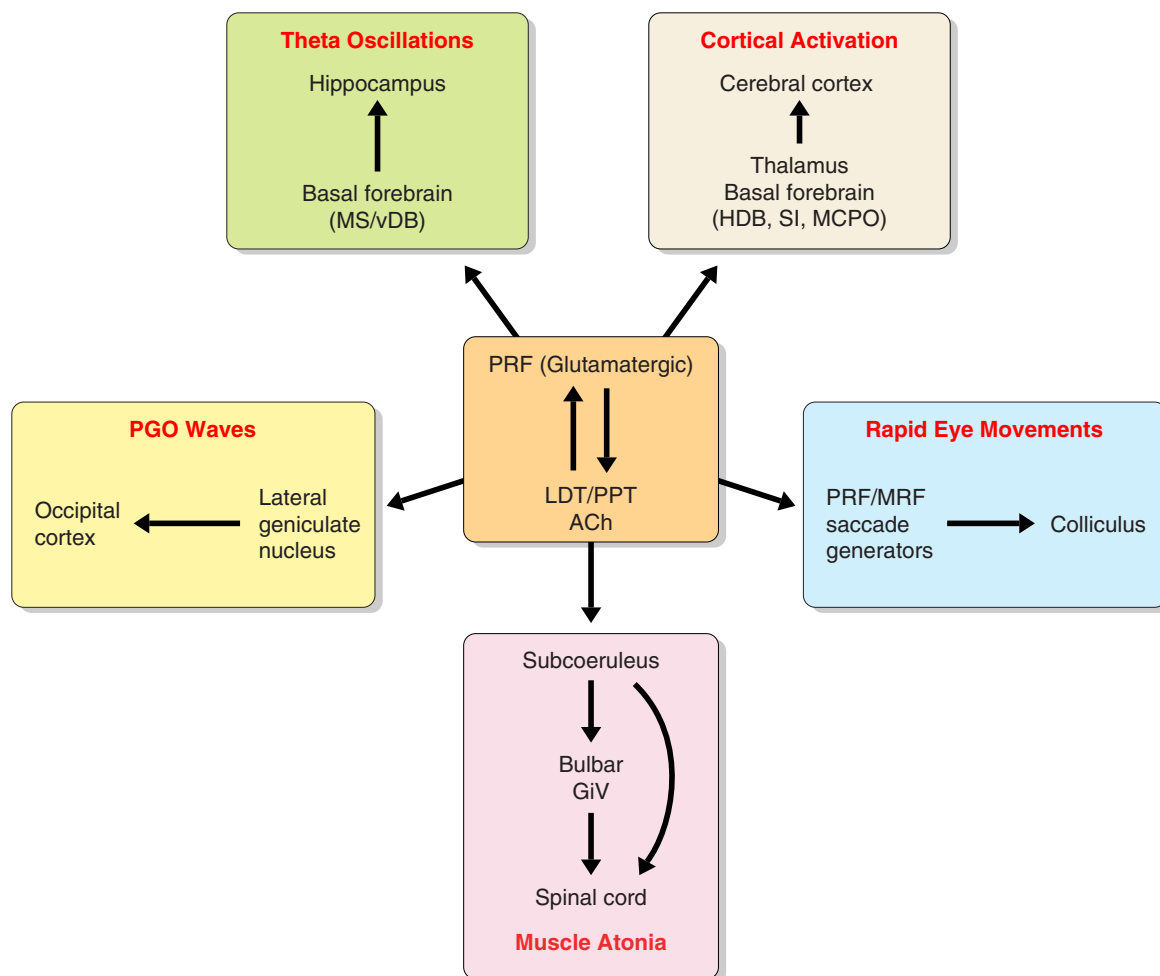
FIGURE 13. Pontine generation of REM sleep phenomena. Interaction between the pontine/mesencephalic reticular formation (PRF Glutamatergic) and cholinergic laterodorsal/pedunculopontine tegmental nuclei (LDT/PPT ACh) produces ascending and descending activation, resulting in REM sleep phenomena, including PGO waves, rapid eye movements, muscle atonia, hippocampal theta oscillations, and cortical activation. GiV, ventral gigantocellular nucleus; HDB, horizontal limb of the diagonal band; MCPO, magnocellular preoptic nucleus; MRF, medullary reticular formation; MS/vDB, medial septum/vertical limb of the diagonal band; PRF, pontine reticular formation; SI, substantia innominata.

ments are limited in temporal resolution, so with current methodologies cannot provide evidence of causality.

II) Evidence supporting the reciprocal interaction model: cholinergic modulation of reticular formation neurons. Anatomical and electrophysiological experiments have confirmed the existence of many of the proposed interconnections of this model. Cholinergic modulation of reticular formation neurons: anatomical and electrical stimulation studies have demonstrated prominent cholinergic projections from the LDT and pedunculopontine tegmentum (PPT) to the reticular formation areas involved in REM sleep control (544, 861). Early in vitro intracellular recording studies in the PnO and PnC regions of the reticular formation revealed excitatory effects of cholinergic agonists mediated by nicotinic and muscarinic receptors in approximately two-thirds of reticular neurons (447, 1241), acting via nonselective cation channels and blockade of leak potassium channels, respectively. Thus these neurons likely represent REM-on or wake/REM-on neurons. In contrast, one-quarter of the neurons were inhibited via activation of an inwardly rectifying potassium conductance (419), consistent with immunohistochemical evidence for the presence of inhibitory M_2 muscarinic receptors on a substantial proportion of non-GABAergic PnO and PnC reticular neurons (141). More recent studies specifically targeting the REM control SubC region in the rat (160, 490) showed that similar mechanisms also operate in this region. The majority of "reticular" (i.e., noncholinergic, nonnoradrenergic) neurons in the SubC were excited by carbachol. Pharmacological analysis revealed that this action is mediated by both ionotropic nicotinic receptors and muscarinic M_1-type (likely M_3) receptors (490). A large subset ($\sim$40%) of SubC neurons were silent at rest (i.e., in the absence of current injection through the recording electrode), were hyperpolarized further by carbachol, and fired in bursts of several action potentials at the offset of hyperpolarizations due to the presence of low-threshold calcium channels (160). Phar-

macological analysis revealed that M_2 muscarinic receptors and activation of a potassium current mediate the outward current responsible for this hyperpolarization (490). These neurons could play a role in PGO-wave generation since hyperpolarization by carbachol would allow deinactivation of the low-threshold calcium currents responsible for burst firing.

III) Evidence supporting the reciprocal interaction model: aminergic inhibition of brain stem cholinergic neurons. Extensive projections exist from brain stem serotonin neurons in the DR and MR to cholinergic LDT/PPT neurons (1149, 1211). Activation of 5-HT_{1A} receptors leads to inhibition of cholinergic LDT neurons in vitro, via activation of inwardly rectifying potassium channels (763). Similarly, LC neurons project to and partially overlap neighboring cholinergic brain stem regions (571, 731, 1001), and norepinephrine inhibits mesopontine cholinergic neurons via activation of α_2 adrenoceptors (1413). In vivo, the firing of REM-on LDT/PPT neurons in the cat was inhibited by application of the 5-HT_{1A} receptor agonist 8-OH-DPAT (presumably explaining their silence during wake), whereas wake/REM-on neurons were unaffected by this agent (1280). Autoradiographic studies in the mouse did not find evidence for 5-HT_{1A} receptors in brain stem cholinergic neurons (120), suggesting either a species difference or mediation of serotonin effects by other receptor subtypes or indirect mechanisms.

IV) Evidence supporting the reciprocal interaction model: cholinergic excitation of aminergic neurons. Cholinergic neurons directly excite LC neurons (1160). Cholinergic agonists acting on nicotinic receptors indirectly excite DRN serotonin neurons via a presynaptic facilitation of excitatory noradrenergic inputs (714).

V) Evidence supporting the reciprocal interaction model: pharmacological experiments. In animals, early studies suggested a REM-promoting role for acetylcholine (410, 504) particularly when monoamines had been previously depleted by use of the agent reserpine (605). In humans, enhancement of cholinergic tone by systemic application of acetylcholinesterase inhibitors or muscarinic agonists (93, 513, 692, 1065, 1185, 1186) consistently decreases REM sleep latency and enhances REM sleep amount, particularly phasic REM events, whereas muscarinic antagonists cause the reverse effect (428, 625, 1051). Enhancement of monoaminergic tone with antidepressants is well known to result in a long-lasting suppression of REM in humans and animals. Following the localization of REM generating sites to the brain stem by Jouvet, enhancement of cholinergic tone or stimulation of cholinergic receptors in the pontine reticular formation of cats or dogs was found to cause a REM-like state (675, 1055, 1228). In rats and mice, a similar effect can be induced, although it is often less robust in these species, perhaps as a result of difficulty in localizing the

drug applications in the smaller brains of rodents and the interaction with circadian control or descending forebrain influences (675, 800, 1228). Activation of the inhibitory 5-HT_{1A} receptor, via perfusion of the serotonin 5-HT_{1A} agonist 8-OH-DPAT, caused increased REM sleep due to activation of autoreceptors when infused in the DRN (1021), whereas perfusion of serotonin in the LDT decreased REM via activation of inhibitory 5-HT_{1A} receptors on cholinergic neurons (522).

VI) Evidence opposing the reciprocal interaction model. Although a large body of evidence supports the suggestion that cholinergic neurons promote REM and aminergic neurons inhibit REM, several lines of evidence appear to contradict this model. However, in each case alternative explanations are also possible: *1)* lesions encompassing the PPT or LDT regions where the majority of brain stem cholinergic neurons are located did not significantly alter the amount of REM sleep (758). Combined lesions of both areas were not performed. Thus, in theory, one area could compensate for the other. We note that large lesions of the LDT/PPT and surrounding areas led to substantial reductions in REM sleep, and these reductions were correlated with the extent of loss of cholinergic neurons (1394). *2)* Knockout mice lacking M2/M4, M3, or both M3 and M2/M4 muscarinic receptors (the main subtypes present in the brain stem) still show REM sleep (434), although REM sleep was reduced by 22% in M3 receptor knockouts. Since these are constitutive knockouts, compensatory responses of the other cholinergic receptors may occur. *3)* Using Fos as a marker of neuronal activation, the Luppi lab did not find activation of ChAT-positive neurons in REM rebound following relatively selective REM sleep deprivation (1354), although these results apparently contradict those of the Jones group (784). Furthermore, Fos is acknowledged as an imperfect marker of neuronal activity, particularly for neurons with complex firing patterns (664). *4)* Inconsistent effects of carbachol in promoting REM sleep in rats and mice may be due to close proximity of REM promoting and REM-inhibiting neurons in these species, making it difficult to restrict the effect to the neurons targeted and due to injections of carbachol during the daytime when rats and mice already sleep maximally, i.e., a ceiling effect. *5)* Lesions/inactivation of norepinephrine neurons do not affect REM sleep amounts. Studies performing neurotoxic or electrolytic lesions of the LC reported no change in the daily amounts of REM sleep (100, 576, 758). Mice lacking dopamine-β-hydroxylase, the enzyme necessary to convert dopamine to norepinephrine, were shown to either have unchanged baseline sleep-wake parameters (539) or a decrease in REM sleep, opposite that predicted by the reciprocal-interaction theory (956). As with other knockouts, compensatory changes may occur, and the differences between these two studies suggest that genetic background or other technical factors may influence the effect. Contradictory effects were also found using neurotoxic lesions of

norepinephrine neurons with DSP-4. Monti et al. (881) found an increase of REM sleep several days after administration, whereas Cirelli and Tononi (244) reported no baseline sleep-wake changes. In all of these studies, it is possible that the activity of serotonin neurons could have masked the loss of norepinephrine neurons since serotonin has similar effects on the REM control neurons as norepinephrine. In contrast to the rather drastic manipulations described above, we have recently found that a partial, reversible knockdown of orexin receptors in LC neurons using RNAi increased REM sleep during the dark period (219). Similarly, reversible inactivation of the LC or DR by cooling increases REM sleep (201).

VII) Alternative models for the contribution of cholinergic and aminergic neurons to REM sleep control. Overall, the question of whether activation of cholinergic neurons and silencing of aminergic neurons are essential for the induction of REM sleep is still not completely resolved. An alternative but related hypothesis is that cholinergic and aminergic neurons are not absolutely required for REM sleep generation but instead bias the system in one direction or another. Another possibility is that these neurotransmitter systems may control particular aspects of REM sleep. For instance, cholinergic agonists consistently promote theta rhythm and PGO waves in rats and cats. In contrast, serotonergic neurons inhibit theta rhythm and PGO waves. The discharge of serotonin neurons is very closely (inversely) correlated with the occurrence of PGO waves (768), and systemic application of the serotonin synthesis inhibitor *p*-chlorophenylalanine (PCPA) in the cat leads to the appearance of PGO waves during the waking state (555). Furthermore, injection of serotonin into the SubC region in the rat suppressed the pontine component of PGO waves (P-waves) without affecting other components of REM sleep (279). Similarly, the silencing of noradrenergic LC neurons has been closely linked to muscle atonia. Cataplexy seen in the sleep disorder narcolepsy is thought to represent inappropriate inactivation of REM muscle atonia. LC neurons completely shut off prior to attacks of cataplexy in genetically narcoleptic dogs, whereas other aminergic neurons (serotonergic and histaminergic) do not reduce their firing to the same extent (564, 1435). These attacks can be reduced by use of norepinephrine selective reuptake inhibitors increasing norepinephrine tone (923). In the future, new techniques (e.g., optogenetics) to selectively excite or inhibit cholinergic and aminergic neurons, in particular the caudally projecting cholinergic neurons, will be of great help in resolving their exact role in REM sleep control.

B) GABAERGIC CONTROL OF REM SLEEP. Recently, there has been increased interest in the role of GABAergic neurons in the control of REM sleep. A large number of mainly small or medium-sized GABA neurons are present in the brain stem, and many of them project to, surround, or are located within brain stem areas involved in REM control (118, 156,

372, 784, 785, 1118). At least two functional groups of brain stem GABAergic neurons seem to be involved in REM control, namely, REM-off GABA neurons preventing activation of REM-on reticular neurons during wakefulness and REM-on GABA neurons inhibiting the activity of aminergic neurons (**FIGURE 12B**). GABAergic inhibition of cholinergic neurons during wake and/or NREM sleep is also a factor in regulating their state-dependent discharge (1303) and neurotransmitter release (1344). Other groups of GABA neurons outside the brain stem regulate the circadian timing and homeostatic control of REM sleep. Although mounting evidence supports a role for these different groups of GABA neurons in controlling REM sleep (reviewed below), we note that in most cases, direct evidence that selective stimulation or inhibition of particular subsets of GABA neurons affects REM sleep occurrence is lacking. Similarly, electrophysiological recordings of identified GABA neurons showing that they have the appropriate discharge patterns to cause a change in state are not available. Thus, as with the cholinergic and aminergic neurons, not all criteria required for firmly establishing the role of GABAergic neurons in REM control have been fulfilled.

I) REM-off GABA neurons. Application of the GABA$_A$ receptor antagonist bicuculline to the SubC or PnO/FTP regions induced a REM-like state in both cats (1441, 1443) and rats (119, 1009, 1112). These results suggested that the REM effector neurons located in this region are normally under inhibitory GABAergic control and are consistent with microdialysis measurement of extracellular GABA levels in the reticular formation across behavioral state which are ordered wake > NREM > REM (1281, 1337). Retrograde tracer injection into the SubC of rats revealed prominent GABAergic inputs from the PnO, ventrolateral periaqueductal grey matter (vlPAG), and the lateral pontine tegmentum (LPT) (118, 758). On the basis of Fos studies and anatomical tracing, it was suggested that GABAergic neurons in the vlPAG and in the LPT region (which encompasses mesencephalic components and is also termed the deep mesencephalic reticular nucleus; DpMe) might be particularly important (758, 1118). Early work in the cat showed that inhibition of this area with the GABA$_A$ receptor agonist muscimol led to a large increase in REM sleep (1120). These findings were confirmed more recently in the rat (1118) and guinea pig (1336). Cell body specific lesions of either the vlPAG or the LPT cause an increase in the amount of REM sleep in rats (758) and in mice (612). The vlPAG lesions increased both REM sleep duration and the number of REM sleep bouts during the dark (active period), whereas the LPT lesions increased the number of REM bouts during the light period and caused occasional episodes of sleep-onset REM/cataplexy-like states. Although the evidence for this region being a REM-inhibiting area is quite strong, a recent study suggests that GABAergic neurons in this region are not involved since inactivation of GABAergic (and glycinergic) neurotransmission did not alter REM sleep (668). Presumably

glutamatergic neurons in this region excite GABAergic neurons located elsewhere in the brain stem, which then inhibit REM-on neurons.

II) REM-on GABA neurons. Another group of GABAergic neurons within the brain stem RF likely play a role in the silencing of REM-off neurons located within the LC and DRN. Microdialysis experiments showed that GABA levels rise in these areas during REM sleep compared with wakefulness (926, 927). Injections of GABA receptor antagonists into the DRN or LC reverse the cessation of firing of 5-HT and NE neurons normally seen during REM (420, 421). However, in the case of the DR, disfacilitation (withdrawal of excitatory noradrenergic, histaminergic, and orexinergic inputs) is also likely to be important (158, 713, 1095). Retrograde tracing studies combined with GAD immunohistochemistry showed that GABAergic neurons in the rostral PnO and vlPAG/LPT region project to the DRN (421) and may be involved in silencing them during REM. GABAergic neurons surrounding the LC norepinephrine neurons express Fos following recovery from REM deprivation (784) and may thus inhibit them during REM sleep. Consistent with this idea, identified SubC GABA neurons were excited by the cholinergic agonist carbachol (156). In addition, the LC receives input from more distally located REM-on GABAergic neurons (1118, 1352). In particular, GABAergic neurons in the dorsal paragigantocellular (DPGi) nucleus of the medulla may be important in silencing the LC (and DR) during REM sleep, since single-unit recordings in this area in unanesthetized rats revealed a population of (unidentified) tonically firing REM-on neurons whose activity preceded the onset of the REM state (435) and Fos studies revealed GABAergic, REM-on neurons in this area (1118).

III) Models of REM sleep control incorporating GABAergic neurons. How can these findings involving REM controlling GABA neurons be reconciled with the cholinergic-aminergic reciprocal interaction theory? It has been hypothesized that acetylcholine and amines modulate the activity of REM-on and REM-off GABAergic neurons and thereby affect REM sleep occurrence (156, 574, 816, 1443) **(FIGURE 12B)**. Several lines of evidence suggest that acetylcholine-excited GABA neurons in the SubC/PnO/LPT areas are REM-on neurons that inhibit LC and DRN neurons. Conversely, acetylcholine-inhibited GABA neurons in the LPT/PnO regions are REM-off neurons which inhibit REM-effector neurons in the PRF during waking/NREM sleep. Muscarinic inhibition of the GABAergic inhibitor neurons would thus disinhibit REM-promoting reticular neurons. This model also resolves the puzzling reports of muscarinic M_2 receptor promotion of REM sleep (61, 252) and cataplexy in narcoleptic dogs (1056), findings that were puzzling in view of the generally hyperpolarizing, inhibitory M_2 actions (332). Unlike the reciprocal-interaction model incorporating GABAergic neurons, two recent models of REM sleep control involve only GABAergic and glutamatergic neurons (758) (REM flip-flop model) or GABA, glutamate, and aminergic/orexin/MCH neurons (765). Aside from the evidence presented above which supports the cholinergic promotion of REM sleep (especially in the cat), these models suffer from the weakness that they do not provide any explanation for how a change in state is achieved or any explanation for the timing of REM-NREM transitions.

C) NITRIC OXIDE CONTROL OF REM SLEEP. nNOS is localized within REM sleep control structures such as the PPT, LDT, and DRN (702, 705). nNOS knockout mice have substantially lower levels of REM sleep than their wild-type controls (218). Microinjection of N^G-nitro-L-arginine methyl ester (L-NAME), a nonspecific inhibitor of NOS, into the PPT reduced REM sleep (281), whereas another NOS inhibitor, N^G-nitro-L-arginine *p*-nitroanilide (L-NAPNA), reduced both NREM and REM sleep (480). Moreover, microinjection of nNOS inhibitor 7-nitroindazole (7-NI) into DRN, in rats, decreased REM sleep (168), and microinjection of L-arginine, a precursor of NO, into PPT increased the duration of NREM sleep and the number of REM sleep episodes (480). Inhibition of NO production in mPRF reduced acetylcholine release and decreased the amount of REM sleep (708, 709). Overall these data suggest that NO, produced by nNOS, mainly in brain stem cholinergic neurons, promotes REM sleep.

3. Forebrain control of REM sleep timing

Although the brain stem appears to be sufficient for generation of REM sleep and NREM-REM cycles (580), other factors controlled by forebrain inputs to the brain stem affect the timing and amount of REM sleep such as the time of day, light exposure, stress, emotion, temperature, nutritional state, and sleep homeostasis (1116). We here focus on diurnal/circadian control. REM sleep occurs predominantly in the inactive period, i.e., night-time in humans and daytime in rats and mice (1439). In an extension of the reciprocal-interaction model of REM sleep (limit cycle model), McCarley and Massaquoi introduced an additional factor to account for the circadian variation in REM sleep across the day. This term provided an excitatory input to REM-off neurons, suppressing REM during the day (in humans) and causing a smaller amplitude and shorter initial first NREM-REM cycle (807, 821, 822).

A) OREXINERGIC CONTROL OF REM SLEEP. Several strong lines of evidence support orexin neurons in the lateral hypothalamus as providing this circadian factor (598). *1*) Orexin neurons receive direct input from the SCN and indirect input via the dorsomedial hypothalamus (52, 224). *2*) Orexin neurons show a wake-on, REM-off pattern of firing (except during phasic periods of REM) (699, 856). Measurements of orexin levels in the squirrel monkey (1472) and rat (296) are consistent with the proposed diurnal fluctuation. *3*) As

hypothesized in the model, orexins excite wake-active, REM inhibiting, serotonergic DRN neurons (157, 158, 735) and noradrenergic LC neurons (524). Surprisingly, they also seem to excite cholinergic brain stem neurons in vitro (169). *4*) The loss of orexins causes narcolepsy (215, 727), a sleep disorder characterized by the presence of excessive daytime sleepiness and several symptoms related to abnormal timing of REM sleep signs (see sect. VII) and loss of diurnal REM control in humans (983). *5*) Orexin loss-of-function experiments in animals (TABLE 1) result in increased REM during the normally REM-poor dark period, arguing strongly that orexinergic activity suppresses the occurrence of REM sleep during the diurnal active phase.

B) PREOPTIC HYPOTHALAMUS CONTROL OF REM SLEEP. In addition to the orexin systems, the preoptic hypothalamic area also plays a role in circadian control of sleep. The preoptic area receives indirect projections from the SCN via the medial preoptic area and dorsomedial hypothalamus (222, 224, 306). Lesion of the area medial and dorsal to the ventrolateral preoptic area (VLPO) of the hypothalamus, an important area in NREM control, was correlated with loss of REM sleep (756). The loss of REM sleep occurred predominantly during the light period (756) (the rat's inactive period). Furthermore, after periods of dark exposure that triggered enrichment of REM sleep, the number of Fos-positive cells in this extended VLPO area was correlated with the amount of REM sleep (755). Thus diurnal variation in REM sleep is caused by an orexin-mediated suppression of REM during the active period and a promotion of REM by the extended VLPO during the inactive period.

C. Relation of REM to Dreams

The lay public is interested in REM sleep largely as a result of its close association with dreaming. Interpretation of dreams is ascribed great significance in many cultures and predates modern science. In western societies, the work of Freud and his counterparts led to a widespread acceptance of dreams as giving important insights into "psychic disturbance." However, the findings of modern neuroscience have led to a view of dreaming which asserts that the features of dreams arise from internally generated patterns of brain activation and deactivation during REM sleep, and dream content does not necessarily have any meaning or message for the individual (509, 510, 815, 820).

A) ACTIVATION-SYNTHESIS HYPOTHESIS OF DREAM GENERATION. The modern neuroscience view of dreams was laid out by Hobson and McCarley as the activation-synthesis hypothesis (510, 815, 820). An expanded state-space version of this hypothesis, the AIM (activation, input gating, modulation) model was developed by Hobson to characterize all conscious states (588). In the activation-synthesis view of dreaming, during the REM state, the brain is activated internally by the activity of the brain stem (described above).

Sensory systems, in particular visual systems (activated by PGO activity), and vestibular systems are activated. Sensations and feedback from the neuronal command signals for muscular activity influence the dream experience, although motor output is inhibited by brain stem muscle atonia generating systems. This mismatch between motor programs and motor output may contribute to common dream experiences of floating, flying, or an inability to flee a dangerous situation. Brain areas involved in emotional behavior and memory formation such as the hippocampus and amygdala are "reactivated" during REM sleep, possibly reflecting memory consolidation processes (562, 1089, 1391) and provide content (especially emotional content) to the dream. The synthesis of these different elements of brain activity, together with their conscious awareness, causes the dream experience. The synthesis process occurring in dreams is in some ways similar to the "confabulation" of patients with various kinds of neurological injuries, which can also be bizarre and nonsensical and makes little sense to observers (1143). An intriguing recent theory of REM sleep and dreams suggests that they represent an evolutionarily early form of conscious awareness (proto-consciousness), a precursor of the conscious awareness seen during the waking state (509).

B) BRAIN IMAGING OF THE REM/DREAMING STATE. Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) during REM sleep and dreaming in humans have supported the scheme proposed in the activation-synthesis hypothesis, which was originally based on animal work (1143). These studies reported increased blood flow/oxygen utilization in a network of interconnected regions during REM sleep: the pontine tegmentum, thalamus, amygdala, basal ganglia and anterior cingulate and occipital cortex (512, 754, 792, 1143). Amygdala activation is likely responsible for the high percentage of dreams featuring negative emotions such as anxiety and fear. In contrast, decreased activity was seen in the dorsolateral prefrontal cortex, parietal cortex, posterior cingulate cortex, and precuneus. Deactivation of frontal areas likely accounts for the lack of insight, distortion of time perception, and difficulty in remembering dreams upon waking (512, 1143). The mechanism responsible for this deactivation is unclear since cholinergic projections to the cortex, thought to be responsible for activation during REM, target prefrontal as well as other cortical areas (500). Another, still to be resolved issue, is how particular dream elements are selected among the massive number of possibilities available to the brain.

C) DO DREAMS REPRESENT INTERNAL DRIVES? Unlike Freud's model, the brain activity in the Hobson/McCarley activation-synthesis model of dreaming was considered motivationally neutral, since it was due to the turning on of a brain stem neural oscillator. However, brain stem cholinergic neurons activated during REM sleep provide a strong excitatory input to dopaminergic midbrain neurons involved

in reward processes, and others have argued that dreaming is closely linked to activation of these pathways (1198). Although the average firing rate of dopamine neurons in the VTA does not vary with behavioral state (858), increased bursting occurs in VTA neurons during REM sleep (271), and an increased number of Fos-positive dopamine neurons was observed in the VTA during REM-rich periods following REM deprivation (786). Furthermore, REM involves a strong activation of limbic brain regions (792), which may feedback onto the brain stem oscillator, although there is no evidence for this. Thus processing of emotionally relevant events may occur during the REM state (1388), as do many other complex functions such as alterations in learning and memory. However, the regular generation of this cyclic state does not depend on motivationally relevant stimuli, such as protection against repressed and forbidden wishes (Freud's hypothesis).

V. SLEEP LOSS AND COGNITION

In humans, sleep loss/disruption alters cognition and performance in a wide variety of behavioral domains including attention/vigilance, executive function, emotional reactivity, memory formation, decision making, risk taking behavior, and judgment (835). In addition, a substantial body of literature supports the intuitive notion that a good night's sleep can facilitate human cognitive performance (339), a literature not to be covered in detail in this review. This section focuses on mechanistic aspects of sleep loss/sleep disruption. Methodological consideration related to rodent models of sleep disruption are covered in a recent review (835).

A. Attention and Executive Function

Executive function is a broad and poorly defined term that is used to describe a set of higher order cognitive functions that involve the prefrontal cortex. Impairments of attention and other aspects of executive function following sleep disruption have been well documented in humans in both experimental and patient populations (396, 621). The mechanisms by which sleep disruption alters executive function are unknown but likely involve functional impairment of the prefrontal cortex and/or its afferents (907). Sleep disturbances in humans alter normal functioning of the prefrontal cortex as well as the posterior parietal cortex, which has dense interconnections to the frontal lobe (1287). Imaging studies have revealed altered activity in the default network, resulting in a dissociation of anterior and posterior midline regions during sleep deprivation (212, 454, 1107, 1108). Sleep deprivation (SD) also increases activity in thalamic regions that project to the cortex and may be involved in maintaining cortical activity in the face of increasing sleep pressure (322, 1297, 1433). Lapses of attention during SD are associated with reduced thalamic and

frontal/parietal cortical activity that contrast with activation of these same regions during successful performance (213). Possible mechanisms underlying impaired prefrontal cortex function during sleep disruption are described next.

1. Sleep loss-induced impairment of high-frequency oscillations

Slowing of the EEG during sleep deprivation is particularly prominent in the frontal cortex and is accompanied by a concurrent reduction in higher frequency beta/gamma rhythms important for normal cognition (see sect. II). Modeling, electrophysiological, and optogenetic studies all support the idea that beta/gamma oscillations and gamma-theta coupling have important functions in attention-dependent stimulus selection (193, 297, 391, 1194) via their ability to synchronize firing between functionally related cortical and subcortical brain areas, reduce noise, and enhance signal transmission. The firing of principal cells relative to the phase of the gamma rhythm has been proposed as a mechanism for coding of information (390, 732). In addition, the frequency of gamma oscillations affects the direction of information flow between brain areas (253).

Changes in the activity of neocortical or allocortical neurons themselves are likely to contribute to the disruption of EEG oscillations. For example, SD or sleep fragmentation (SF) in rats leads to reduced excitability of pyramidal neurons in area CA1 of the hippocampus (837, 1271). In the neocortex, a recent study found that as wake duration increases, individual cortical neurons can enter OFF states, accompanied by slow waves in the local field potentials, similar to NREM sleep, while other nearby neurons show normal wake activity and overall the EEG shows a wake pattern (1383). The incidence of these local OFF states increases with the duration of the wake state and is correlated with impairments in a sugar pellet reaching task (1383). Thus alterations in the excitability of cortical neurons lead to a disruption of higher frequency EEG rhythms, impacting attention and higher cognitive function.

2. Inhibition of cholinergic and other BF projections to prefrontal cortex

Inhibition of BF cholinergic neurons by adenosine and/or NO during SD (see sect. IIIC) is likely to impair beta/gamma oscillations, since acetylcholine released from these neurons is a potent facilitator of such rhythms (see sect. IIC). Aside from their major role in basic cortical arousal and behavioral activation, evidence suggests that the BF and pontine cholinergic systems play a significant role in visual attention, short-term spatial (working) memory, and responsiveness to novel and motivationally relevant stimuli during the acquisition of new associations (1066). Thus the BF cholinergic system figures prominently in models of the effects of sleep disruption on behavior and cognition (1119). As re-

viewed in section III, an upregulation of BF adenosine and adenosine A_1 receptors occurs during SD or SF, which may lead to inhibition of BF cholinergic and noncholinergic neurons. Also, during SD, adenosine A_1 receptors are upregulated in the human PFC, which may consequently produce inhibition of PFC activity (341). The role of BF adenosine in attentional deficits following sleep disruption were directly investigated using a rat model of the human psychomotor vigilance task (PVT) (226). Microdialysis administration of adenosine directly into the BF mimicked the effect of 24 h of sleep deprivation, producing an increase in vigilance lapses relative to baseline, or to control perfusion of artificial cerebrospinal fluid (ACSF). This effect of AD was reversed by the coperfusion of AD with an A_1 receptor antagonist. Thus an inhibition of cholinergic neurons by adenosine during sleep deprivation causes deficits in attention.

3. Alterations in catecholaminergic systems

Dopaminergic and noradrenergic arousal systems projecting to the PFC and striatum have also been strongly implicated in working memory and attention (1066, 1067). The level of dopamine required for optimal function follows an inverted U-shaped curve; thus increases or decreases may negatively impact function. Early animal studies suggested that SD causes an increase in dopamine levels (424) and a supersensitivity of dopamine receptors (1310). More recent human studies support increased striatal dopamine levels (1376) that correlate negatively with performance on a visual attention task (1375). Pharmacological treatment of the behavioral consequences of SD also suggests a role for dopaminergic mechanisms. Thus the stimulants commonly used for the treatment of sleep disorders (sect. VII), such as modafinil, inhibit the dopamine transporter leading to increased catecholamine levels (1425). Similarly, in *Drosophila*, dopamine is important in the control of arousal and the response to SD (679, 1153, 1438). Dopamine D_1 receptor activation in the mushroom bodies rescues sleep loss-induced learning impairments (1154). Changes in the norepinephrine system may also be involved in sleep disruption-induced deficits. One day of REM SD produced a decrease of activity in the LC and a decrease of NA release (783, 1016). A more extended REM SD showed the opposite effect, as NA levels and turnover increased (77, 992, 1016). Studies monitoring changes in norepinephrine receptors report inconsistent results (745, 1423). Overall, the data suggest that changes in dopamine systems may be more important than changes in norepinephrine or its receptors in causing behavioral alaterations.

4. Interindividual differences

The neurobehavioral response to SD shows large interindividual differences in both humans and rats (1330, 1331). Very recent genetic studies suggest that polymorphisms in genes related to adenosine metabolism or signaling (59)

affect interindividual differences in susceptibility to cognitive disruption following SD. In addition, a polymorphism of the gene that encodes catechol-O-methyltransferase (COMT), an enzyme which degrades catecholamines, was predictive of the interindividual variability in performance of an executive function task after SD, as well as EEG alpha frequency activity during wakefulness (112).

B. Emotion

1. Mood

Changes in mood and motivation are common subjective experiences during sleep disruption. Recent human studies have begun to investigate these changes under controlled experimental conditions. Mood is often elevated during SD (108, 521), particularly in subjects with a evening-type circadian profile (1147). The effect of acute SD can be used to treat severely depressed patients (sect. VII), although unfortunately the effect is reversible once the patients are allowed to sleep. At the same time as the basal mood changes, sleep-deprived subjects show increased reactivity to negative stimuli (31, 1274, 1334), reduced facial expressiveness (859), and impaired recognition of human emotions (622, 1328). The mechanisms underlying these changes are largely unknown but have been hypothesized to reflect a loss of REM sleep (453), since REM sleep is characterized by a strong activation of brain areas regulating emotional responses such as the amygdala, hippocampus, and frontal cortex (sect. IV). Emotional memory is enhanced across sleep intervals with high amounts of REM sleep (1387), and a recent imaging study showed that sleep enhanced the memory of emotional pictures by increasing functional connectivity between the ventromedial PFC and the precuneus, amygdala, and occipital cortex (1240). Increased amygdala activation due to a loss of top-down control from the medial prefrontal cortex may explain the increased response to negative emotional stimuli (455, 1465). At the same time, activity in brain mesolimbic reward networks is also enhanced (455), consistent with reports of increased dopamine release (1375, 1376) and positive effects on mood and motivation.

2. Anxiety/fear

Both anxiogenic (1088, 1180) and anxiolytic (806, 1248) effects have been reported in experimental investigations of sleep disruption. Self-reported increases in anxiety have been observed in humans after SD (58, 1088), consistent with reports of the increased reactivity to negative stimuli described above. Several studies have examined negative emotional memory formation in animals in association with sleep disruption. Contextual fear conditioning, a hippocampus-dependent task, was impaired by 72 h of SD before training (1085) or by REM (441) or total SD (468) 5–6 h following training. REM SD was also reported to

impair extinction of cued fear extinction, a prefrontal cortex and amygdala-dependent task (1181). In humans, recollection of negative emotional stimuli 72 h later was associated with increased amygdala activation in subjects sleep-deprived on the night following initial exposure (1239). The relevant factors that predict whether sleep disturbance will increase or decrease anxiety are not known. Duration of exposure, method used to disrupt sleep, type of sleep disturbance, and how the findings are interpreted are potential factors that may help to explain seemingly contradictory findings.

C. Learning and Memory

A substantial body of evidence from both humans and experimental animals suggests that normal sleep facilitates certain forms of learning and memory (309, 339, 1007, 1389), although these data, particularly the link between REM sleep and memory, have been criticized (1173, 1361). A full review of the controversial topic of the role of sleep in learning and memory is beyond the scope of this review, and the reader is referred to the reviews cited above. A more consistent literature describes impairments in learning and memory produced by sleep disruption (339, 835). A variety of mechanisms could mediate deficits in learning and memory associated with sleep disruption. These mechanisms are discussed next.

1. Role of hormonal stress responses

A problem inherent in conducting experiments to assess behavioral and cognitive impairments associated with sleep disruption is that the reported deficits might be due to a stress response associated with the method employed to disrupt sleep. Sleep deprivation induced by the treadmill method (1272), rotating wheels (846), or the flowerpot method (1469) enhance corticosterone levels. It is important to point out, however, that the effects of stress on learning and memory are not always deleterious, but instead are dose-dependent. High levels of chronic stress (258) or chronic administration of the adrenal stress hormone corticosterone (114) impair spatial learning and memory. Conversely, stressors of lessor intensity sometimes facilitate learning and memory and long-term potentiation (307). Thus stressors may facilitate or inhibit learning and memory processes, depending on the type, magnitude, and timing of the stressor. Although an indirect effect of stress is always possible, several lines of evidence suggest that the effects of sleep disturbance on learning and memory are predominantly direct. For instance, there are REM sleep periods, or "windows" of time during which prior learning is highly sensitive to selective REM SD (1190, 1191). Such time-dependent sleep disturbances would not likely result from a nonspecific stress response.

The most compelling evidence that effects of sleep disturbance on learning and memory are independent of stress is from studies on adrenalectomized animals. In rats, 72 h of SD prior to training impaired acquisition on the water maze task (1084), but surgical removal of the adrenal glands (with corticosterone replacement to normal, nonstressed levels) did not significantly alter this effect. Similarly, at the cellular level, 96 h of SD was found to inhibit adult hippocampal neurogenesis, but this effect was also observed in adrenalectomized rats that were maintained via subcutaneous minipumps on continuous low-dose corticosterone replacement (902). Hence, the effect of sleep loss on adult neurogenesis was independent of adrenal stress hormones (902). Another study found that adrenalectomy and subsequent corticosterone replacement significantly altered sleep architecture but did not alter the homeostatic sleep response to 6 h of SD (131). Taken together, these studies suggest that both the homeostatic response to sleep disruption as well as the subsequent deficits in learning and memory are mediated by mechanisms that are largely independent of endocrine status.

2. Sleep loss impacts cellular mechanisms of learning and memory occurring during NREM sleep

Sleep disruption could prevent memory consolidation by impacting the following mechanisms that normally occur during NREM sleep: *1*) synaptic homeostasis. The synaptic homeostasis theory of sleep posits that the amplitude and slope of delta and slow oscillations downregulate synapses so as to avoid a ceiling effect of synaptic potentiation occurring during waking (sect. III). Increases of delta waves during waking are a prominent feature of short-term SD and mounting sleep pressure, suggesting that they are important for maintaining function. Indeed, boosting slow oscillations during sleep potentiates memory (805) and EEG delta power during recovery sleep after SD predicts cognitive recovery (787). *2*) Replay of firing patterns: hippocampal CA1 pyramidal place cells, which are known to fire together when an animal occupies a specific spatial location (939), were also found to fire together during subsequent sleep (985). Moreover, cells that were not active during wake, or that were active but had nonoverlapping spatial patterns of firing, did not show increased firing during subsequent sleep (1417). Hippocampal place cells also encode temporal information concerning the order of events; replay of the firing of these neurons in sleep has been shown to exhibit a pattern that reflects the temporal order in which these cells fired initially during waking exploration (1188). Hence, reactivation of these hippocampal neuronal ensembles during sleep is postulated to represent the "consolidation" of labile memories into more stable forms. This reactivation of hippocampal neurons occurs in a compressed manner during high-frequency ripples occurring in the hippocampus during NREM sleep, a possible endogenous mechanism for the generation of LTP (175, 179) and sleep loss will impact this process. *3*) Sharp-wave ripple complexes: the large and high-frequency depolarization of CA1

neurons occurring during sharp-wave-ripple complexes (sect. III) induces synaptic potentiation in a Hebbian manner reminiscent of in vitro tetanic stimulation protocols used to induce long-term potentiation (LTP) (179, 628). LTP-like stimuli induce sharp waves in vitro (89), and LTP is occluded in hippocampal slices that produce spontaneous sharp waves (254), supporting the idea that sharp waves represent an endogenous trigger for LTP-like synaptic plasticity. Buzsaki (1989) proposed in his two-process model of memory formation that these events are involved in the consolidation and transfer of short-term memory traces from the hippocampus to the neocortex during sleep (175). Hippocampal sharp waves occur just prior to the transition from neocortical down states to up states, suggesting that they facilitate down-to-up transitions. Furthermore, in combined recordings from hippocampus and prefrontal cortex in naturally sleeping rats, prefrontal neurons consistently fired 100 ms following hippocampal neurons participating in hippocampal sharp waves, suggesting a hippocampal-neocortical dialogue (875, 1408). In animals, an elevated sleep spindle density has been observed after learning in rats (345, 346, 876). Several human studies suggest that disruption of stage 2 sleep, when spindles occur, is linked with impairments in procedural memory (1390). *4)* Reduced acetylcholine levels: low acetylcholine levels occurring during NREM sleep are important for declarative memory consolidation (402).

3. Sleep loss impacts cellular mechanisms of learning and memory occurring during REM sleep

Disruption of REM sleep neuronal processing events represents another potential mechanism affecting learning and memory formation. *1)* Neuronal replay during REM sleep may reflect neocortical activation of hippocampal circuits during a later stage of the memory consolidation process (499, 1244) since the duration of replay of hippocampal neuronal ensemble activity during REM sleep was comparable to that during waking task performance (753) (i.e., on the order of tens of seconds to minutes), much longer than replay recorded during NREM sleep. The existence of replay of hippocampal ensemble activity during REM sleep leads to speculation concerning the information content in dream states (linked to REM sleep) and its potential significance in memory processing, perhaps especially for procedural memory which is known to be REM sleep-dependent (607). *2)* Theta rhythms: behavior-dependent modifications of subcortically driven theta rhythms are also reproduced during REM sleep. *3)* P-waves: work from Datta and colleagues has shown that activation of the P-wave generator in the dorsolateral pons (sect. IV) facilitates learning and memory, particularly involving dorsal hippocampus activation, whereas inhibition causes the reverse effect (275, 280, 284, 285, 813, 814). Disruption of any of these three processes during sleep disruption may affect memory formation.

4. Inhibition of synaptic plasticity

It is generally accepted that long-lasting changes in hippocampal synaptic efficacy, examined experimentally in LTP or LTD paradigms, underlie declarative memory formation (109). Multiple studies in recent years have shown an impairment of the induction or maintenance of LTP by periods of total SD (184, 1074, 1350), REM SD (288, 749, 797, 837, 1074, 1155), or sleep fragmentation (46, 1273). Interestingly, the sleep disruption effects on synaptic plasticity appear to be specific for LTP since short-term presynaptic plasticity (paired-pulse facilitation) and long-term depression were unaffected (837, 1273). In addition to these physiological changes in LTP and LTD, sleep disruption reduces hippocampal neurogenesis (459–461, 469).

A) NMDA RECEPTOR COMPOSITION AND LTP/LTD. One likely mechanism underlying the loss of LTP by sleep disruption is altered subunit composition of NMDA receptors (216, 655, 746). Following long-periods of REM SD (24 or 72 h), a reduction in the NMDA receptor-mediated component of excitatory synaptic currents was shown in the CA1 region of the hippocampus (836) and dentate gyrus (216). This reduction was associated with reductions in the surface expression of the obligatory NR1 subunit of the NMDA receptor (216, 836). An increased NR2A/NR2B subunit ratio was observed in the CA1 region using a milder form of SD (4–6 h) and electrophysiological analysis of isolated synaptic currents and immunoblot analysis of purified synaptosomes (655). Furthermore, immunogold labeling of NR2A and NR2B subunits and electron microscopy revealed a 1.6-fold increase in the amount of NR2A subunits at synaptic sites in the CA1 region. Greater NR2A receptor content was shown to facilitate the induction of LTD elicited by stimulation in the theta-frequency range (746). Thus the sliding threshold for inducing LTD or LTP was shifted in the direction of LTD by SD (655, 746). Changes in LTP/LTD were not observed following SD in NR2A knock-out mice, suggesting that the change in NR2A subunits was sufficient to explain the changes in synaptic plasticity by sleep loss (746). Theoretically, reduced LTP produced by NMDA receptor downregulation or altered composition could be overcome by increasing the amplitude or duration of depolarization produced by the AMPA/kainate subtype of glutamate receptors so that increased calcium enters the postsynaptic cell either via NMDA receptors or voltage-dependent calcium channels. Along these lines, a positive allosteric modulator of AMPA receptors (AMPAkine CX717), which prolongs AMPA receptor-mediated EPSP decay time, was shown to strikingly enhance the performance of monkeys following a single night of sleep deprivation (477, 1019). In addition to alterations in NMDA receptors, SD also impairs the late-phase of hippocampal LTP via impaired cAMP signaling (1350), perhaps suggestive of impaired cellular energy (323). Consistent with this idea, the energy sensor AMPK regulates the late phase of hippocampal LTP (1023).

B) LTP AND LTD DURING NORMAL SLEEP AND WAKEFULNESS. In contrast to the well-replicated inhibition of LTP with sleep loss, there is less consensus regarding synaptic plasticity processes occurring during natural waking and different stages of sleep. Early studies showed that the strength of synaptic transmission varies according to the time of day (72). More recently, Cirelli and Tononi, based on an examination of gene transcripts expressed during waking and sleep, proposed that LTP occurs mainly during waking, whereas LTD occurs mainly during sleep (sect. III). Buzsaki, on the other hand, based on hippocampal neuronal activity patterns proposed a two-stage model of memory formation which postulated that sharp waves occurring during NREM sleep in the CA3 region would be an ideal trigger for LTP-like processes in the CA1 region (175). Also in line with the idea that synaptic strengthening can occur during sleep are findings of strengthened cortical responses in the visual system of developing cats which required NMDA receptors and PKA activity (53, 561).

5. Increases in extracellular adenosine

Adenosine can inhibit LTP via A_1 receptors (38), and both extracellular adenosine levels and A_1 receptors have been shown to increase in cortical areas during SD (sect. III). Several experiments have shown that disruption of this process leads to deficits in working or spatial memory: *1)* conditional knock-out mice for the adenosine A_1 receptor (99); *2)* rats with VLPO lesions had disruption in LTP that could be partially rescued by adenosine A_1 receptor antagonism (46); and *3)* dn-SNARE mice which cannot release adenosine from astrocytes also had disrupted cortical slow waves (360) and memory formation (367).

E. Conclusion

Sleep disruption-induced impairments in cognitive performance have many real world consequences. Increased industrial and car accidents are an obvious correlate, but sleep disruption also has more subtle effects that affect individuals and the economy. For instance, recent studies showed that acute SD increases risk-taking behavior (623, 841, 1351) and impairs the ability to integrate emotion and cognition to guide moral, emotionally evocative, judgements (624). On the positive side, acute SD has a rapid mood-elevating effect in some depressed patients. Current evidence suggests changes in synaptic transmission, neuronal oscillations, and neuromodulatory projections to the cortex, in particular cholinergic and dopaminergic systems, may be particularly important in mediating the behavioral alterations which result from sleep loss.

VI. GENOMICS AND PROTEOMICS

The description of sleep and wakefulness described in sections II-V of this review has primarily relied on electrophys-

iological, behavioral, and pharmacological studies. However, there are multiple aspects of sleep and wakefulness that are regulated in concert, suggesting contributions of genes and their protein products. Thus many recent studies have focused on the genetics and proteomics of sleep.

The earliest indications of genetic influences on sleep were from studies of mono- and dizygotic twins in the 1930s (287). Although most early twin studies used relatively small numbers of subjects, many aspects of sleep, such as sleep latency, awakening measures, amount of REM sleep, and temporal pattern of eye movement, were significantly correlated in mono- but not in dizygotic twins. Moreover, the EEG spectral patterns showed striking similarities between monozygotic twins (287). More recent genomic studies have utilized various techniques including: *1)* subtractive hybridization, *2)* nylon membrane macroarrays, *3)* microarrays used in conjunction with specific quantitative methods such as in situ hybridization and real time polymerase chain reaction, and *4)* transgenic mice with constitutive or conditional loss or gain of gene function. Several animal model systems have been used to understand the fundamental nature of sleep including sparrows, mice, the fruit fly *Drosophila melanogaster*, the nematode round worm *Caenorhabditis elegans,* and zebrafish. In the past decade, several reviews have been written on this topic of genome-wide gene expression (230, 287, 1145). Similarities in the sleep markers (genes and proteins) across different species have not only underscored the universal nature and the need for sleep but also revealed a plethora of information on various functional categories of genes and proteins. In this section we review the genes and proteins associated with sleep and wakefulness in humans and animals, grouped according to function at the cellular or network level.

A. Genes Associated With Sleep-Wake Regulation

1. EEG

Zung and Wilson in 1966 (1479) were the first to perform polysomnographic studies in twins. These authors demonstrated striking similarities in the temporal pattern of sleep stages between monozygotic twins. One of the first genetic loci responsible for low voltage EEG was mapped to human chromosome 20q (1212). Later, several twin studies reported that EEG delta, theta, alpha, and beta frequencies are heritable traits that are highly correlated in monozygotic twins (24, 34, 292, 1324). These results were corroborated by findings in rodents, showing strong heritability in EEG traits in inbred mice (382, 383, 1258, 1322). Quantitative trait loci (QTL, stretches of DNA that have clusters of genes related to a trait, in this case "sleep") studies among different strains of mice identified several heritable genes for specific sleep parameters (383, 938, 1258), especially differ-

ent EEG frequencies. QTL analysis identified a single gene encoding the retinoic acid receptor beta (*Rarb*), located on chromosome 14, that controls delta frequency EEG activity (796). Targeted disruption of this gene confirmed the importance of retinoic acid signaling in control of EEG delta frequencies (796), although the mechanism remains unclear. Theta frequency (5–8 Hz) activity during REM sleep is controlled by a single autosomal recessive gene, known as acylcoenzyme A dehydrogenase for short chain fatty acids (*Acads*) that is localized to chromosome 5 in mice (1260). The ion channels that contribute significantly to the characteristic EEG frequency bands of NREM and REM sleep are discussed in detail below.

2. Neurotransmitter systems

A) ACETYLCHOLINE. Few genetic studies of sleep and wakefulness have targeted the cholinergic system, although, as described in other sections of this review this system has been extensively investigated with other methodologies. In muscarinic receptor 3 (M_3) knockout mice, REM sleep was decreased, whereas M_2/M_4 double knockouts had normal sleep (434). Brain stem cholinergic neurons provide a strong innervation of midbrain dopamine neurons involved in brain reward processes (see sects. II and IV). The VTA dopamine neurons express exclusively the M_5 muscarinic receptor (1207) and not other muscarinic receptor subtypes. A reduced activation of dopamine midbrain neurons projecting to the nucleus accumbens was seen in M_5 knockout mice (374). These mice also showed a reduced locomotor response to morphine (1207). Similarly, rats that had M5 antisense oligonucleotides injected into the VTA had reduced lateral hypothalamic self-stimulation (1461). Cholinergic nicotinic receptor mutations have little impact on sleep wake behavior (371, 703), possibly due to the large number of alternative subunits. The complexity of the gene encoding the synthesizing enzyme choline acetyltransferase (ChAT) has precluded a genetic analysis of its role in sleep-wake control.

B) SEROTONIN. Genetic studies confirm that the serotonergic system has important roles in arousal, suppression of REM sleep, and the sleep response to restraint stress. Mice in which serotonin neurons are deleted by deletion of the LIM homeobox transcription factor Lmx1b revealed a deficit in thermoregulation that led to an increase in wakefulness due to increased movement to generate heat (162). Furthermore, in these animals there was an impaired arousal response to CO_2 reminiscent of sudden infant death syndrome (sect. VII). Serotonin 5-HT$_{1A}$ and 5-HT$_{1B}$ receptor knockout mice exhibited higher amounts of REM sleep during both the light and dark periods, consistent with the inhibitory role of serotonin in REM sleep control (sect. IV). In addition, a reduced rebound REM sleep response following restraint stress was observed in these animals (8, 130). Similarly, genetic ablation of the serotonin transporter in mice led to enhanced spontaneous REM sleep (19, 1427)

and a blunted REM sleep response to stress. Attenuation of restraint stress-induced enhancement of REM sleep in these animals was attributed to an overproduction of orexin, since it was reversed by blocking orexin receptors (1034). 5-HT$_{2A}$ receptor knockout mice showed a significant decrease in NREM sleep, with an increase in wake that was attributed to a decreased sensitivity of 5-HT$_{2B}$ receptors due to developmental alterations (1014), an important consideration in constitutive knockout studies. The homeostatic sleep response following 6 h of sleep deprivation was also attenuated in 5-HT$_{2A}$ mutant mice while changes in REM sleep were minimal. In *Drosophila*, mutations of 5-HT$_{1A}$ receptors resulted in short and fragmented sleep that was rescued by expressing the receptor in the mushroom bodies, a structure associated with learning and memory. On the other hand, 5-HT$_{1B}$ and 5-HT$_2$ receptor mutations did not impact sleep wake behavior in this species (1471).

C) NOREPINEPHRINE. The noradrenergic system modulates the expression of several immediate early genes in brain regions that receive projections from the LC. In rats, lesions of noradrenergic neurons of the LC using the neurotoxin 6-hydroxydopamine downregulated the expression of Fos, nerve growth factor-induced A (NGF-IA), and the phosphorylation of CREB protein, to levels similar to those observed during sleep (238). On the contrary, in transgenic mice with disinhibition of NE neurons by conditional expression of chlorotoxin (Cltx), a scorpion venom that partially blocks small-conductance chloride channels preventing inhibitory GABAergic and glycinergic input, the level of NGF-IA expression was increased (1104). In both of these conditions the sleep-wake behavior was not altered, but the wakefulness-associated gene expression patterns were changed, suggesting norepinephrine is important for coding for arousal-dependent gene expression that promotes synaptic plasticity.

D) HISTAMINE. Genetic studies suggest that histamine neurons are involved in the control of cognitive aspects of wakefulness (29). Mice with a knockout of the histamine synthesizing enzyme histamine decarboxylase (HDC) displayed reduced brain histamine, shortened sleep latencies, and a deficiency of wakefulness and exploration when mice are faced with the behavioral challenge of a novel environment (978). During the light period, sleep in these mice is fragmented whereas REM sleep increases (29). These mice show impaired cortical activation and a reduction in the differentiation of EEG signals seen between NREM sleep and wakefulness.

E) OREXINS. One of the most significant genetic contributions to sleep research is the identification of the gene and receptors of the orexin (hypocretin) peptide and their role in sleep. The orexins were discovered simultaneously by two groups in 1998 (290, 1101). The study of De Lecea (290)

reported the isolation of two novel peptides expressed at high levels in the hypothalamus using directional tag PCR subtraction technology. They named these peptides hypocretins based on their hypothalamic localization and weak homology to the secretin/incretin family of peptides. Simultaneously Sakurai and colleagues used a reverse pharmacology approach to identify ligands for the orphan G protein-coupled receptor HFGAN72 (now renamed OX_1R or Hcrtr1) and named the peptides orexin A and orexin B (from the Latin orexis = appetite) since their cell bodies were located within the lateral hypothalamic feeding area and because they stimulated feeding upon intracerebroventricular administration (1101). They also discovered a second receptor for these peptides: OX_2R or hcrt2. Shortly after, two laboratories independently linked the orexin system to narcolepsy (sect. VII). In dogs, the gene responsible for narcolepsy was mapped to the gene encoding orexin receptor 2 (hcrtr2) (727). On the other hand in mice, orexin peptide mutation was associated with narcoleptic behavior (214). In humans, narcolepsy results from the selective loss of orexin-producing neurons in lateral hypothalamus (475, 924, 999, 1284). The prominent reduction in orexin peptides in the cerebrospinal fluid is associated with the human leukocyte antigen haplotype DQB1*0602, leading to the suggestion that narcolepsy in humans is the result of an autoimmune attack on orexin-producing neurons (270, 520, 855) (see sect. VII). For a detailed discussion of the effects of orexin knockout/knockdown on wakefulness and REM sleep in rodents, see sections II, IV, and VII.

I) Orexin system in zebrafish. Orexins also play an important role in fish behavior (966). The orexin gene from zebrafish was cloned in 2004 (608). As in mammals, this gene is expressed in a localized manner within a cluster of hypothalamic cells and encodes for two peptides. The orexin-expressing neurons innervate several aminergic nuclei involved in sleep-wake regulation (608), and orexins are needed for promoting wakefulness as well as sleep consolidation. Overexpression of the orexin peptides in transgenic fish increases wakefulness (1024), while orexin knockout mutants display sleep fragmentation (1464). Studies in zebrafish orexin knockouts suggest that orexin regulates sleep-wake via regulating the pineal melatonin production (37). In *Drosophila melanogaster,* no genes with close homology to preproorexin have been found, but a group of cells which may serve a similar functional role to the orexins express the pigment dispersing factor (PDF). PDF released from central clock neurons promotes waking and consolidates sleep (977, 1157). Mutation in the PDF gene or its receptors, or ablation of PDF neurons leads to reduced activity at the beginning of the day, resulting in increased sleep and increased transitions from wake to sleep (1157).

F) DOPAMINE. In mice, knocking out the D_2 receptor gene leads to decreased wakefulness with a concomitant increase in NREM and REM sleep and an increase in NREM delta power. Sleep-wake durations were shorter during spontaneous sleep, but the homeostatic sleep response following 2, 4, or 6 h of sleep deprivation was not affected by the absence of the D_2 receptor (1032). Conversely, in the absence of dopamine uptake from the synapse in dopamine transporter (DAT) knockout mice, waking was increased and NREM sleep was reduced (1425). Similarly, flies with DAT mutation were short sleepers and lacked a homeostatic sleep response (679).

G) GABA. The receptors for the inhibitory neurotransmitter GABA are the major target of hypnotic agents. However, genetic manipulations of the GABAergic system have so far shown only minor effects on spontaneous sleep wake regulation. At the receptor level, the large number of possible subunit compositions seems to allow compensatory changes in other subunits in response to the absence of one subunit. Such a strong compensatory response reflects a resistance to change and possibly emphasizes the importance for normal functioning of the GABAergic system in the brain. Point mutations in $GABA_A$ receptor alpha1–3 subunits failed to alter sleep-wake pattern (656, 657, 1295), although gene linkage analysis indicates significant linkage between the β frequencies of the human EEG and $GABA_A$ receptor genes (1015). $GABA_A$ receptor alpha3 subunit knockout mice also showed no gross changes in the EEG spectral analysis during sleep and wake (1421). However, EEG power in the spindle frequency range (10–15 Hz) was significantly lower at NREM-REM transitions in mutants. The homeostatic sleep response was normal in these mice (1421). GABA receptors containing the delta subunit show a predominant extrasynaptic localization (936, 1249) and mediate nondesensitizing "tonic" inhibition, in contrast to "phasic" inhibition controlled by synaptic $GABA_A$ receptors (357). $GABA_A$ delta receptor subunit knockouts did not show any differences in EEG (1422). In one study, $GABA_A$ receptor beta3 subunit knockout mice showed no difference in 24-h baseline sleep-wake recordings compared with wild-type mice (689), although another group of researchers reported that NREM delta and REM sleep were significantly increased in knockouts (1424). Mice lacking $GABA_B$ receptor 1 or 2 had an altered distribution of sleep across the day, suggesting that $GABA_B$ receptors play a role in the diurnal regulation of sleep (1369).

3. Sleep factors

A) ADENOSINE. Considerable genetic evidence in mice and humans supports the role of adenosine in spontaneous sleep-wake control and in the homeostatic sleep response (discussed in sect. *IIIC)*. QTL studies in mice demonstrated that a genomic region containing the genes of two adenosine metabolizing enzymes, adenosine deaminase and *S*-adenosyl-homocysteine hydrolase, impact the rate at which sleep need accumulates during wakefulness (378). In humans, a homologous region in chromosome 20 containing an adenosine deaminase gene polymorphism at nucleotide

22 (coding DNA 22G→A, leading to a substitution of asparagine for aspartic acid at codon 8) influences sleep. Individuals with the G/A genotype reported fewer awakenings at night, spent longer in NREM sleep, and showed higher delta power during sleep than individuals with the G/G genotype (1059). The enzyme adenosine kinase, responsible for conversion of adenosine to adenosine monophosphate, is also important in the regulation of adenosine metabolism and sleep-wake behavior. A transgenic mouse model, *Adk-tg*, with enhanced constitutive expression and activity of cytoplasmic adenosine kinase, had reduced adenosine tone, suggested to be due to enhanced intracellular conversion of adenosine to adenosine monophosphate, which in turn facilitates adenosine uptake into the cell resulting in lower levels of extracellular adenosine (358). A recent study of these mice (960) showed a significant reduction of EEG power at low frequencies in all vigilance states and in theta activity (6.25–11 Hz) in REM sleep and waking. These mice spent significantly less time in NREM and REM sleep compared with wild-type mice. The homeostatic delta power response following 6 h of sleep deprivation was attenuated compared with the wild-type mice (960).

I) Adenosine receptor knockouts and polymorphisms. Both A_1 and A_{2A} adenosine receptors are implicated in mediating the sleep-inducing effects of adenosine. Studies in receptor knockout mice highlight the possible confounds arising from developmental compensations for the absence of a specific gene. For example, despite ample physiological, pharmacological, and electrophysiological evidence for the role of A_1 adenosine receptor in sleep wake regulation, constitutive A_1 receptor knockout mice failed to show any changes in the sleep patterns and EEG parameters under baseline conditions or following sleep deprivation (1214). However, in the absence of any developmental compensatory changes, mice with a conditional A_1 receptor deletion in forebrain and brain stem after 6–8 wk of age showed a decreased homeostatic sleep response after sleep disruption (99). In A_{2A} receptor knockout mice, the homeostatic sleep response was attenuated (485). A comparative study of the A_1 and A_{2A} receptor knockout mice showed that the wake-promoting effect of caffeine was absent only in A_{2A} knockout mice but not in A_1 knockouts, suggesting that A_{2A} has a more prominent role in sleep-wake regulation (529). However, in light of the pronounced A_{2A} receptor-mediated locomotor effects of caffeine (338, 1460, 1470), the reported decrease in wakefulness in A_{2A} but not A_1 knockout mice in response to caffeine, needs careful interpretation. In humans, self-rated, caffeine-sensitive individuals showed impaired performance on a psychomotor vigilance task after one night without sleep. Individuals with the lowest sensitivity to caffeine were least sensitive to the detrimental effects of sleep debt (1058). Further investigations reported that a distinct polymorphism within the A_{2A} receptor gene (c.1083T>C) determines the caffeine responsiveness to sleep in humans (1060). Together, these genetic studies strongly support the importance of adenosinergic mechanisms in sleep-wake regulation.

B) NITRIC OXIDE. As discussed in other sections of this review, nitric oxide produced by nNOS or iNOS plays an important role in several aspects of sleep-wake control. Mice lacking nNOS showed a significant reduction in REM sleep during 24 h baseline sleep recording. In contrast, iNOS knockout mice showed a significant increase in REM sleep during 24 h baseline sleep and a decrease in NREM sleep during the dark period (218). Consistent with these observations are the results from studies performed to evaluate the effect of selective inhibitors of nNOS and iNOS on recovery NREM and REM sleep that follows prolonged sleep deprivation (589, 593). In rats, in vivo microdialysis of specific inhibitors of iNOS, 1400W, prevented NREM recovery, while an inhibitor of nNOS, L-N-propyl-arginine, decreased REM recovery but did not affect NREM recovery (589, 593).

C) CYTOKINES AND OTHER HUMORAL FACTORS. Cytokines involved in host defense mechanisms have been implicated as sleep factors (see sect. IIIC). The effect of the loss of function of many of these cytokines on sleep-wake pattern has been studied using specific gene knockout mouse models. Mice lacking the IL-1β receptor spent less time in NREM sleep during the light period (354), whereas IL-6-deficient mice spent 30% more time in REM sleep during 24 h of baseline without any significant change in NREM sleep or wakefulness (896). In response to SD, IL-6 knockout mice took much longer to recover from the sleep loss, suggesting a role for IL-6 in the dynamics of responses to SD. Like IL-1β receptor knockout mice, the TNF receptor 1 knockout mice also sleep less during the light period (353). The levels of TNF mRNA and protein increase during the light periods in rats suggesting their involvement in sleep (135, 368). TNF and lymphotoxin-α are the ligands for two TNF receptors (TNFR1, 55 kDa; TNFR2, 75 kDa in size). In mice deficient in both of the ligands, a 15% decrease in REM sleep during the baseline light period was observed. A similar reduction in REM sleep is also observed in TNFR2 knockout mice (295). The slow wave parameters of the recovery sleep that followed 6 h of sleep deprivation varied in different mice. In the double ligand knockout and TNFR2 knockout mice, the SWA activity selectively increased in the 2.75–4.0 Hz range, whereas in TNFR1-deficient mice, the intensity of low range SWA (0.75–2.5 Hz) increased during recovery sleep (295). In mice lacking both IL-1β type 1 receptor and TNFR1, the power spectra of the NREM sleep EEG showed differences compared with wild-type mice for 24 h. Following sleep deprivation, the increase in delta power during NREM sleep of IL-1R1/TNFR1 knockout mice was of greater magnitude and of longer duration than that observed in control mice (69). These genetic experiments suggest a role for these cytokines in normal sleep-wake regulation in addition to their more well-known role in the response to infection.

D) GROWTH HORMONE AND GROWTH HORMONE RELEASING HORMONE. Growth hormone (GH) and GH releasing hormone (GHRH) are additional factors associated with sleep. Rats with mutation of the GH gene exhibit stunted growth and a higher expression of GHRH in the hypothalamus (995) as well as higher NREM sleep and decreased REM sleep during the light period. While the homeostatic NREM sleep response was normal in these rats, the NREM delta activity was not enhanced during the recovery sleep that follows sleep deprivation (995). On the other hand, dwarf rats (207) show reduced responsiveness to GHRH and thus exhibit moderate growth retardation and decreased plasma and pituitary GH (207). The dwarf rats show decreased spontaneous sleep compared with wild-type controls (942). Decreased spontaneous sleep was also reported for a mouse model with a point mutation in GHRH receptor (941). Thus genetic studies support a role for the GH/GHRH system in the control of sleep.

4. Transcription factors

Transcription factors, a large class of DNA binding proteins, respond to the transduced intracellular signals originating from membrane proteins (receptors, ion channels) and induce the expression of specific target gene(s) that code for different physiological processes.

A) FOS. One of the first, and most commonly studied transcription factors with respect to the sleep-wake cycle, is the immediate early gene Fos (243). Many studies have investigated the distribution of Fos protein in specific populations of neurons to determine their activity during spontaneous wake or sleep or in sleep homeostasis (78, 235–237, 440, 444, 842, 930, 1010, 1011, 1162, 1169–1171, 1459). Although lacking in temporal resolution, this technique has been extremely useful in identifying the location and neuronal phenotype of neurons involved in sleep-wake control. However, it should be noted that typically only a small subset of any particular neuronal subpopulation is labeled with Fos in any particular behavioral state (243). Fos expression primarily reflects intracellular calcium increases rather than neuronal firing per se (664). Fos controls the expression of other genes, some of which are listed below and may be involved in functions related to sleep-wakefulness control such as synaptic plasticity (243). Fos knockout mice have increased wakefulness with a concomitant reduction in NREM sleep, whereas REM sleep is not affected (1167). Knockout of another member of the Fos family, fosB, caused decreased REM sleep without other changes in sleep or wake (1167).

B) cAMP RESPONSE ELEMENT-BINDING PROTEIN. Another stimulus-induced transcription factor, the cAMP responsive element binding protein (CREB), is implicated in memory formation and sleep in both flies (496) and rodents (442). Flies with mutations resulting in increased cAMP (resulting in increased CREB activity) rested significantly less, whereas

mutations that abolish CREB activity rested more with increased recovery sleep (496). Similarly, mice lacking the alpha and delta isoforms of CREB had reduced time spent awake and more NREM sleep (442).

C) TRANSCRIPTION FACTORS ASSOCIATED WITH THE CIRCADIAN PACEMAKER. Several transcription factors and inhibitors of transcription factors involved in circadian behavior also directly impact the sleep EEG parameters associated with sleep homeostasis (379). Homeostatic sleep regulation is considered independent of the circadian regulation since it is intact in animals with lesions of the SCN, the circadian pacemaker (860, 1293, 1305). However, in animals with intact SCN, several transcription factors originally recognized as circadian factors also impact homeostatic sleep parameters, as described next.

I) The neuronal Per-Arnt-Sim-type (NPAS) and cryptochromes. The NPAS domain protein 2 combines sensor and effector functions by sensing the redox state of the cell (1086) and regulating the transcription of metabolic genes such as lactose dehydrogenase1 (ldh1) and the period gene (per-2 gene), the latter of which is also implicated in sleep homeostasis. Sleep characteristics are altered in the absence of Npas-2 as demonstrated by the study of NPAS2-GENE knockout mice. These mice showed a decrease in NREM sleep time, even after periods of sleep deprivation (380). During NREM sleep, the spindle activity was reduced and the EEG activity within the delta range was shifted to faster frequencies. Sleep is also altered in mice lacking cryptochromes (Cry), transcriptional regulators integral to circadian oscillations. Cry 1 and 2 knockout mice exhibit longer bouts of NREM sleep and higher EEG delta power during NREM sleep (1426). In these mutants, the absence of transcriptional inhibition of Clock and NPAS2 proteins is suggested to cause the increased sleep duration. In contrast, in clock gene knockout mice, NREM sleep durations are decreased, as was observed in NPAS-2 gene knockout mice (912). The deletion of yet another transcription factor associated with circadian rhythmicity, the albumin D-binding protein (Dbp), results in decreased sleep consolidation and NREM sleep delta power (381).

Regulators of circadian rhythms can impact sleep timing, duration, and intensity. The transcriptional factor NPAS2 regulates the expression of the Period proteins, per1 and per2. Per1 and per2 mutant mice have altered circadian rhythmicity (18), but sleep homeostasis is unaltered (654). In humans, per2 gene mutations were shown to contribute to 4 h advance of the sleep/wake rhythm in some cases of familial advanced sleep-phase syndrome (1296). A recent report further confirmed the role of Per proteins in sleep timing in relation to the light-dark cycle. A polymorphism in the Per3 gene has been associated with morning/evening sleep-wake preferences. Individuals with a 5-repeat allele ($per3^{5/5}$) show increases in alpha activity in REM sleep,

theta/alpha activity during wakefulness, and slow wave activity in NREM sleep (310). Sleep deprivation results in greater cognitive deficits, as demonstrated by brain fMRI-assessed responses to executive tasks compared with individuals with the wild-type allele (310). In one family, a mutation in the casein kinase 1δ gene which interacts with the Per protein, and a per mutation in another family, were associated with familial advanced sleep phase syndrome (1296, 1447). Another protein, Dec2, suggested to repress the expression of Clock/Bmal1, was shown to regulate sleep time in humans. Point mutations in the *dec2* gene were identified in a family of short sleepers (6 h sleep) (487). These reports in humans collectively suggest interactions between regulations of circadian rhythms and sleep timing, duration, and intensity.

5. Ion channels

A) POTASSIUM CHANNELS. Voltage-dependent potassium channels (Kv channels). The Kv channels are activated by depolarization and are present in a wide range of tissues. They are composed of four alpha units that form a pore and four beta units closely associated with the alpha units, forming an octameric channel. Nine Kv channel alpha subunit families (Kv1–9) have been described (250). Genetic studies have shown strong associations of some of these Kv channels with sleep-wake regulation.

I) The voltage-gated potassium channel, Shaker. This channel has been shown to play a major role in sleep in *Drosophila melanogaster* (231). Shaker mutants had reduced sleep and were resistant to the effects of sleep deprivation (231). Further studies in *Drosophila* identified a novel glycosylphosphatidyl-inositol-anchored protein/gene, which as indicated by the name, SLEEPLESS (SSS), prevents sleep (650) and regulates the function of Shaker (1437). Flies carrying a defective *shaker* gene, the null allele minisleep (*Shaker^{mns}*), or other null alleles of Shaker, are short sleepers (3–4 h/day), while the wild-type controls sleep 8–14 h/day (231). Similarly, loss-of-function mutations in another gene, *Hyperkinetic*, that codes for the regulatory (beta) subunit of the Shaker channel, results in reduced sleep (170). Thus there is ample evidence in flies demonstrating the importance of voltage-gated potassium channels in normal sleep-wake regulation. In mice, the Kv1 alpha subunit family of potassium channels is closely related to Shaker in flies. A null mutation in the Kv1.2 gene, *Kcna2*, in mice, when homozygous, generates seizures in pups after P17 and the pups die at a young age (postnatal day 28). However, sleep measured at P17 shows significantly less NREM sleep (315). The sleep studies in these mutant mice, while limited to young ages, are nevertheless indicative of the importance of the Kv1.2 channels in sleep regulation.

II) Delayed rectifier Kv3.1 and Kv3.3 channels. Subunits of fast-activating/deactivating, high-threshold voltage-gated potassium channels, encoded by the genes *Kcnc1* and *Kcnc3*, are widely expressed in several brain regions including the thalamus, basal ganglia, and cerebellum, areas implicated in the control and modulation of arousal states and motor activity (1083). Although Kv3.1 and Kv3.3 subunits are expressed throughout the brain, their expression is restricted to distinct neuronal subpopulations (204, 1146, 1396, 1397). In neocortex, thalamus, hippocampus, and striatum, Kv3-type channels are found in GABAergic cells that also express the calcium-binding protein parvalbumin (PV), a marker for fast-spiking neurons. Kv3-type channels are involved in the rapid repolarization of the action potential, and their presence in neurons correlates with narrow action potentials, fast afterhyperpolarization, and high-frequency firing. Single Kv3.1 mutation or double Kv3.1/Kv3.3 mutations led to an increase in action potential duration of 20 and 60%, respectively (349). Mutation of these genes showed profound effects on sleep-wake patterns in mice. Mice with a knockout of Kv3.1 show increased gamma oscillations and markedly reduced delta oscillations (566). Mice with double mutations display severe sleep loss (40% decrease in the light period and 22% decrease in the dark period) as a result of unstable slow-wave sleep (349, 567). Absence of these two gene products led to a 70% reduction in the cortical spectral power at frequencies <15 Hz. In addition, the number of sleep spindles in vivo as well as rhythmic rebound firing of thalamic reticular neurons in vitro is diminished in double mutant mice (349). The mice show a 70% reduction in the absolute power in the delta band and fail to show a homeostatic sleep response following 6 h of acute SD (349). It was suggested that the Kv3.1 and Kv3.3 channels in the GABAergic thalamic reticular neurons play an important role in the thalamocortical network in generating oscillations typical for sleep (567).

Another member of the voltage-gated potassium channel family, Kv3.2, is also expressed abundantly in the thalamus, neocortex, and hippocampus and is moderately expressed in medial septum, LC, and basal ganglia (1082, 1397). Deletion of the Kv3.2 gene in mice results in reduced power in the NREM EEG frequency range 3.25–6 Hz, suggested to be a consequence of decreased efficacy of GABAergic interneurons that express Kv3.2 in cortex. Unlike the deletion of Kv3.1 subtype channels which increases wake EEG at gamma frequencies (20–60 Hz)(566), the Kv3.2 deletions do not affect waking EEG parameters (1382).

III) Potassium-selective leak channels. Potassium-selective leak channels possess two pore-forming domains in each subunit (431). The leak currents generated by these channels (also known as resting or background conductances) control the resting membrane potential and input conductance, thereby influencing the excitability of the neurons (431). As described in section II, many neurotransmitters excite neurons by inhibition of resting K^+ leak currents. This is crucial to the regulation of "state-switching" in cortical and thalamic neurons. Recently, one such acid-sensi-

tive and anesthetic activated, two-pore domain potassium channel subtype, TASK-3, was shown to be involved in the regulation of cortical type II theta oscillation (also known as arousal theta) in the frequency range 4–9 Hz (965). Mice with TASK-3 gene knockout showed an absence of such type II theta oscillations. They displayed a slower progression into sleep (increased sleep latency) during spontaneous sleep in the lights-on period. In these mice sleep was also fragmented, with a higher number but shorter duration of sleep episodes.

B) CALCIUM CHANNELS. Genetic evidence suggests that the low-threshold, voltage-activated, T-type calcium channels are involved in the regulation of sleep and particularly in sleep rhythms. Low-threshold calcium channels are crucial for shaping subthreshold membrane fluctuations and thereby contribute to such behaviors as rebound burst firing (740) and rhythmic oscillation (64, 458). The α_{1G} subunit of T-type calcium channels is widely expressed in the brain, including thalamocortical neurons, and thalamic reticular neurons and cortex (1269). Both constitutive and targeted deletions of the $\alpha 1G$ ($Ca_v3.1$) subunit of T-type channels have been studied in the context of sleep regulation. Conflicting observations in sleep parameters were reported. In one study, power spectral analysis showed that the power of low frequencies (2–6.5 Hz) in NREM sleep was significantly reduced compared with their wild-type littermates (695). Another study showed that in mice with either a α_{1G} constitutive knockout or a localized thalamic specific knockout, the cortical EEG delta power during NREM sleep was increased (32). These mice have difficulty in initiating and maintaining sleep. The differences in the observations may reflect differences in the manner the knockout mice were constructed.

In the dendrites of thalamic reticular neurons, the calcium-dependent small-conductance (SK)-type K^+ (SK2, Kcnn2) channels and the T-type calcium channels act in concert with the sarco/endoplasmic reticulum calcium-ATPases (SERCAs) to influence the characteristic frequency bands of NREM sleep (55, 64). In SK2−/− knockout mice NREM sleep is fragmented, with more frequent awakenings, indicative of decreased sleep depth (266). Consistent with this behavior, the EEG spectral profile showed a fourfold reduction in the delta (1–4 Hz) frequency range and a more than threefold reduction in the sleep spindle (10–15 Hz) band. During waking and REM sleep, a pronounced reduction was observed in the 10-Hz range, i.e., a slowing of EEG theta oscillations.

6. Genes implicated in sleep functions

A) SYNAPTIC PLASTICITY, LEARNING, AND MEMORY. Cellular functions such as transcription, cell signaling, and synaptic plasticity are integral to learning and memory. Alteration of these functions also affects sleep-wake regulation. Mutations in many of the genes associated with the molecular cascades underlying learning and memory have been shown to alter sleep-wake cycles. On the other hand, alterations in sleep-wake patterns impact learning and memory (see sect. V) (503).

One signaling pathway implicated in both processes involves the signaling molecule cAMP and cAMP-dependent protein kinase A (1350). Activation of the cAMP signaling pathway promotes waking. In flies, the expression of cAMP and protein kinase A in the mushroom bodies, an important region for memory formation (488), regulates sleep (568, 1006). In transgenic mice, with a dominant negative mutation in the regulatory subunit of protein kinase A in neurons, NREM sleep is fragmented with increased NREM delta activity and reduced spindle amplitude, whereas REM sleep is increased, suggesting protein kinase A is involved in sleep-wake regulation (491). cAMP affects gene expression via the cAMP response element binding protein (CREB). Mice lacking CREB have reduced LTP and memory formation and exhibit shorter wake bouts, whereas NREM bouts are longer (441, 442). These studies are broadly consistent with the idea that synaptic potentiation predominates during waking as discussed in section III, in the context of the synaptic homeostasis theory of sleep.

Another protein involved in synaptic plasticity that has been investigated in the context of sleep is Homer1a. The Homer proteins are a family of proteins broadly expressed in the brain where they serve as molecular scaffolds at synapses. Increased expression of Homer 1a reduces glutamate-induced intracellular calcium release and thus downregulates synapse formation (1103, 1432). All the homer proteins are expressed constitutively except for Homer1a, an immediate early gene originally isolated as a neural activity-regulated gene product from seizure-stimulated rat hippocampus. In rodents, the expression of Homer1a is modulated during sleep and wakefulness and is highly upregulated during sleep deprivation (233, 914). Further evidence for sleep deprivation-induced upregulation of Homer1a comes from transcriptome profiling of inbred mouse strains where Homer1a is consistently increased in all strains following sleep deprivation (795). QTL analysis showed a significant association of Homer1a with sleep-wake regulation and sleep homeostasis (771).

A recent study (425) monitored the expression of synaptic genes over the course of the normal sleep-wake cycle, as well as following periods of sleep deprivation in *Drosophila*. The expression of synaptic proteins decreased in a sleep-dependent manner (425). The *Drosophila* Fragile X mental retardation gene (*dfmr*) is one synaptic plasticity related gene that has been shown to regulate sleep need, although the exact mechanism is unknown (171). This gene codes for a protein (dFMRP) that is present in dendritic spines. The expression of this gene is high during development when sleep is higher and synaptic plasticity is high. Increased

expression of dFMRP, even if restricted to mushroom bodies, decreases daily sleep and decreased expression increases sleep. Both gain and loss of dFRMP expression result in loss of sleep homeostasis (171).

B) SLEEP AND ENERGY. Brain energy use varies between sleep and wakefulness. During waking, higher levels of energy are consumed compared with sleep (see sect. III*D*). Gene expression studies have shown that increased ATP use during waking leads to the upregulation of enzymes involved in the synthesis of ATP by oxidative phosphorylation. Five, multsubunit enzyme complexes, complexes I to V (Cox I-V) constitute the mitochondrial oxidative phosphorylation system, and enzymes belonging to each complex are upregulated during waking, indicating an increased need for ATP synthesis. For example, the expression of Nadh2, cytochrome *c* oxidase (CoxI), Cox4, and Atp5a genes increase during sleep deprivation in mammalian cortex (233, 239, 240, 242). A concurrent increase in the activity of cytochrome *c* oxidase has been reported in mice and rats (919, 920). The expression of mitochondrial uncoupler protein 2 is also increased during sleep deprivation (245). The nuclear transcription factors Nrf1 and 2 (known as nuclear respiratory factors) involved in the transcription of the components of oxidative phosphorylation are also upregulated during sleep deprivation (919). The essential nature of the genes coding for oxidative phosphorylation prevents any studies using knockout mice, but conditional knockouts may prove useful in further examining the effect of these genes in the regulation of sleep and wakefulness.

B. Proteomic Studies

Changes in gene expression are suggestive of potential cellular alterations associated with different vigilance states. However, the complexity of the regulation of downstream processes such as translation of mRNA into protein, post-translational modifications of translated proteins, and protein-protein interactions prevents a direct assessment of the effect of gene expression on physiological processes. Since proteins are the ultimate players capable of influencing vigilance states, it is important to understand their regulation. Proteomics is an experimental approach to examine the proteins involved in the control of biological processes and pathways. The proteome indicates the quantitative expression profile of a cell, an organism, or a tissue under defined conditions. In contrast to the temporally constant genome, the proteome is dependent on intracellular and extracellular parameters. Thus the analysis of a proteome represents an important supplement to the genome analysis.

The use of proteomic approaches for investigating the regulation of vigilance states is relatively new. As the efficiency of proteomic methodology is being refined for increased sensitivity and inclusion of a wider range of proteins, a few attempts have already been made to explore overall protein changes during sleep-wake cycle or during prolonged waking (75, 234, 986, 1008, 1345, 1346). Most of these studies in the cortex, BF, or hippocampus of rat brain have compared protein profiles during sleep with those during prolonged sleep deprivation. So far, only two studies have examined protein changes after 10 min of spontaneous sleep or wake (1345, 1346), and no studies have examined proteomic changes selective to REM sleep. Major challenges for such studies originate from the short durations of sleep-wake episodes in rodents, especially REM sleep. During spontaneous sleep-wakefulness and prolonged waking, the major groups of proteins in the rat BF and cerebral cortex that showed alterations were associated with the following four functions: *1*) synaptic plasticity, e.g., SNAP25, Amphyphysin, and vesicular *N*-ethylmaleimide fusion (NSF) protein; *2*) the cytoskeleton, e.g., RhoB and GTP binding protein rab3D, Cofilin; and *3*) cellular energy metabolism, e.g., creatine kinase, NADH dehydrogenase, pyruvate dehydrogenase, glutathione synthase, and glyceradehyde-3-phosphate dehydrogenase (75, 1345). Surface-enhanced laser desorption-ionization (SELDI) studies identified increases in hemoglobin alpha 1/2 and beta as well as cytochrome *c* in rat cerebral cortex (234). *4*) Cellular stress responses, as discussed next.

Taking a lead from the wide-spectrum genomic and proteomic screening, one group of proteins, the heat shock/chaperone proteins, has been studied in more detail. Short periods of sleep deprivation (3–12 h) result in an increase in these proteins that are involved in preventing misfolding of proteins in the endoplasmic reticulum (153, 909). This unfolded protein response is considered to be a protective action that counteracts the cellular stress associated with sleep deprivation (153). The mRNA level of one such protein, the immunoglobulin binding protein, BiP, the most abundant protein in the endoplasmic reticulum (also known as glucose regulated protein 78, GRP78 or heat shock protein 5A, HSP5A) increases with prolonged wakefulness (229, 233, 772, 795, 1275). BiP binds to the hydrophobic domains of the nascent peptides and helps to prevent misfolding while the rest of the protein is being synthesized (423). In *Drosophila*, BiP levels regulate the quantity of recovery sleep (908). Transgenic animals that overexpressed BiP displayed increased recovery sleep following deprivation compared with animals that had reduced BiP levels.

C. Summary

A variety of genes and proteins have been associated with sleep and wakefulness by means of genetic and proteomic studies. Comparative studies have underscored the universal nature of sleep-wake regulation in different species. Perhaps unsurprisingly, mutations or knockouts of genes encoding ion channels or proteins involved in neurotransmitter release/uptake/transduction exert major effects on the

sleep-wake cycle. In addition, genetic techniques have been instrumental in the identification of novel peptide neurotransmitters controlling the sleep-wake cycle such as the orexins, and their connections to human sleep physiology and pathophysiology. Furthermore, genetic and proteomic studies have provided important clues as to sleep function by identifying the major classes of genes and proteins that vary according to the sleep-wake cycle, in particular those involved in synaptic plasticity, cytoskeletal function, and cellular stress and energy regulation.

VII. SLEEP PATHOLOGY AND TREATMENT

In this section we summarize current knowledge of disorders of wakefulness and sleep and how they relate to the brain mechanisms of waking as well as NREM and REM sleep described in previous sections. Although epilepsy can be considered a disorder of wakefulness, this large topic is beyond the scope of this review (for more information, see Steriade and McCarley, Ref. 1228).

A. Coma

Profound changes in wakefulness and consciousness occur in patients with brain injury resulting in comatose, vegetative, or minimally conscious states. The EEG shows variable changes depending on the type and stage of coma, with alpha/theta rhythms, spindles, and triphasic/delta waves most common (139, 602). In general, faster rhythms typical of wakefulness are diminished and unresponsive to external stimuli.

In those coma patients who do not have widespread, diffuse loss of forebrain neurons, coma is normally associated with loss of activity and neurons at the origin or along the pathways of the ARAS, as described in section II. In the upper brain stem, damage is observed along the midline at the origin of the ARAS encompassing raphe nuclei, LC, LDT, parabrachial nucleus, and PnO (980). In rodents, cell-specific lesions of parabrachial but not neighboring brain stem neurons caused a comalike state (see sect. II*B*), suggesting that this nucleus may be particularly important in maintaining wakefulness (397). Glutamatergic neurons in this region were shown to provide a major input to the BF (397). Surprisingly, a cat model of unconsciousness induced by cerebral concussion reported increased glucose utilization in the dorsomedial tegmentum adjacent to the VTG, suggesting that neurons in this dorsomedial area were activated (486). Infusions of carbachol in this area produced behavioral suppression (486), similar to cat models of REM sleep utilizing this pharmacological agent (see sect. IV). Along the ascending dorsal pathway, coma is observed following bilateral lesions of the regions of the thalamus supplied by the paramedian artery, i.e., dorsomedial nuclei and intralaminar centromedial, parafascicular and cen-

trolateral nuclei (1137). Surprisingly, in rodents, extensive lesions of the thalamus failed to have pronounced effects on the EEG (397).

In some brain-damaged patients, imaging studies have indicated appropriate brain responsiveness to external commands or stimuli, indicating some preservation of function (1135, 1136). In these patients, partial restoration of function has been observed following deep brain stimulation of the central thalamus, administration of dopaminergic agents, or administration of the sleep aid and GABAergic receptor modulator zolpidem (Ambien). It has recently been postulated (1135) that all of these interventions act by enhancing activity in nonspecific thalamic projections to the cortex either directly (deep brain stimulation) or by reducing the inhibitory input from the basal ganglia (dopaminergic agents, zolpidem) to nonspecific thalamic nuclei. The paradoxical alerting effect of zolpidem may be due to a preferential inhibition of globus pallidus neurons, which project to the thalamus and are potently inhibited by zolpidem (220, 1135). The strong wake-promoting effects of the dopaminergic system and the weaker arousal effects of adenosine A_{2A} antagonists in normal humans/animals may also be explained by such interactions of the basal ganglia and intralaminar thalamus.

Coma in humans is rarely associated with damage to the final node of the ventral pathway, the BF, presumably because its blood supply arises from multiple cerebral arteries so it is less susceptible to stroke. However, recent studies in animals suggest that extensive cell-specific lesions of the BF can also result in a comalike state (397, 611).

B. Insomnia

Insomnia, defined as insufficient quantity or quality of sleep, is the most prevalent sleep disorder. Approximately 50% of adults complain of occasional insomnia, and 10–15% of chronic insomnia, persisting for at least 1 mo (892). Insomnia can involve difficulty falling asleep, staying asleep, or poor quality of sleep. Consequences of insomnia including daytime sleepiness, lack of energy, and cognitive impairment (835). Insomnia may even precipitate or accompany the development of psychiatric disorders (913). Insomnia is classified into two types: comorbid, with other psychological and/or physical pathologies; and primary, existing independent of other conditions (931).

1. Animal models of insomnia

Clinical and animal studies have employed a variety of sleep disruption techniques to mimic the symptoms of various types of insomnia (835). Other animal models investigate the neural mechanisms causing insomnia (1061). Stress-related models include classical fear conditioning with foot shock, cage change, or disturbing stimuli such as noise,

unpleasant odors, cold, and pain (987, 1061). Some forms of insomnia may be due to hyperarousal (121, 929). Thus insomnia may also be induced pharmacologically in animals through manipulations of the vigilance-state circuitry described in earlier sections, e.g., through serotonergic synthesis inhibition by parachlorophenylalanine (PCPA) (899), adenosine receptor antagonism with caffeine (384), or enhancement of histaminergic (1044), dopaminergic (129), or orexinergic tone (1024, 1073). Genetic models that involve manipulation of circadian clock genes may also be regarded as insomnia models (see sect. VI). A rare autosomal dominant genetic disorder, fatal familial insomnia, involves a gene mutation of the prion protein gene *prnp* (878). Transgenic mice with a mutation of the *prnp* gene exhibit very fragmented sleep, as well as an exaggerated response to sleep deprivation (313, 1294) correlating with damage to the thalamic branch of the ARAS.

2. Possible neural circuits mediating insomnia

Recent preclinical investigations have begun to unravel the neural mechanisms by which cognitive, emotional, and sleep neural circuitry may interact to generate insomnia (186, 1116). For example, the sleep-promoting VLPO as well as the wake-promoting orexinergic zone of the lateral hypothalamus receive projections from mnemonic and emotion-related regions such as the infralimbic cortex, lateral septum, bed nucleus of stria terminalis, amygdala (central nucleus), and ventral subiculum (222, 1102, 1466). In an insomnia model involving cage change as a stressor, Fos protein was expressed in arousal, autonomic, and surprisingly, also in sleep-promoting regions, suggesting coactivation of arousal and sleep systems (186). Consequently, it was suggested that, in contrast to development of sleep-promoting compounds, attenuation of arousal systems may be a more effective approach to treat insomnia.

3. Imaging of insomnia

Functional imaging studies in humans have described brain regions with altered activity in insomnia (303, 304, 929). SPECT and PET studies have revealed that, during transition into NREM sleep in the insomniac, the normal reduction of glucose consumption is attenuated in the anterior cingulate cortex, the medial prefrontal cortex (mPFC), and limbic/arousal systems. Furthermore, during wakefulness, decreased glucose metabolism was evident in the cortex, thalamus, hypothalamus, and reticular formation relative to controls (303, 304, 929).

4. Insomnia treatment

Pharmacological treatment of insomnia usually involves sleep aids acting as agonists of the $\alpha1$ subunit of the GABA receptor, such as benzodiazepines and the "Z" drugs (zolpidem, zalpelon, zopiclone) (329) which potentiate the ac-

tion of sleep-promoting GABAergic neurons. Newer compounds to promote sleep that do not primarily involve manipulation of GABAergic systems have been recently introduced, such as the melatonin receptor agonist ramelteon (964); ritanserin, an antagonist of both 5-HT_{2A} and 5-HT_{2C} receptors (1372); and antidepressants such as trazadone (848) and agomelatine, a unique compound that acts as both a serotonergic 5-HT_{2C} antagonist and melatonin receptor agonist (879). A variety of other compounds used to treat insomnia antagonize histaminergic (676) and orexinergic wake-promoting nuclei. In preliminary studies, dual orexin receptor antagonists, almorexant and MK4305, were shown to enhance both NREM and REM sleep and reduce wakefulness in animals, healthy humans, and insomniacs (140, 505).

C. Sleep Apnea

In sleep apnea, the patient stops breathing (the apneic moment) during sleep, leading to blood oxygen desaturation (hypoxia), as well as an elevation of carbon dioxide levels (hypercarbia, also known as hypercapnia). Sleep apneas are divided into three categories: central, obstructive, and complex (a combination of obstructive and central sleep apneas). Central sleep apnea involves dysfunction of the central respiratory control centers in the brain (1401). Obstructive sleep apnea (OSA) affects nearly 7% of the general population (1468) and is characterized by episodic cessation in breathing during sleep due to closure of the airway, of at least 10 s in length, and usually accompanied by hypoxia and hypercarbia (301, 1401). The apneic moment is usually terminated by a slight arousal, as well as an increase in sympathetic tone, as airway patency is reestablished. OSA diagnostic criteria include a rate of 5 or more apneic episodes per hour, and the most severe cases may experience upwards of 70–80 moments per hour. The sleep profile of an OSA patient includes sleep fragmentation and decreased prevalence of both deep stage NREM and REM sleep.

1. Mechanism of apnea

A reduction of activity in motoneurons innervating the upper airway during sleep is the cause of sleep apnea, occurring during both NREM and REM sleep. As described in section IV, a reduction in the activity of motoneurons occurs during NREM sleep and progresses to complete silence during tonic periods of REM sleep so that the upper airway is more susceptible to collapse during inhalation in susceptible individuals (369, 614, 760, 852, 948, 1189). Respiratory motoneurons follow a similar pattern, with expiratory pharyngeal and upper airway (hypoglossal, XII) motoneurons being the most strongly suppressed whilst phrenic motoneurons that drive the diaphragm are the least affected (398). Following the apneic moment, the upper airway reflex occurs, during which dilator muscles activate, reestablishing the patency of the airway (1401).

2. Cognitive consequences of apnea-induced sleep disruption

The abnormal sleep profile of OSA patients leads to daytime sleepiness, which is often comorbid with impaired cognitive function (626). Deficits in executive function among apneic patients have been assumed to be related to prefrontal lobe dysfunction caused by intermittent hypoxia (IH) (88). Consistent with this idea, rats exposed to IH exhibited spatial learning and memory impairments (437). However, sleep disruption itself can affect both "lower" level processes, such as arousal, as well as "higher" cognitive processes, such as memory and executive function (835). Thus the extent of behavioral impairment in OSA patients correlates with both the degree of hypoxemia and with the degree of fragmentation (87). Animal models mimicking the SF that occurs during OSA (see sect. V) revealed increased sleepiness and cognitive decrements in attention and working memory-tasks (844, 1273) as well as impaired hippocampal LTP (1273). Thus one cannot assume that the deficits in higher cognitive function observed in apneic patients are due solely, or even primarily, to hypoxemia during sleep. In fact, a functional imaging study suggested that working memory deficits exhibited in patients with sleep apnea may be due to the sleep fragmentation, not nocturnal hypoxia (1288).

3. Pathological features of OSA

Apneic episodes during OSA are accompanied by abnormal blood gas levels of oxygen (hypoxia) and carbon dioxide (hypercarbia). Animal models of intermittent hypoxia revealed cognitive deficits, oxidative stress, an increase of gene products related to apoptosis, and a decreased number or functional activity of catecholaminergic and cholinergic BF neurons (301, 835). However, whether apoptosis actually occurs is controversial (301). Clinical and animal studies have determined that exposure to intermittent hypoxia promotes reactive oxygen species, and in turn oxidative stress (301, 693). Reactive oxygen species formation has been shown to lead to physiological pathology, including cardiovascular morbidity, sympathetic activation, and hypertension. Accordingly, OSA has been confirmed to be a risk factor for stroke, atherosclerosis, heart attack, and hypertension (301, 1156).

4. Brain imaging of OSA patients

Investigations of brain anatomical abnormalities in OSA patients have provided some evidence of structural injury. MRI studies have reported gray matter morphological abnormalities in the frontal, anterior cingulate, and parietal cortices, mammillary bodies, temporal lobe, hippocampus, and cerebellum (678, 769). Most recently, diffusion tensor imaging revealed extensive abnormalities in white matter, including the corpus callosum, cingulum bundle, fornix, cerebellar peduncle, as well as within structures such as the deep cerebellar nuclei and the cingulate, prefrontal, and parietal cortices (770). Thus neural damage may occur in OSA. However, such findings were not replicated by other investigators (937), a discrepancy that may be due to differences in analysis methodology and subject variation (770).

5. Apnea treatment

Effective treatments for apnea include the CPAP (continuous positive airway pressure) device, dental devices, weight loss, and surgery (672). Pharmacological interventions to treat OSA increase the activity of the upper airway dilator muscles, as well as the ventilatory drive, e.g., noradrenergic and serotonergic agents, progestogens, and bronchodilators. Some patients experience the majority of apneic moments during REM sleep. Therefore, treatment with serotonergic agents that suppress REM sleep may be useful (1349). The stimulant modafinil has been prescribed to address the daytime hypersomnia experienced by the OSA patient (616).

6. Sudden infant death syndrome

Although not strictly an apneic syndrome, sudden infant death syndrome (SIDS) may be considered under the umbrella term of sleep-disordered breathing. SIDS deaths are usually caused by hypotension and bradycardia, due to an abnormal response to respiratory challenge (634). SIDS involves aberrant brain stem control of cardiorespiratory mechanisms by the developing brain. In one study, attenuated muscarinic cholinergic receptor binding of the arcuate nucleus, which is involved in cardiorespiratory mechanisms, was documented in SIDS cases (632). Also, serotonergic abnormalities in SIDS cases were recently shown (633), including deficient receptor binding and decreased tissue levels of both serotonin and the serotonergic synthetic enzyme tryptophan hydroxylase (318). Due to such abnormalities, the infant may have an attenuated response to respiratory challenges such as hypoxia or hypercapnia. An unusually high reoccurrence rate of SIDS has been documented within families, suggesting genetic susceptibility (634).

D. Metabolic Syndrome

Metabolic syndrome (MetS) consists of a combination of symptoms (low high-density lipoprotein cholesterol levels, abdominal obesity, elevated triglycerides, hypertension, insulin resistance/glucose intolerance) which increase the likelihood of developing cardiovascular disease (330). If at least three of these five criteria are present, the patient is considered to be suffering from MetS (330). Epidemiological studies indicate that poor sleep is associated with MetS symptoms (1200), although the direction of causality in patients with MetS remains to be determined; thus sleep distur-

bances may cause MetS symptoms or vice versa. Conversely, treatment of sleep disorders may help alleviate glucose and energy metabolism abnormalities (1200). An association of MetS with sleep is perhaps not surprising considering that one function of sleep appears to be regulation of energy metabolism (see sect. III).

Behavioral alterations of sleep are also associated with increased risk for MetS (1333). Shift work enhances the risk for a number of MetS symptoms by increasing oxidative stress (1158). Short or long sleep duration is associated with increased likelihood of MetS symptoms (405), with the incidence doubling in those that slept less than 6 h a night. Disturbed circadian/diurnal regulation of sleep also leads to MetS in animals. Homozygous *Clock* mutant mice with attenuated diurnal rhythms of feeding ate more, gained more weight, and had increased peripheral metabolic hormones such as insulin and leptin and abnormalities in hypothalamic hormones which regulate food intake (1313). Knockout of other circadian regulatory genes causes similar metabolic defects (41).

E. Narcolepsy

Narcolepsy is defined by a tetrad of symptoms: excessive daytime sleepiness, cataplexy, hypnagogic hallucinations, and sleep paralysis (1467). Narcolepsy affects all three stages of sleep and wakefulness, with a prevalence of ~1 in 2,000 individuals and an onset in early adulthood (1127, 1261). As originally described by Westphal (1400) and Gelineau (408) at the end of the 19th century, in this disorder there is a pronounced fragmentation of wakefulness, disrupted night-time sleep and intrusion of REM signs into wakefulness. Particularly striking and disabling are involuntary sleep attacks and episodes of (REM-like) muscle atonia induced by emotional arousal (cataplexy) with preservation of consciousness resulting from both abnormal control of REM control mechanisms (see below) and alterations in emotional processing (202, 303, 1309). Additional REM-like symptoms are hypnagogic hallucinations (hallucinations occurring around sleep onset or awakening) and sleep paralysis (inability to move following awakening from REM sleep).

Narcolepsy is caused by loss of orexin neurons or orexin receptors. Following the seminal discoveries of the gene defect responsible for a heritable form of narcolepsy in dogs (alteration of orexin type 2 receptor) (727) and narcolepsy-like symptoms in orexin knockout mice (214), this disease is now known to be caused by a loss of orexin/hypocretin neurons, orexin peptides, or their receptors. A marked reduction in the CSF levels of these peptides is found in living narcoleptic patients, whereas post mortem brains of human narcoleptics show a loss of orexin neurons (924, 999, 1284). A mutation in the preproorexin gene was found in a rare early-onset case of narcolepsy (999). Orexin neurons

can also be damaged following stroke (1129) or traumatic brain injury (82), leading to excessive daytime sleepiness. Animal studies (217) show a narcoleptic phenotype following *1*) knockout of orexin peptides or orexin receptors (214, 640, 870, 1415), *2*) nonspecific lesion of the lateral hypothalamic area where orexin neurons are concentrated (414), and *3*) genetic modification introducing a toxic transgene (ataxin-3) specifically in the orexin neurons (96, 479). However, the complete narcoleptic phenotype including cataplexy is not observed following short-term pharmacological blockade of orexin receptors (140) or RNAi-mediated knockdown of orexin peptides (221), suggesting that a more prolonged loss of orexin signaling is required to observe the full narcoleptic phenotype . This idea is consistent with studies which revealed neurodegenerative changes (1178), alterations of emotional arousal, and upregulations of cholinergic and dopaminergic systems involved in REM sleep control in narcolepsy (923).

1. Mechanisms underlying cataplexy

The multiple mechanisms by which orexins promote consolidated wakefulness and suppress REM sleep were discussed in sections II and IV, respectively. Early pharmacological studies in narcoleptic dogs suggested increased activity of cholinergic REM-on and decreased activity of aminergic REM-off systems is important for causing cataplexy. Infusions of cholinergic agonists in the pontine reticular formation caused cataplexy in normal dogs and exacerbated symptoms in narcoleptic dogs (1055, 1056). Furthermore, enhanced acetylcholine release was detected in the pons during cataplexy (1054). Recent data report an association of the choline kinase β (CHKB) gene involved in acetylcholine synthesis with susceptibility to narcolepsy (864). Enhanced cholinergic enzyme levels were detected in brain stem cholinergic neurons in orexin knockout mice (594). Electrophysiological studies in narcoleptic dogs revealed a cessation of firing of REM-off LC norepinephrine neurons (1435) and an increase in firing of muscle atonia related neurons in the medial medulla (1176, 1177) preceding and during cataplexy. Behavioral arrest reminiscent of cataplexy was observed following intense activation of the locus coeruleus with optogenetic techniques (196). More recent recording studies confirmed the cessation of firing of LC neurons and demonstrated its selectivity, since histaminergic neurons do not change their firing and DRN serotonin neurons show only a reduction and not a complete cessation of activity (564, 1436). Thus neuronal activity in cataplexy does not exactly parallel that observed during REM sleep, a finding confirmed by recordings of neuronal activity in the lateral pontine tegmentum REM control area (1283).

2. Narcolepsy treatment

Current treatment of narcoleptic symptoms normally involves the use of stimulants acting on the dopaminergic

systems (e.g., modafinil) to alleviate excessive daytime sleepiness and antidepressants (especially those promoting increased noradrenergic tone) for suppression of REM-like phenomena such as cataplexy (923). γ-Hydroxybutyrate (GHB, sodium oxybate) is prescribed to improve nighttime sleep in narcoleptics (151). GHB is a metabolite of GABA that modulates sleep via activation of $GABA_B$ receptors (1369). Pharmacological agonists of the orexin receptors and histamine H_3 receptor antagonists/inverse agonists (increasing histaminergic tone) are under development for the treatment of narcolepsy (395, 723, 854). Transplantation of orexin neurons (42) and orexin gene therapy (733, 734) are also being explored in preclinical animal studies. A dual orexin receptor antagonist has recently been promoted as a potential sleep aid (140), although development of narcoleptic symptoms could be a potential side effect of such compounds (no cataplectic events have been observed as yet).

3. Evidence that narcolepsy is an autoimmune disorder

Narcolepsy has long been considered an autoimmune disorder (728) due to its late onset, its association with the human leukocyte antigen (LHA) class II allele DQB1*0602 (728, 1259), and more recently due to the observed loss of orexin neurons in the hypothalamus in most human cases of the disease (1261). However, direct connections to the immune system have been hard to demonstrate. The strongest evidence comes from very recent findings of a linkage to a polymorphism in the T-cell receptor alpha gene (475) encoding the major receptor for HLA peptide presentation, findings of autoantibodies against the Tribbles Homolog 2 (TRIB2) gene product which is produced in orexin neurons (270, 613, 1304), and findings of anti-streptococcal antibodies (39) in a proportion of patients in the early stages of the disease. Although tantalizing, whether these markers are related to the cause, the progression, or are incidental to the disease process remains to be determined (721).

F. Other Sleep Muscle Tone-Related Disorders

1. REM sleep behavior disorder

REM sleep behavior disorder (RBD) is a human manifestation of the syndrome originally observed in cats (583) following large lesions of the brain stem reticular formation including sites involved in muscle atonia (893)(sect. IV). Sporadic cases can also be observed in cats and dogs without experimenter-induced lesions (493, 494). This disorder was first formally described in humans in a landmark study by Schenck, Mahowald and colleagues in 1986 (1131) and has a reported prevalence of 0.5% (779). RBD involves uncontrolled movements and muscular expression of dream sequences leading to sleep fragmentation and injury to patients and their sleeping partners (1134). In the sleep laboratory such activity is correlated with enhanced EMG activity during sleep, whereas other aspects of REM sleep are normal. It is more common in people aged over 50 years old and affects more men than women. Acute RBD can be induced by various medications (e.g., antidepressants acting to increase serotonergic or noradrenergic tone) (401, 982, 1418), whereas the cause of the chronic form is unknown. The acute form of RBD is managed by withdrawal of the offending medication, whereas the chronic form can be well managed symptomatically by clonazepam (first choice) or melatonin treatment prior to bedtime (401, 779).

Importantly, RBD has been shown to precede and predict the later development of neurodegenerative diseases known as synucleinopathies (115, 400) including Parkinson's disease (117, 399, 1132), dementia with Lewy bodies disease (116, 1314, 1315), and multiple system atrophy (547, 1291). These studies suggest that a neurodegenerative process in the generation of idiopathic RBD, presumably occurring in the brain stem REM muscle atonia generation zones in the dorsolateral pons and medulla. RBD may be an important marker allowing early-stage preventative treatments of synucleinopathies since RBD often occurs many years earlier than the other conditions (400, 547, 1132, 1270, 1291). In fact, post mortem studies in idiopathic RBD have revealed damage to the LC-SubC area (1314, 1315). MRI scans revealed a discrete infarct in the upper pons in several cases (267, 627), although not all studies have found such abnormalities. Surgery involving damage to the upper pons can also result in RBD (1025). A recent advance in RBD research is the identification of an animal model which recapitulates many of the features of RBD (148). This model consists of transgenic mice that have deficits in inhibitory glycinergic and GABAergic neurotransmission due to the expression of a mutant glycine receptor α1 subunit, consistent with the substantial evidence for a role of these neurotransmitters in controlling muscle atonia during REM sleep (see sect. IV).

2. Restless legs syndrome

Restless legs syndrome (RLS) is a compelling urge to move limbs, particularly the legs, in the evening, due to unpleasant sensations, such as tingling, which can be relieved by movement. RLS is a very common in older subjects, particularly in western countries such as the United States, where ~9% of adults are affected (946). RLS can lead to severe insomnia and subsequent daytime hypersomnia (335).

A) PATHOGENESIS OF RLS. Recent investigations implicate iron deficiency and abnormalities of dopaminergic systems as possible root causes of RLS (21). Iron is a cofactor for tyrosine hydroxylase, required for synthesis of dopamine; thus iron deficiency may lead to dopaminergic dysfunction. CSF iron levels are low in a minority of RLS patients (327, 868), and iron supplementation decreased symptoms of

RLS in some cases (328). Studies of post mortem brain tissue revealed reduced iron content (257), confirmed by neuroimaging techniques such as MRI (326). Furthermore, the severity of RLS symptoms correlates with low levels of ferritin, an intracellular protein that binds iron (327, 673, 868), as well as high levels of transferrin, a plasma glycoprotein involved in iron transport (327, 868). Experimentally induced iron deficiency in animal studies produced an increase of wakefulness during the inactive (light) period (294). This model, although incomplete, paralleled the circadian aspect of RLS, whereby symptoms mostly occur during the early part of the inactive/rest period (952). Genetic studies have identified polymorphisms in three loci encoding developmental factors as predisposing to RLS (1204, 1420) and in particular to periodic limb movements during sleep (see next section).

B) TREATMENT AND ANIMAL MODELS OF RLS. Dopaminergic agonists alleviate RLS symptoms (497), and blocking dopaminergic transmission worsens symptoms (887, 1419). Dopaminergic cell-specific lesioning of the A11 region, by means of the toxin 6-hydroxydopamine, produced an increase in sleep latencies, as well as less sleeplike behaviors (951). Excitotoxic (NMDA) lesions of another dopaminergic region, at the ventral mesopontine junction, produced an increase of wakefulness, as well as periodic leg movements during NREM sleep, similar to that seen in the RLS patient (682). A combination of A11 lesions and an iron-deficient diet led to a significant increase in locomotor activity, which was elevated compared with either manipulation (lesion or diet) alone (1030). Furthermore, symptoms were improved following treatment with D_2/D_3 agonists (such as ropinirole), as well as worsened with a D_2 antagonist (haloperidol). D_3 receptors, specifically in the dorsal horn (246, 712, 1142), may play a role in RLS symptomatology (247). D_3 antagonists and D_3-receptor knockout mice both exhibited increased locomotor activity, and D_3 antagonist treatment leads to a decrease of total sleep (2, 71). Therefore, dopaminergic systems may be abnormally affected in RLS patients, particularly the A11 dopaminergic cell group and its efferent projections to the spinal cord (1187).

3. Periodic limb movements

RLS is usually accompanied by stereotyped periodic limb movements (PLM) during sleep, which are involuntary repetitive extensions of the toes, feet, and occasionally the knee and hip. Interestingly, two genetic studies of RLS identified a locus, BTBD9, which also predispose individuals to PLM (1204, 1420). PLM may also be evident in narcolepsy (886), apnea (392), and RBD (688).

4. Other disorders of motor control during sleep

Inappropriate activation of motor programs during sleep also occurs in bruxism (grinding of teeth during sleep),

sleepwalking (occurring during NREM sleep), nocturnal sleep-related eating disorder (NSRED), and sexsomnia (automated sexual behavior during sleep).

G. Posttraumatic Stress Disorder

The diagnostic criteria for posttraumatic stress disorder (PTSD) include hyperarousal and disturbed sleep including sleep-onset insomnia, inability to stay asleep, excessive daytime sleepiness, and traumatic nightmares (1183). Approximately 8% of the adult population suffers from PTSD (617) caused by exposure to either emotional or physical trauma. NREM-related symptoms include an increased latency to fall asleep, as well as a decrease of overall NREM amounts (429, 847). The majority of studies also report REM-related symptoms, including decreased REM episode length, increased episode number, and an increased number of arousals from REM sleep (847, 1078).

1. Nightmares in PTSD

The chief subjective sleep complaint reported by PTSD patients is an increased prevalence of frightening dreams/nightmares (1329), suggesting a pathological enhancement of the normal activation of brain areas involved in emotion during REM sleep (sect. IV). In particular, increased activation of the amygdala and its connections with the hippocampus and prefrontal cortex may be important (719). The amygdala is a key player in the formation of fearful memories, and amygdala activity is abnormally elevated in PTSD patients following exposure to visual trauma-related stimuli (538). PTSD is also associated with endocrinological alterations that may contribute to disturbed sleep, including an attenuation of catecholamine plasma levels and an elevation of corticotrophin-releasing factor (CRF) levels (917).

2. Medication for PTSD

Numerous medications have been prescribed to decrease the hyperarousal associated with PTSD, with varying degrees of improvement of sleep disturbances (389). Treatments include benzodiazepines, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, atypical antidepressants (such as nefazadone and trazodone), beta blockers (such as propranolol), and α-adrenergic antagonists (prazosin). Norepinephrine plays a key role in the brain's response to stress and anxiety and in the suppression of REM sleep (sect. IV). Activation of α_1 norepinephrine receptors is involved in the REM suppressing effect of norepinephrine (644, 782, 990, 1079). Therefore, manipulations of this receptor may lead to improvement of sleep-related PTSD disturbance. Administration of the α_1 receptor antagonist prazosin to PTSD patients increased total sleep amounts, normalized the REM sleep profile, and decreased traumatic nightmares (674, 1049). Another system

that may be targeted in the future is the orexin system. Recent work in a rat model demonstrated a role for the orexin system in panic anxiety (565).

H. Depression

There are several intriguing links between depression and sleep (1208, 1228). Both monopolar and bipolar depression are associated with sleep disturbances, and acute sleep deprivation has a potent and rapid antidepressant action in severely depressed individuals. Furthermore, commonly used antidepressants that enhance serotonergic and noradrenergic tone strongly inhibit the expression of REM sleep (sect. IV). Conversely, light deprivation produces damage to monoamine neurons and a depressive behavioral phenotype in rats (433). Major (monopolar) depression is associated with sleep fragmentation, decreases in NREM sleep intensity, and promotion of REM sleep (173, 1208, 1228). EEG delta power, a measure of sleep intensity (sect. III), is reduced in depressed patients (124). REM alterations most commonly observed are a decrease in REM latency, sometimes resulting in sleep-onset REM periods, a prolonged duration of the first REM period, and increased phasic REM events. Consistent with the reciprocal-interaction theory of REM sleep control (sect. IV), pharmacological challenge experiments with cholinergic or serotonergic agents suggested an increased sensitivity of cholinergic systems and/or decreased activity of aminergic systems may cause these REM abnormalities (426–428, 1228).

VIII. CONCLUSIONS

The past century witnessed an enormous explosion in our knowledge of the brain mechanisms that control wakefulness and sleep. Ethological and genetic studies have revealed the presence of NREM sleep-like states even in invertebrates such as *Drosophila* and have revealed that homologous genes/proteins control rest/sleep in flies, fish, mice, and humans. Multiple interacting neurotransmitter systems making up the ARAS arouse the brain and produce wakefulness in response to physiological challenges as diverse as increases in blood CO_2, decreases in ambient temperature, and the presence of rewarding stimuli. Increases in arousal are observed as an increase in low-amplitude fast EEG rhythms important for synchronization of neuronal assemblies involved in attention, working memory, and conscious awareness. Conversely, NREM sleep is associated with high-amplitude slow waves produced by the combination of a circadian inhibition of ARAS neurons mediated by GABAergic neurons in the preoptic hypothalamus and basal forebrain and by the action of a plethora of homeostatic sleep factors acting locally in the cortex or basal forebrain. Multiple interacting lines of evidence support a role for NREM sleep in the control of energy metabolism and synaptic plasticity/memory formation. REM sleep is induced by the increased firing of glutamatergic and cholinergic neurons in the dorsolateral pons, resulting in muscle atonia coupled with both tonic and phasic activation of the cortex. Phasic activation of visual cortex and limbic regions during REM sleep, coupled with deactivation of prefrontal cortex, is responsible for the bizarre imagery of dreams and may reflect a role for REM sleep in emotional regulation and/or memory consolidation in the adult or establishment of neural circuitry in the developing animal. Sleep deprivation leads to an inhibition of arousal mechanisms at subcortical and cortical sites, leading to impairments in cognitive function, which in turn can result in accidents at home and in the workplace. Deficits in arousal mechanisms and high-frequency rhythms are observed in sleep disorders and conditions such as coma, schizophrenia, Alzheimer's disease, and epilepsy. Consistent with a role for sleep in energy metabolism, sleep deprivation is a major contributor to metabolic syndrome, a leading public health issue. Furthermore, dysregulation of sleep is a feature of depression, PTSD, and a variety of sleep disorders related to muscle control. Thus studies of the mechanisms controlling sleep and wakefulness can reasonably be expected to lay the groundwork for therapies to treat a multitude of afflictions affecting mankind.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

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