Neurotransmitters, Drugs and Brain Function.
Edited by Roy Webster

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Section D

NEUROTRANSMITTERS AND BEHAVIOUR

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22 Sleep and Waking

R. A. WEBSTER AND S. C. STANFORD

INTRODUCTION

There have been many references in this book to the role of neurotransmitters in the control of CNS excitability. It is therefore appropriate, but possibly foolhardy, to see if the two natural extremes of that excitability, namely sleep and waking, can be explained in terms of neurotransmitter activity. Of course, these states are not constant: our sleep can be deep or light and, even when we are awake, our attention and vigilance fluctuate, as the reading of these pages will no doubt demonstrate. Also, the fact that we sleep does not mean that our neurotransmitters are inactive: this would imply that sleep is a totally passive state, whereas all the evidence suggests that it is an actively induced process, subject to refined physiological control.

In order to explain the physiological characteristics of the sleep–waking cycle, as well as how this might be controlled by different neurotransmitters and modified by drugs, we need to know which areas and pathways in the brain are vital to the induction and maintenance of this rhythmic behaviour. Essentially, these brain systems can be resolved into two interacting networks. One is responsible for the basic circadian rhythm and ensures that our sleeping and waking periods normally occur at regular intervals. A second system fine-tunes this process and ultimately determines our precise functional status on the sleep–waking continuum.

THE NEURAL BASIS OF CIRCADIAN RHYTHMS

It is most probable that sleep and waking stem from an inherent cycle of neuronal activity that can be influenced dramatically by changes in sensory stimulation. This is demonstrable not only in humans and laboratory animals, but also in invertebrates. Thus, while we cannot be sure that other animals sleep in the same way that we do, they do show a circadian cycle of motor activity. In some (nocturnal) species, such as the rat, this activity is actually highest during darkness. Even aplysia, the sea hare, has such a rhythm but this is more like that of humans in being maximally active during daylight (diurnal).

These rhythms seem to be innately programmed although they can be adjusted. For instance, in a normal environment, the sleep–waking cycle of humans is obviously synchronised ('entrained') with the (24-h) dark–light cycle whereas it assumes a period of around 25–27 h in a (time-free) environment where there are no diurnal cues. Interestingly, when humans are in a time-free environment, the change in the rhythm of

body temperature does not follow the change in the sleep–waking cycle. Generally, it becomes shorter (to as little as 20 h), rather than longer, which suggests that these cycles are regulated in different ways. Entrainment has also been shown in aplysia which, after exposure to a normal dark–light cycle, retains a cyclic pattern of activity for a number of days even if subjected to continuous light.

At its most fundamental level, the circadian cycle rests on the influence of so-called 'clock genes'. These genes have been studied most extensively in insects but they have also been found in humans. Their protein products enter the cell nucleus and regulate their own transcription. This feedback process is linked to exposure to light and so it is not surprising that visual inputs are important for maintenance of circadian rhythms. However, it is not the reception of specific visual information, transmitted in the optic nerve to the lateral geniculate nucleus (LGN) and visual cortex (i.e. visual discrimination), that is responsible for the rhythm but the more simple, almost subconscious, reception of light.

The fibres conveying this sensation arise in the retina but diverge from the optic nerve and travel in the retinohypothalamic tract (RHT) to innervate the suprachiasmatic nucleus (SCN), a small nucleus which is found in the anterior hypothalamus above the optic chiasma (Fig. 22.3). Destruction of the RHT leads to 'free-running' rhythmic behaviour and so this pathway seems vital for coupling the circadian rhythm to the light cycle. A deficit in information carried in this pathway could help to explain why the blind often suffer from disrupted sleep patterns. Another prominent input to the SCN comes from the intergeniculate leaflet (in the lateral geniculate nucleus (LGN) complex) via the geniculohypothalamic tract (GHT) and, whereas the retinohypothalamic pathway seems to be essential for light-entrainment of the circadian rhythm, the LGN seems to be influenced by rhythmic variations in non-photic inputs such as changes in motor activity. Of course, the LGN is obviously influenced too by visual inputs and, together with the GHT projection to the SCN, can be regarded as an indirect retinohypothalamic pathway which appears to be inhibitory on SCN neurons. A neuronal input to the SCN from 5-HT neurons in the median Raphé nucleus is another possible route for setting the circadian clock (entrainment) by non-photic stimuli (Fig. 22.1).

Destruction of the SCN, the target of all these pathways, abolishes the synchronised circadian rhythms in locomotor and autonomic function which clearly points to this nucleus as a crucial centre for the control of cyclic function. However, there seems to be some topographical organisation of the neurons in the SCN in respect of their function and the transmitters they release. Whereas those in the dorsomedial zone of this nucleus (or nuclei, since it is paired) contain arginine vasopressin (AVP) or angiotensin II and GABA, neurons in the ventrolateral zone contain vasoactive intestinal peptide (VIP), gastrin-releasing peptide (GRP) and GABA. It is these latter neurons which form the core of the nucleus and show rhythmic pacemaker function. In fact, when maintained in culture, they even display a metabolic rhythm which has the same phase as that of SCN neurons *in vivo*. Unfortunately the presence of GABA in these neurons means that they must be inhibitory and so could not directly stimulate any brain function when activated, e.g. by light inputs, although they could dampen melatonin secretion (see below).

Neurons within the SCN innervate those hypothalamic areas which have a crucial role in the regulation of the reproductive cycle, mood and sleep/arousal, as well as regions such as the basal forebrain and the thalamus which help to determine the state of arousal. They also project to the pineal gland to govern the synthesis and release of

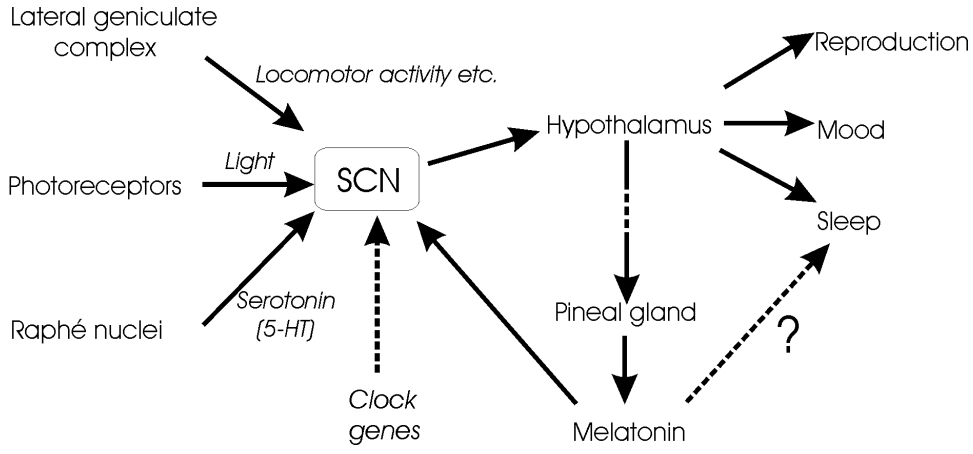

Figure 22.1 Pathways projecting to and from the suprachiasmatic nucleus (SCN). Inputs from photoreceptors in the retina help to 'reset' the circadian clock in response to changes in the light cycle. Other inputs derive from the lateral geniculate complex and the serotonergic, Raphé nuclei and help to reset the SCN in response to non-photic stimuli. Neurons in the SCN project to the hypothalamus, which has a key role in the regulation of the reproductive cycle, mood and the sleep–waking cycle. These neurons also project to the pineal gland which shows rhythmic changes in the rate of synthesis and release of the hormone, melatonin

the hormone, melatonin, which is another factor involved in the control of the 24-h cycle.

MELATONIN

Some lower vertebrates (e.g. frogs and lizards) have what is commonly described as a 'third eye': the pineal gland. This is found in the dorsal cranium and is linked to the diencephalon. Despite its trivial name, the pineal gland does not contribute to discriminative vision and its role is merely to detect changes in light intensity so that, in animals with a clear photoperiod, it couples physiological rhythms with the length of the day–light cycle. In mammals, the pineal is not exteriorised but it persists as a brain appendage for the secretion of the hormone, melatonin. (*N*-acetyl 5-methoxytryptamine) which, like 5-hydroxytryptamine (5-HT), is an indole derivative (Fig. 22.2). Melatonin is not a normal metabolite of neuronal 5-HT but it is synthesised from that amine in the pineal gland by the enzyme, 5-hydroxytryptamine *N*-acetyltransferase. This is a rate-limiting process that shows a circadian rhythm with maximal activity occurring during darkness. The product of this reaction, *N*-acetyl 5-hydroxytryptamine, is methylated, to form melatonin, by the enzyme hydroxyindole-*O*-methyltransferase.

The rate of melatonin synthesis is controlled primarily by the release of noradrenaline from sympathetic fibres originating in the superior cervical ganglion. The activity of these neurons and, consequently, the synthesis and release of melatonin, follows a circadian rhythm such that sympathetic input and melatonin synthesis are both increased in the dark. This coupling with the light cycle certainly involves the SCN since destruction of this nucleus greatly reduces the fluctuations in melatonin production. Moreover, retrograde transneural tracing has shown that there is a neuronal pathway

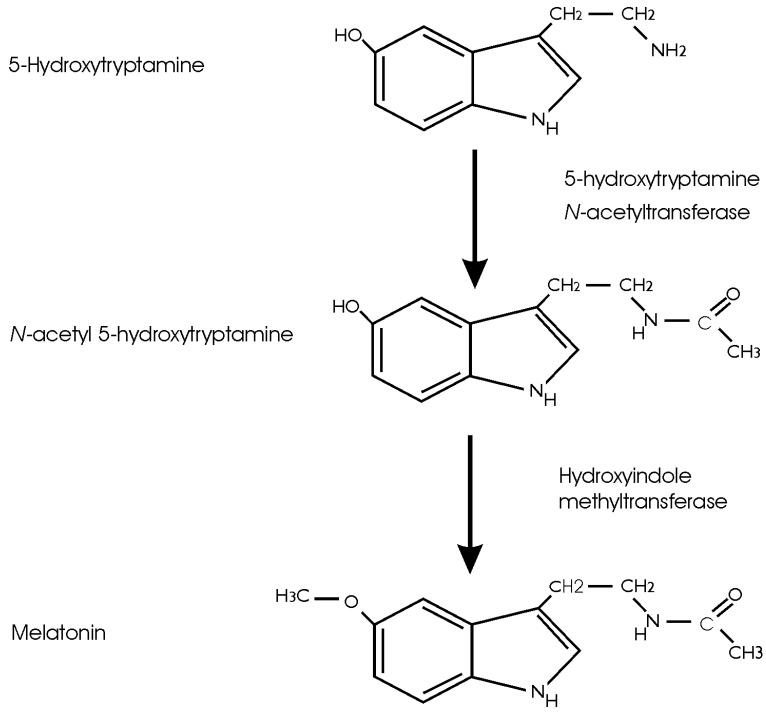

Figure 22.2 The biosynthetic pathway for melatonin

that connects the SCN with sympathetic innervation of the pineal via the paraventricular nucleus of the hypothalamus.

The effect of noradrenaline on melatonin synthesis appears to be mediated through β-adrenoceptors, using cyclic AMP as their second messenger, although studies on cultured pinealocytes suggest that this process is potentiated by activation of α_1-adrenoceptors (see Hagan and Oakley 1995). However, there is evidence that melatonin synthesis in the pineal is also regulated by dopamine and 5-HT. Finally, some melatonin is synthesised in the retina where the rate-limiting enzyme is tryptophan hydroxylase; this process is rhythmic, even in cultured retinal cells, and it seems to adjust to shifts in the light–dark cycle.

The precise role of melatonin in sleep and waking is uncertain but it seems to act as a 'go-between' for the light and biological cycles and evidence suggests that it has a reciprocal relationship with the SCN (Fig. 22.3). Its actions are mediated by (ML_1) receptors which are found predominantly in the SCN as well as thalamic nuclei and the anterior pituitary. These are G protein-coupled receptors, with seven transmembrane domains, that inhibit adenylyl cyclase. Their activation by melatonin, or an ML_1 agonist such as 2-iodomelatonin, restores the impaired circadian cycle in aged rats.

In humans, poor sleep correlates with low plasma melatonin and can be improved by melatonin administration. This therapeutic approach has been tried especially in individuals whose sleep rhythms are disrupted by shift-work, blindness or 'jet-lag' but its benefits are as yet unconfirmed and, in any case, the mechanisms by which it might reset sleep patterns are unclear. Of course, it must be remembered that other body

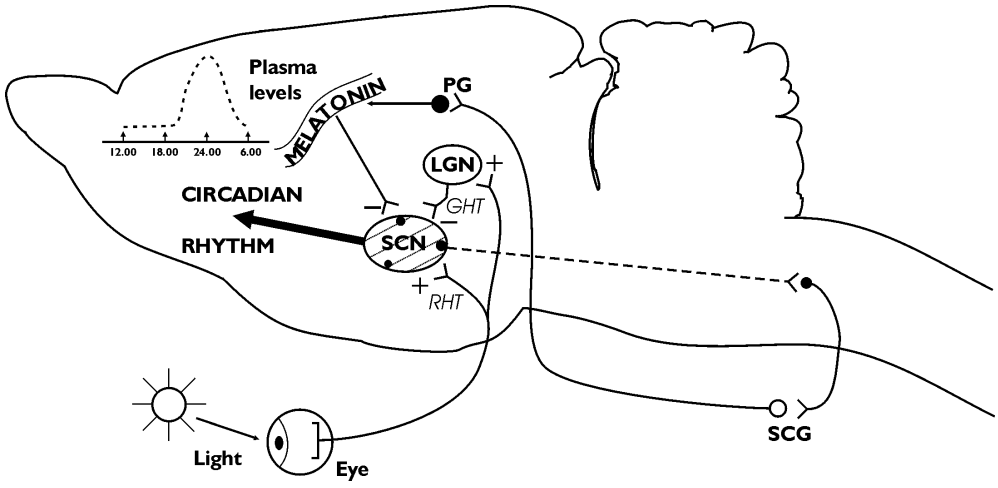

Figure 22.3 Possible links in the induction of circadian rhythm between daylight, the suprachiasmatic nucleus and melatonin release from the pineal gland. Some fibres in the optic nerve, projecting from the eye to the lateral geniculate nucleus (LGN) in the thalamus, innervate the suprachiasmatic nucleus (SCN) in the anterior hypothalamus, via the retinohypothalamic tract (RHT). Others project to the SCN from the LGN in the geniculohypothalamic tract (GHT). The release of melatonin into the circulation from the pineal gland (PG) is maximal at night and appears to be controlled partly by noradrenaline released from sympathetic nerves originating in the superior cervical ganglion (SCG). Melatonin receptors are found in the SCN, the removal of which dampens melatonin secretion

functions show a circadian rhythm, some of which, such as corticosteroid production (high in morning) and body temperature (low during sleep) could all influence the state of arousal. However, the night-time peak for melatonin secretion normally coincides with the trough for body temperature, and these two events could well be linked. Nevertheless, whether melatonin affects sleep itself, rather than merely the entrainment of the sleep rhythm, is controversial (for a detailed review of this topic see Arendt *et al.* 1999).

SLEEP

Defining sleep is not at all straightforward but its general features comprise (see Hendricks, Sehgal and Pack 2000) (1) a sterotypical, species-specific posture; (2) an absence of voluntary movements; (3) elevated threshold for arousing stimuli; (4) reversibility on stimulation of the individual (or organism). The following sections outline what is known about how these changes come about and how they are regulated.

THE ELECTROENCEPHALOGRAM (EEG)

Probably the most important breakthrough in sleep research came in the mid-1930s when it was discovered that the profile of the electroencephalogram (EEG) changed markedly during the sleep–waking cycle (Fig. 22.4). To this day, the EEG is a major

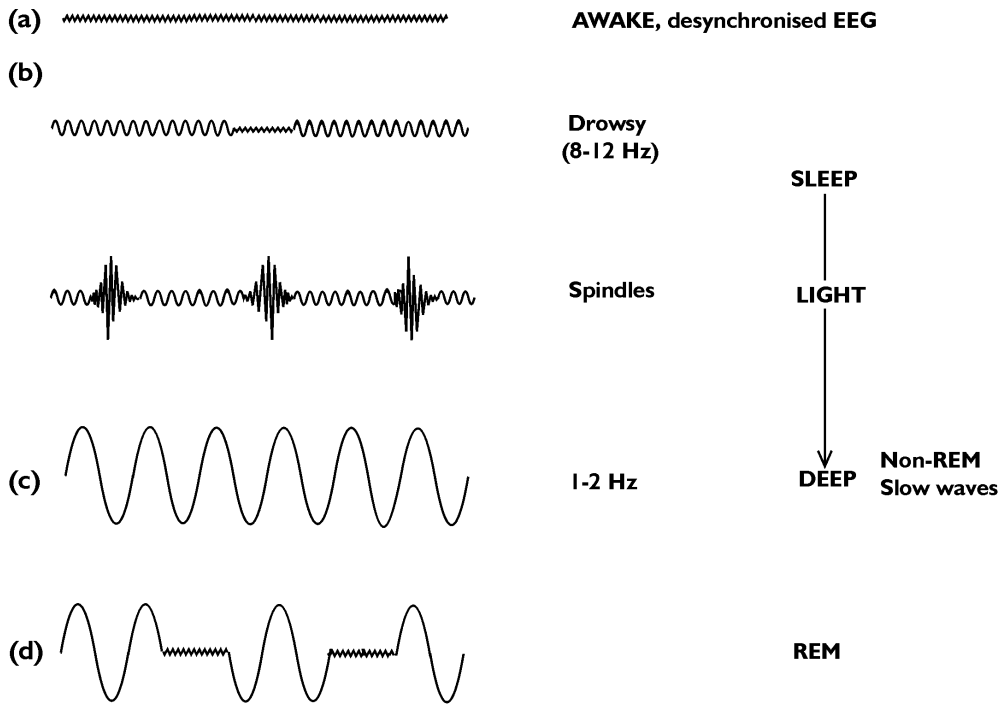

Figure 22.4 Idealised EEG-like patterns in sleep and waking. When we are awake and aroused the EEG is desynchronised (a). As we become drowsy and pass into sleep the EEG waves become more synchronised with 8–12 Hz alpha waves (b), sleep spindles then appear (c) before the EEG becomes even more synchronised with slow (about 1–2 Hz) high-voltage waves characteristic of deep slow-wave sleep (SWS). About every 90 min this pattern is disrupted and the EEG becomes more like that in arousal (d) except that the subject remains asleep. This phase of sleep is also characterised by rolling, rapid eye movements, the so-called REM sleep. SWS is consequently also known as non-REM sleep. These tracings have been drawn to show the main features of the different EEG phases of sleep and as such are much simpler than those that are actually recorded

focus of sleep research but is usually complemented by measurements of muscle tone (the electromyogram, EMG) and eye movements (the electro-occulogram, EOG) which also show marked changes during the sleep cycle.

When we are aroused and awake, the EEG is random (desynchronised) with multiple high-frequency (of at least 15 Hz), low-amplitude γ(gamma)-wave forms. As we become drowsy and close our eyes, the EEG becomes more synchronised and a clear rhythm emerges (stage 1 sleep): this is α(alpha)-rhythm which has a frequency of 8–12 Hz. At the onset of sleep (stage 2), θ(theta)-waves (4–7 Hz) are evident but these are disrupted to some extent by the intermittent appearance of waves, known as K-complexes and 'sleep spindles'. The former are single spikes whereas the latter are short trains of pulses (12–14 Hz). Progressing still further into the sleep state (as assessed by the EMG and EOG), the EEG becomes even more synchronised so that slower (about 1–2 Hz) and larger waves become more prominent. These are the δ(delta)-waves which are associated with stage 4 (deep) sleep, often called 'slow-wave sleep' (SWS). At the same time as all these changes are developing, the threshold for arousal by sensory stimuli increases.

It was not until much later (1953) that another phase of the sleep cycle was discovered. At about 90 min after the onset of sleep, the EEG becomes desynchronised and, in fact, it bears a strong resemblance to that seen in stage 1, apart from the appearance of so-called 'PGO-waves' (see below). Also, rapid eye movements, resembling those while reading in the awake state, are evident on the EOG: this is REM (rapid eye movement) or 'paradoxical' sleep. However, in adults, other physiological changes that occur during REM sleep are quite different from those of stage 1. In particular, there is a flaccid paralysis of the limb muscles together with a loss of fine control of body temperature and other homeostatic mechanisms. It is often maintained that dreaming is restricted to these periods of REM sleep, which occur some three or four times during the night, each lasting about 30 min. However, it is now thought that dreams also occur during SWS but that these are more logical and more consistent with normal life events than are those occurring during REM sleep.

This sleep pattern, seen in adults, takes some time to develop and appears in infants only around 6 months to one year after birth. Instead, as new parents will testify, young babies have a sleep cycle that lasts only around 3–6 h. Further striking differences are that babies' REM sleep accounts for as much as half the sleep cycle (compared with only a quarter in the adult) and is accompanied by increased motor activity with spasmodic movements of the limbs and facial muscles, rather than the muscle atonia seen in adults. In fact, the adult sleep cycle can take up to 20 years to stabilise and its pattern changes again in the elderly who show a reduction in the duration of SWS, an increase in the proportion of REM sleep, and increased daytime 'napping'.

The functions of these different phases of sleep are not at all clear but chronic sleep deprivation does eventually lead to death. It seems to be the slow-wave component of sleep (SWS) that is vital and it is thought to serve a restorative purpose. This would be consistent with its greater occurrence during the early stages of the sleep cycle when hormone secretion supports anabolic metabolism. If subjects are wakened every time they enter a period of REM sleep (evidenced by the EEG) there appears to be no overt harmful effect on their behaviour. In fact, REM sleep deprivation has even been used, with some claims of success, as a treatment for minor depression. However, there is an unproven belief that REM sleep is important for memory consolidation.

ORIGIN OF THE EEG

It appears that the voltage waves recorded in the EEG represent the summation of synaptic potentials in the apical dendrites of pyramidal cells in the cortex. These cells generate sufficient extracellular current for it to reach, and be recorded from, the cranium and scalp. Although these waves originate from the cortex rather than the SCN, the distinctive REM and non-REM phases of sleep still remain after destruction of the SCN but they then occur randomly over the 24-h cycle. This is a further indication that the SCN is at least partly responsible for setting the overall circadian rhythm of the sleep cycle.

The more synchronised the activity of the cortical neurons, the greater the summation of currents and the larger and slower the EEG wave, as in the sleep pattern (Fig. 22.4). While there are some dissociations between EEG pattern and behavioural states, the EEG offers one way of determining experimentally the pathways (and neurotransmitters) that control arousal and sleep, and can be regarded as an important objective measurement of the cortical correlates of sleep and waking.

The slow (deep sleep) δ-waves probably originate in the cortex because they survive separation from, or lesions of, the thalamus. However, the rhythm and appearance of spindles in earlier phases of the sleep cycle do depend on links with the thalamus (see Steriade 1999). Unlike stimulation of the specific sensory relay nuclei in the thalamus, which only affects neurons in the appropriate sensory areas of the cortex, the non-specific nuclei can produce responses throughout the cortex and may not only control, but also generate, cortical activity. Certainly, *in vitro* studies show that neurons of the non-specific reticular thalamic nucleus (NspRTN) can fire spontaneously at about 8–12 Hz (equivalent to EEG α-rhythm) or lower, and that low-frequency stimulation of this area can induce sleep.

Maintenance of these frequencies relies on the degree of depolarisation of the thalamic neurons (Jahnsen and Llinas 1985) and this, in turn, depends on the nature and intensity of their afferent inputs. The NspRTN and other thalamic nuclei receive reciprocal inputs from the cortex and it is possible that it is the ensuing oscillations in neuronal activity in this circuit between the cortex and thalamus that give rise to the sleep spindle waves in stages 2–4. In fact, it has been suggested that the stronger and clearer these oscillations become, the more likely it is that there will be loss of consciousness.

Apart from neuronal inputs originating in the cortex, thalamic afferents (see Fig. 22.5) come from:

(1) *Collaterals from neurons of neighbouring specific thalamo-cortical relay nuclei.* Because these neurons are themselves activated by sensory inputs transmitted along the spinothalamic tract, this provides one way in which sensory stimuli can influence cortical activity generally, as well as specifically.
(2) *Ascending inputs from the brainstem ascending reticular activating system (ARAS).* As described below, these seem to be particularly important and probably disrupt the thalamo-cortical synchrony.

SLEEP AND WAKING CENTRES

One of the first experiments to investigate the brain mechanisms that might be involved in regulation of sleep and waking showed that after transection of the brain of cats, so that the cerebrum was separated from the brainstem, the animal displayed continuous sleep. Conversely, transection that separated the entire brain, including the brainstem, from the spinal cord (at the level of Cl) caused continuous arousal. Jouvet (1974) extended this work by showing that a lesion at a specific site in the pons abolished REM sleep, together with the associated muscle atonia and EEG changes, but did not affect SWS. All this work suggested the existence, not only of 'sleep' and 'waking' centres in the brain, but also that a separate brain area was responsible for REM sleep. Later studies confirmed the existence of these brain centres in that stimulation of the anterior hypothalamus, at a frequency similar to that of the sleep spindles in the EEG, induced sleep whereas stimulation of a zone of the brainstem, that came to be known as the ascending reticular activating system (ARAS), induced arousal (Moruzzi and Mayoun 1949).

The generally accepted view is that the stimulatory drive for the ARAS comes from collaterals of the classical ascending sensory pathways. Indeed, this is another way in which sensory stimuli can affect our state of arousal (Fig. 22.5). The diffuse activating

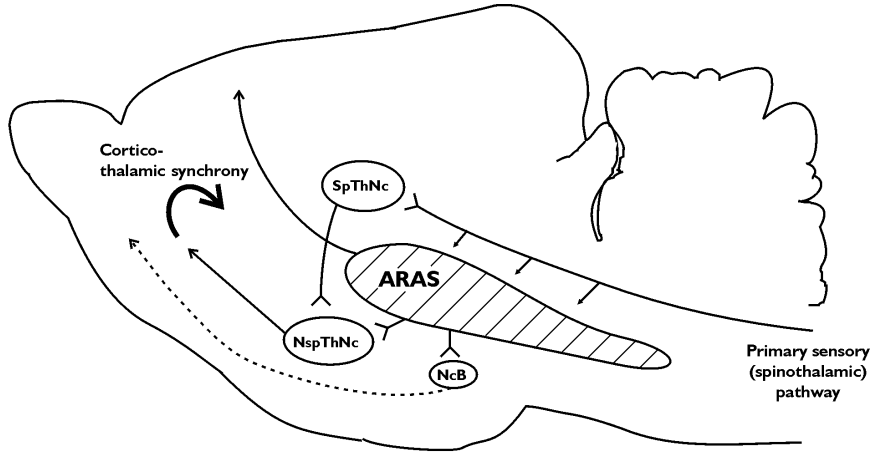

Figure 22.5 Pathways involved in cortico-thalamic synchrony and EEG arousal. The ascending reticular activating system (ARAS) extends from the cephalic medulla through the pons and midbrain to the thalamus (see Moruzzi and Mayoun 1949). It is activated by impulses in collaterals of the spinothalamic sensory pathway running to specific thalamic nuclei (SpThNc) and in turn activates much of the cortex, partly through the non-specific thalamic nuclei (NspThNc), which also receive inputs from SpThNc and also via the nucleus basalis (NcB). Its stimulation is followed by EEG arousal. It is probable that reciprocal links between cortical areas and the thalamus, particularly NspThN, lead to slow-wave (8 Hz) cortical EEG synchrony and, in the absence of appropriate sensory input and ARAS activity, a sleep state

system ensures that all sensory stimuli, whatever their strength or modality, contribute collectively to cortical arousal. This is possible because part of any sensory input is diverted to the ARAS and so prevents the cortex from reverting to its basic slow-wave oscillating rhythm. Thus, not only will the sensory cortex be more responsive to any primary sensory input it receives, but its activation keeps us alert. In this respect, the ARAS can be considered to contribute to our circadian rhythm by helping to ensure that we have an active cortex and so stay awake when we have adequate stimulation. Nevertheless, humans deprived of diurnal cues (such as when they are confined in an insulated, 'time-free' chamber) still show a sleep–waking cycle, although it progressively adopts a longer time period.

In addition to the excitatory drive, there are also inhibitory neurons from the anterior hypothalamus which provide one route for suppressing activity in the ARAS. Another inhibitory influence comes from the spinal cord. Together, these links could help to ensure smooth progression from one state of arousal to another. Also, during REM sleep, pontine–geniculate–occipital (PGO) waves travel to the cerebral cortex and spinal cord and it is this wave of activity, passing through intermediate brain regions, that is thought to blunt sensory and motor function.

It is important to emphasise that a lesion of the reticular system disrupts a number of afferent inputs to the cortex. Particularly important in this respect are the monoaminergic (especially noradrenaline, 5-HT and histamine) and cholinergic pathways. When the ascending inputs from these neurons are destroyed, sleep is passive and not at all like natural sleep which, as detailed above, has distinct phases and depends on brainstem influences on cortical function. How these different neurotransmitters might influence sleep and arousal will be considered next.

NEUROTRANSMITTER SYSTEMS

Based on the above account of the neuronal pathways thought to be responsible for the basic sleep–wake cycle, the neurotransmitters that are most likely to be involved in the cycle are those which:

(1) Are released either in the cortex or the non-specific thalamic nuclei.
(2) Augment, or more probably, break up thalamic-cortico synchrony and its tendency to promote slow-wave EEG activity and non-REM sleep. Whether this results in full arousal, or merely a temporary disruption of sleep to give REM periods without full awaking, will depend on the balance of inputs and the overall state of cortical activity.

Some of these inputs come from cholinergic, histaminergic, noradrenergic and 5-HT neurons. These neurons innervate the cortex more than the thalamus and their possible roles will be considered in the following sections. This material draws on studies designed to show: which neurotransmitters are associated with those brain structures concerned with sleep and waking; how their function may change during the cycle; to what extent pharmacological manipulation of their activity influences the cycle; and how drugs which modify our state of arousal affect neurotransmitters.

ACETYLCHOLINE

Studies of several animal species, ranging from rats to sheep, have shown that the release of acetylcholine (ACh) into cortical cups (see Chapter 4 and 6) is increased in proportion to cortical (EEG) activity, being maximal during convulsions and lowest under deep anaesthesia. These findings are consistent with evidence that cortical arousal (EEG desynchronisation) is increased by injection of ACh into the carotid artery of animals, or by direct stimulation of the ascending reticular system (ARAS), and that both these actions are blocked by the muscarinic receptor antagonist, atropine. It has even been shown in humans that REM sleep is induced by intravenous infusion of centrally-acting cholinomimetic agents, such as arecoline or physostigmine (an acetylcholinesterase inhibitor), and, again, the effects of these treatments are inhibited by atropine. Yet antimuscarinic drugs do not have any marked sedative effects on behavioural arousal. This could mean that sedation requires recruitment of the 'sleep' system, as well as blockade of arousal.

As outlined previously (Chapter 6), cholinergic neurons are located in two broad groups of nuclei, both of which are linked to the ARAS and thalamus (Fig. 22.6). One group lies rostrally in the basal forebrain, within the nucleus basalis, medial septum and diagonal band. This system is more active during the waking state than during sleep and blocking its effects could well explain how antimuscarinic drugs inhibit EEG desynchronisation. The nucleus basalis, which sends diffuse projections to the cortex and hippocampus, has also been linked with memory function (Chapter 18).

The second cluster of neurons lies more caudally, near the pons, in the pedunculo-pontine (PPT) and laterodorsal tegmental (LDT) nuclei (see Fig. 22.6) and could be regarded as part of the ARAS (see McCormick 1992). It innervates the non-specific thalamic nuclei as well as some more specific ones like the lateral geniculate nucleus (visual pathway), the pontine reticular formation and occipital cortex. Because long

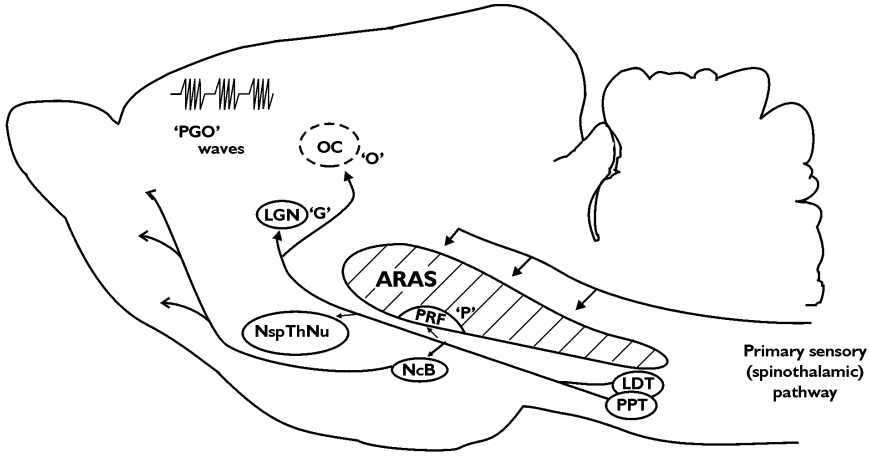

Figure 22.6 Cholinergic influences on sleep and arousal. Cholinergic neurons are found primarily either rostral to the ascending reticular activating system (ARAS) in the nucleus basalis (NcB) caudally in the pedunculo pontine tegmentum (PPT) nucleus. The former, which innervate much of the cortex, receive inputs from the ARAS and appear to be partly responsible for maintaining the EEG and behavioural arousal. The latter innervate non-specific (NspThNu) and specific (SpThN) thalamic nuclei, including the lateral geniculate nucleus as well as the pontine reticular formation (PRF) and occipital cortex (OC). The high-voltage pontine–geniculo–occipital (PGO) waves they initiate in all three areas are characteristic of REM sleep, which is reduced by their destruction

bursts of high-voltage waves occur in all these three terminal areas during REM sleep, forming the pontine–geniculo–occipital (PGO) waves described above, they could derive from the PPT (see Hobson 1992).

In fact, there is a good deal of evidence to support this suggestion. First, more than half the neurons in the PPT fire rhythmically only when PGO waves are evident and their firing starts immediately before the PGO waves appear. Second, in cats, REM sleep is augmented by direct injection of either carbachol, or more selective muscarinic agonists, or the anticholinesterase, neostigmine, into the pontine reticular formation (one of the projection sites for PPT). Third, REM sleep is abolished by lesion of the PPT nucleus but, interestingly, not by lesion of the LDT.

Overall, there are compelling reasons to believe that cholinergic pathways not only play a part in arousal but also contribute to the induction of the 'arousal-like' features of REM sleep.

HISTAMINE

Although histamine has mixed excitatory and inhibitory effects on central neurons, those antihistamines (H_1-receptor antagonists) that enter the brain produce sedation; this indicates that the predominant overall effect of histamine is excitatory. The preferred explanation for this rests on evidence that histaminergic neurons in the posterior hypothalamus are active in waking and silent in deep SWS and REM sleep.

The histamine neurons in the tuberomammillary nucleus, in the posterior hypothalamus, project to the cortex and thalamus and receive an afferent input from

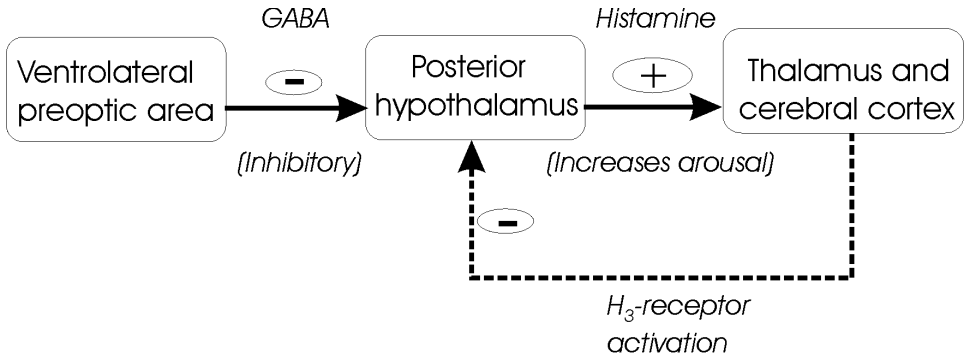

Figure 22.7 Histamine influences on sleep and arousal. The activity of histamine-releasing neurons increases with arousal and diminishes during sleep. Both H_1 antagonists and agonists of H_3-autoreceptors depress release of histamine and reduce arousal (see text for details)

GABAergic neurons in the ventrolateral preoptic area (VLPO). Since the VLPO is more active in SWS sleep, this phase of the sleep cycle could depend in part on GABAergic inhibition of histamine-releasing neurons that project to the cortex (Fig. 22.7). What activates the VLPO is not clear, however. There also seems to be some feedback control of histamine release because H_3-receptor agonists, that activate the autoreceptors on histamine-releasing neurons and reduce release of this transmitter, augment SWS while H_3-receptor antagonists have the opposite effect. Finally, other effects of histamine that could contribute to increased arousal are increasing the activity of excitatory cholinergic neurons in the basal forebrain and inhibition of neurons in the hypothalamic preoptic area which promote sleep.

A much higher profile has recently been claimed for histamine in the control of circadian rhythm (see Jacobs, Yamatodani and Timmerman 2000). When injected intracerebroventricularly in rats it appears to alter locomotor and drinking rhythms in a somewhat complex manner depending on when it is given in the light–dark cycle, being most active when the animals are in constant darkness. Some of the effects can also be mimicked by increasing the amount of endogenous histamine released with the H_3 autoreceptor antagonist thioperamine. Certainly histamine has both excitatory (H_1) and inhibitory (H_2) effects on SCN neuron firing and autoradiography has revealed the presence there of H_1 receptors. Since glutamate and 5-HT have been shown to increase histamine release in the SCN and GABA to inhibit it, the above authors consider histamine to be the final mediator of their effects. Whether this is so remains to be seen for, despite the sedative effects of some H_1 antagonists, rhythm changes have not been reported with their long-term clinical use.

NORADRENALINE

Although some studies show that noradrenaline inhibits neuronal firing it is generally considered to increase behavioural activity and arousal. This impression is borne out to the extent that CNS stimulants, like amphetamine, increase release of noradrenaline and produce behavioural and EEG arousal, while reserpine, which reduces noradrenaline storage and hence release, causes psychomotor retardation. It is also supported by

evidence that the firing rate of neurons projecting from the locus coeruleus is greater during waking (1–2 Hz) than during SWS (0.2–0.5 Hz) and is increased even more as behaviour progresses from vegetative or consummatory activities (e.g. grooming or feeding) to vigilance. Furthermore, stimulation of the locus coeruleus in cats causes EEG desynchronisation and increases arousal, while a neurotoxic lesion of these neurons leads to EEG synchrony, increases SWS and reduces REM sleep. In fact, some ('REM-off') cells in the locus coeruleus stop firing altogether during REM sleep. Because a reduction in the activity of noradrenergic neurons precedes the onset of sleep, this change in activity is thought to have a permissive role in sleep induction.

How all these actions of noradrenaline are manifest is not clear and, unfortunately, most experiments in this area have been carried out on anaesthetised animals which, arguably, are not ideal for investigating mechanisms underlying arousal! One of the few investigations to have been carried out in unanaesthetised rats has shown that infusions of noradrenaline into the nucleus basalis of the medial septum increases waking (and the γ-wave activity of the waking phase), but reduces the γ-waves of SWS.

These changes, which are thought to be mediated by activation of β-adrenoceptors, suggest that noradrenaline increases cholinergic influences on arousal, in the nucleus basalis, at least (Cape and Jones 1998). However, a fairly common side-effect of β-adrenoceptor antagonists, used clinically to relieve hypertension, is sleep disturbance which is expressed as nightmares, insomnia and increased waking. Clearly, these drugs must have additional actions either in other brain centres, or non-selective effects on other (possibly 5-HT_{1A}) receptors that have quite different effects on arousal. It has even been suggested that β-blockers disrupt sleep patterns by inhibiting melatonin synthesis and release, but this is controversial.

In contrast, α_2-adrenoceptor agonists are well-known for their sedative effects. Since their activation of presynaptic α_2-autoreceptors will reduce noradrenergic transmission, by depressing the firing of neurons in the locus coeruleus and release of noradrenaline from their terminals, this action is entirely consistent with the proposal that increased noradrenergic transmission increases arousal. Although this presynaptic action of α_2-agonists would explain their sedative effects it must be borne in mind that many α_2-adrenoceptors in the brain are in fact postsynaptic. Their role (if any) in sedation is unclear but it must be inferred that, if they make any contribution to sedation, then either a specific brain region or a specific α_2-adrenoceptor subtype is involved. Another possible confounding factor is that many α_2-adrenoceptor ligands have an imidazoline structure (see Chapter 8) and the recently discovered imidazoline receptors are also thought to influence the sleep cycle and arousal. Even less is known about the role of α_1-adrenoceptors on arousal partly because most drugs acting at these receptors do not readily cross the blood–brain barrier.

The role of noradrenergic neurons from the locus coeruleus on behaviour during the waking phase is rather controversial. It is doubtful that noradrenaline release is actually required for waking because animals with more than a 90% lesion of these neurons are still capable of staying awake, although they are rather subdued. Nevertheless, the single-unit activity of these neurons is increased by sensory stimuli ranging from those that cause physical discomfort (e.g. tailpinch) to environmental stimuli (e.g. tones and light flashes), especially those that provoke orientation to the stimulus (e.g. approach of the experimenter). The evoked neuronal response typically shows a brief (phasic) burst of activity followed by a quiescent period of post-stimulus inhibition but this response, along with behavioural arousal, habituates on successive presentation of the stimulus.

Such findings have led to suggestions that neurons in the locus coeruleus complex serve as a central 'alarm' system while others have argued that their increased neuronal firing during the waking period mediates changes in 'selective attention'. It has even been suggested that the tonic activity of these neurons could determine overall arousal, whereas the more transient, phasic, response determines 'attentiveness'. In fact, these neurons could serve all these purposes, thereby helping to protect the individual from threatening stimuli as well as directing attention to interesting, or salient environmental features (see also Chapter 8).

Few studies have investigated the role in behaviour of noradrenergic neurons originating in the nuclei of the lateral tegmental area (see Chapter 8). However, what little evidence there is suggests that they respond primarily to unconditioned environmental stimuli but are capable of adaptive changes in their activity on repeated presentation of the stimulus. Because noradrenergic neurons arising in the lateral tegmental nuclei have numerous reciprocal connections with other brainstem nuclei involved in homeostasis (e.g. regulating blood pressure and heart rate), it is likely that they make an important contribution to the adjustments in the activity of the peripheral autonomic system during the various states of sleep and waking (see Goldstein 1995).

DOPAMINE

The role of this neurotransmitter in the sleep–waking cycle has not received as much attention as that devoted to noradrenaline and interpretation of existing evidence is not straightforward. On the one hand, the firing rate of neurons projecting from the dopaminergic neurons in the ventral tegmental area does not vary across the sleep–waking cycle and, in any case, the dopaminergic innervation of the cortex is much more restricted than that of noradrenaline or 5-HT. On the other hand, drugs that modify dopaminergic transmission do affect arousal albeit in complex ways (see Gottesmann 1999).

Low doses of the dopamine agonist, apomorphine, induce SWS and, in humans, dopamine agonists can induce somnolence which is a problem when treating Parkinson's disease. This action is thought to be due to activation of presynaptic D_2-autoreceptors and some antagonists of this receptor increase waking state and reduce both non-REM and REM sleep. That a reduction in firing of dopaminergic neurons is associated with reduced arousal is consistent with evidence that local infusion of GABA into the dopaminergic ventral tegmental area also reduces waking. However, others have suggested that activation of postsynaptic D_2-receptors in the dorsal striatum is responsible.

By contrast, high doses of dopamine agonists increase arousal and cortical desynchronisation, possibly by activating postsynaptic D_2-receptors. Indeed, local infusion of dopamine into the nucleus accumbens increases waking, an effect blocked by the D_2-receptor antagonist, haloperidol. Such an action is consistent with the general improvement in sleep (especially sleep continuity) in patients treated with neuroleptics, such as haloperidol and clozapine, which share D_2-receptor antagonism as a common target. However, the various changes seen in the different phases of the EEG seem to depend on the actual compound tested.

5-HYDROXYTRYPTAMINE

This neurotransmitter presents something of a paradox in respect of its role in sleep and waking behaviour, although its importance to both is undoubted. Early experiments

suggested that an increase in 5-HT transmission actually helps to induce sleep (see Jouvet 1974). Thus *p*CPA, which blocks the synthesis of 5-HT, causes insomnia in cats and reduces SWS; this insomnia is reversed by giving the 5-HT precursor, 5-hydroxytryptophan (5-HTP), which bypasses the *p*CPA block. Also, a lesion of the dorsal Raphé nucleus (DRN) produces insomnia, the degree of which is proportional to the loss of 5-HT neurons and the decrease of 5-HT turnover in their projection areas. Despite such lesions, sleep patterns return to normal after some days and, if they are made in new-born rats, sleep patterns normalise after a few weeks, suggesting that they are not solely dependent on 5-HT.

In contrast to this evidence that 5-HT activity decreases arousal, antidepressants are generally thought to increase serotonergic transmission while the central depressant, reserpine, reduces it, although it must be remembered that both these treatments affect central noradrenergic transmission as well. Nevertheless, direct stimulation of Raphé neurons, or systemic administration of a 5-HT precursor, actually increases waking. This suggests that 5-HT has either an excitatory influence on behaviour and/or an inhibitory effect on sleep. This view is supported by electrophysiological recordings of the activity (firing frequency) of neurons in the cat DRN. Insofar as it can be certain that it is serotonergic neurons that are being monitored in this nucleus, these studies have shown that, during quiet waking, their activity is about 2–3 spikes/s, but that this rate decreases progressively and becomes less regular as sleep progresses to SWS. In fact, these neurons become virtually totally quiescent during REM sleep and this reduction in activity is probably effected by GABAergic inputs to the DRN. For a review of all this evidence, see Jacobs and Azmitia (1992).

Assigning a particular role for changes in 5-HT transmission in sleep is confounded by the existence of 5-HT neurons in several distinct Raphé nuclei (Fig. 22.8; see also Chapter 9). These project to different regions of the brain but the differences in their functional influences are, as yet, poorly understood. Most studies have in fact investigated the DRN, which innervates forebrain areas, but it does seem that other serotonergic nuclei in the medulla show a similar pattern of responses. Thus, neurons in the 'inferior' Raphé nuclei (the Raphé magnus (NRM), the nucleus Raphé obscurus (NRO) and the nucleus Raphé pallidus (NRP)) (see Fig. 22.8) which project to the lower brainstem and spinal cord, all show a reduced discharge during SWS when compared with that in the awake subject. However, their firing rate is generally higher than in the DRN. Moreover, unlike DRN neurons, those in the NRO and NRP continue to fire, albeit at a reduced frequency, during REM sleep. The implications of these differences in the regulation of the sleep cycle are unclear.

The role of 5-HT transmission in waking behaviour is even less clear. The tonic activity of DRN neurons during 'active' waking is certainly greater than during 'quiet' waking but it is not increased further by arousing or threatening stimuli. However, environmental stimuli that provoke behavioural orientation induce a marked phasic increase in serotonergic neuronal activity (see Chapter 9) suggesting that they do have some role in the response to stimuli requiring attention.

A link between 5-HT release and increased waking is supported by evidence from *in vivo* microdialysis of cats and rats. This has confirmed that the extracellular concentration of 5-HT in all brain regions studied to date is lower during both SWS and REM sleep than in the awake state (see Portas, Bjorvatn and Ursin 2000). Interestingly, if behaviour is maintained at a constant level, the activity of 5-HT neurons does not show circadian variation although 5-HT turnover in the brain areas to which they project

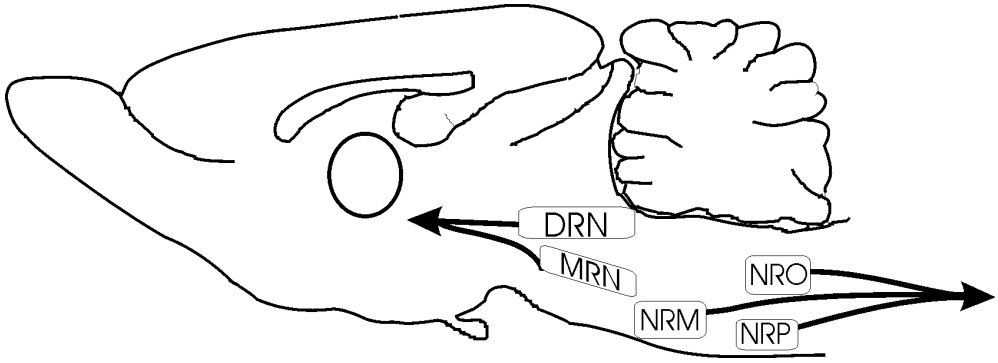

Figure 22.8 The distribution of brainstem Raphé nuclei. Neurons that release 5-HT are clustered in two groups of nuclei in the pons and upper brainstem. The 'superior' group, which projects to forebrain areas, includes the dorsal Raphé nucleus (DRN) and the median Raphé nucleus (MRN). The 'inferior' group projects to the medulla and spinal cord and includes the nucleus Raphé pallidus (NRP), the nucleus Raphé obscurus (NRO) and the nucleus Raphé magnus (NRM)

does show such a rhythm. The reasons for this apparent dissociation between firing rate and transmitter release are not clear but it does suggest that neuronal firing rate is not necessarily a reliable indicator of transmitter release in the terminal field.

One specific theory for the role of 5-HT in arousal suggests that serotonergic transmission serves to coordinate target cell responses by adjusting their excitability to match the subjects' general level of arousal. In so doing, they are responsible for gating motor output and coordinating this with homeostatic and sensory function (Jacobs and Azmitia 1992; Jacobs and Fornal 1999). This would be consistent with evidence that, like the noradrenergic system, increases in the firing rate of neurons in the DRN precede an increase in arousal. The frequency of discharge would code the state of arousal and prime target cells for forthcoming changes in the response to sensory inputs.

Apart from the problem of trying to associate the effects of 5-HT with specific nuclei, there is also no clear picture of which 5-HT receptors mediate any of these changes in sleep and waking. This is not least because of the large number of receptor subtypes, the limited receptor selectivity of most test drugs, species differences in the response, as well as time- and dose-related differences in the response to any given agent. 5-HT is also known to affect noradrenaline and dopamine release in the brain (see Stanford 1999) and such interactions undoubtedly explain some of the inconsistencies between the early findings and recent studies of the role of these different 5-HT neurons in sleep.

Nevertheless, it is evident that activation of many different receptor subtypes affect the sleep–waking cycle. For instance, recent evidence suggests that activation of 5-HT_{1A}, 5-HT_{1B}, 5-$HT_{2A/C}$ and 5-HT_7 receptors in the SCN all affect circadian rhythms. Activation of 5-HT_{1B} (presynaptic) receptors in the retinohypothalamic tract is thought to attenuate 5-HT release and so blunt light inputs to the SCN and reduce its phototic regulation. In contrast, postsynaptic 5-HT_7 receptors, 5-HT_{2C}, and possibly postsynaptic 5-HT_{1A} receptors, are thought to have an important role in phototic entrainment and to mediate phase-shifts in circadian rhythms (reviewed by Barnes and Sharp 1999). In addition to these effects on circadian rhythms, it is clear that 5-HT receptors affect sleep more directly. A detailed review of this subject is to be found in Portas, Bjorvatn and Ursin (2000) but key findings are summarised here.

Table 22.1 Effects of activation of 5-HT receptors on sleep–waking cycle

Receptor	REM	Waking	Location	Effect on 5-HT transmission
5-HT_{1A}	↑	↓	Presynaptic	↓
5-HT_{1A}	↓	↓	Postsynaptic	↑
5-HT_{1B}	↓	↑	Not known	?
5-$HT_{2A/2C}$	↓	↑	?Postsynaptic	↑
5-HT_3		↑	Postsynaptic	↑

The actions of 5-HT_{1A} receptor agonists in rats depend on their route of administration (Bjorvatn and Ursin 1998). When they are given systemically they cause a transient increase in waking time and a reduction in SWS and REM sleep which is followed by a delayed increase in SWS. This latter response is possibly mediated by activation of inhibitory postsynaptic 5-HT_{1A} receptors in the nucleus basalis (Table 22.1). Certainly, local infusion of 5-HT_{1A} agonists into this area increases SWS. Another contributory factor is suggested by the reduction in waking and increase in SWS following intrathecal infusion of 8-OH-DPAT. This is thought to reflect inhibition of primary sensory afferents, by activation of presynaptic 5-HT_{1A} receptors, an action which would be conducive with induction of sleep. However, infusion of low concentrations of the 5-HT_{1A} agonist, 8-OH-DPAT, into the DRN to activate autoreceptors induces a type of REM sleep which is explained by a reduction in the firing rate of 5-HT neurons. In turn, this is presumed to result in disinhibition of mesopontine cholinergic neurons in the PPT and LTD nuclei which are responsible for REM sleep. Such a scheme is supported by evidence that local infusion of a 5-HT_{1A} agonist into these areas reduces REM sleep, presumably by inhibition of mesopontine cholinergic neurons by postsynaptic 5-HT_{1A} receptors.

Administration of 5-HT_{1B} receptor agonists increases waking time and reduces REM sleep. This is consistent with recent evidence gathered from 5-HT_{1B}-receptor knock-out mice which exhibit more REM sleep and less SWS than the wild-type. Moreover, 5-HT_{1B} agonists reduce, while antagonists increase, REM sleep in the wild-type mouse, but neither type of compound has any effect in the knock-outs (Boutrel *et al.* 1999). Unfortunately, it is not known whether these actions are mediated by presynaptic, postsynaptic or heteroceptors and therefore whether 5-HT activity is increased or decreased. It is also not helped by the limited selectivity of test agents.

5-$HT_{2A/2C}$ agonists increase waking and reduce SWS and REM sleep in humans and rats, possibly through an action in the thalamus. Conversely, blockade of 5-HT_{2A} receptors, e.g. by ritanserin, increases SWS, an action that might contribute to the beneficial effects of antidepressants that share this action. However, these findings are confounded by evidence that activation of 5-HT_{2C} receptors increases SWS.

Infusion of 5-HT_3 receptor agonists into the nucleus accumbens increases waking and reduces SWS, although REM sleep is unchanged. These effects of 5-HT_3 receptor activation are prevented by co-administration of a D_2-receptor antagonist. This is consistent with evidence that activation of 5-HT_3 receptors can increase dopamine release and points to functional interactions between these two groups of neurons that affect the sleep–waking cycle. Such interactions will certainly confound any attempts to define the specific role of 5-HT in the regulation of sleep and arousal.

Overall, 5-HT transmission seems to increase during waking and to decline in sleep although it may only reach its minimal level, in some neurons anyway, during REM

sleep. Whether its role is simply to prime target cells to enable an increase in the motor activity associated with waking, as has been suggested, remains to be seen.

ADENOSINE

It is perhaps not surprising that, since adenosine has been presented as an endogenous inhibitor of neuronal function with its antagonists, like theophylline, being stimulants (see Chapter 13), it should have been implicated in sleep induction.

In fact EEG studies have shown that administration of an adenosine A_1 agonist increases SWS in humans and induces it in sleep-deprived rats while adenosine also inhibits the important cortical activating brainstem cholinergic neurons. Of more physiological significance is the finding from microdialysis in rats that the extracellular concentration of adenosine progressively increases in the hippocampus, reaching a maximum at the end of the animal's active (lights off) period. After that, it falls sharply within an hour as the animal enters the quiet (lights on) sleepy period (see Huston *et al.* 1996). Of course, the hippocampus is not generally associated with sleep patterns and whether these studies establish adenosine as a potential sleep inducer, or merely as an 'activity-restrictor' that facilitates sleep, is unclear.

AMINO ACIDS

Since most excitatory transmission is mediated by glutamate this must be involved in the sleep–waking cycle. It certainly mediates the input of the retinohypothalamic tract to the SCN, apart from afferent inputs more generally to the ARAS, etc. So far, specific *in vivo* manipulation of the direct glutamate input to the SCN has not been possible.

The fact that SCN neurons contain GABA, and that this appears to be the neurotransmitter released by the geniculohypothalamic tract onto the SCN, clearly puts it in a prime position for regulation of sleep rhythms. However, its precise role is unclear, not least because it can act as an excitatory, as well as an inhibitory, neurotransmitter in this nucleus and that these varied responses appear to follow a circadian rhythm (see Chapter 11). Again, specific manipulation of this pathway is difficult although GABA enhancement generally (e.g. by benzodiazepines) is, of course, sedative (see later section on drug-induced sleep).

SLEEP FACTORS

In classical times, sleep was thought to be induced by sleep factors (vapours) emanating from food in the stomach. To this day, and despite the encyclopedic evidence that neurotransmitters have discrete effects on sleep and arousal, the idea still lingers that there are sleep-inducing ('somnogenic') factors. These are thought to have a pervading influence on sleep throughout the brain, although the stomach is no longer regarded as their source! This view was strongly encouraged by experiments, carried out in the early twentieth century, by Pieron in Paris, who showed that the CSF of sleep-deprived dogs contained a substance that had a somnogenic effect when infused into non-sleep-deprived animals. Since then, many candidate sleep substances have emerged, some of which are more convincing than others.

The first serious attempts to identify and characterise an endogenous somnogenic agent was carried out by Pappenheimer and colleagues (see Pappenheimer 1983) who found that transferring samples of CSF from sleep-deprived goats into normal rabbits

increased the latter's REM sleep. Chemical extraction from thousands of rabbit brains and many gallons of human urine yielded a sleep factor and established it as a muramyl peptide. Unfortunately muramyl peptides are not synthesised by mammalian cells but are components of bacterial cell walls. Apart from the obvious possibility of mere contamination, it is not clear how the substance turned up in the CSF and brain tissue. Despite this setback, and some scepticism about whether somnogenic peptides exist at all, research still continues in this area and many candidates have been suggested. These include well-known peptides such as prolactin, CCK-8, VIP and somatostatin as well as some novel ones such as δ-sleep-inducing peptide. (For a full review of this subject, see Garcia-Garcia and Drucker-Colin 1999.)

Another line of research has produced convincing evidence that the pro-inflammatory cytokines, interleukin IL-1β and TNFα modify the sleep cycle: these agents generally increase non-REM sleep and suppress REM sleep. IL-6 also reduces REM sleep and SWS in the first half of the sleep cycle but subsequently increases SWS. However, all these responses vary with dose, test species and even time of day. These factors are produced by T-cell lymphocytes but their receptors are associated with neurons, astrocytes, microglia and endothelial cells. Because these agents induce nitric oxide synthase, and there is some evidence that nitric oxide increases waking, possibly through modulation of ACh release in the medial pontine reticular formation, there is no need for them to cross the blood–brain barrier (although there is evidence that they do). Nevertheless, how these factors actually cause changes in the sleep cycle is as yet unclear. An indirect effect via changes in the rate of prostaglandin synthesis (see below) is one possibility but others include modulation of 5-HT_{2A}-mediated serotonergic transmission and suppression of glutamatergic neuronal activity through an adenosine-dependent process.

Prostaglandins, in particular PG_{D2}, have also been shown to act as sleep-promoting substances. PG_{D2} is synthesised in the arachnoid membrane and choroid plexus and its receptors are prevalent in the basal forebrain. Moreover, its concentration in the CSF shows a circadian rhythm and increases during sleep deprivation. It is not yet known how PG_{D2} influences sleep but when it is infused locally, it changes the firing rate of neurons in the preoptic and basal forebrain areas in ways suggesting that it promotes sleep. Like the interleukins, and TNFα, mechanisms proposed to explain these actions include modification of monoaminergic or adenosinergic transmission.

Finally, the endogenous fatty acid amide, oleamide, has somnogenic effects. This compound is chemically related to the endogenous ligand for cannabinoid receptors, anandamide. Although oleamide has even been reported to augment anandamide binding to cannabinoid (CB_1) receptors, it is still not known whether this action is relevant to its somnogenic effects. Oleamide has been shown to potentiate (benzodiazepine-sensitive) $GABA_A$ receptor responses through a mechanism that seems to involve the γ-subunit. However, modifications of 5-HT_2, muscarinic, metabotropic glutamate and NMDA receptor function have all been suggested as possible mechanisms.

DRUG-INDUCED SLEEP

Setting aside the general anaesthetics, which do not directly modify the function of any particular neurotransmitter, all the drugs that are used to induce sleep, i.e. the 'hypnotics', augment the function of GABA and so directly depress neuronal function and probably facilitate cortico-thalamic synchrony. Most of them are benzodiazepines

and even those that are not, like zopiclone (a cyclopyrrolone) and zolpidem (an imidazopyridine), act on the benzodiazepine receptor (see Chapter 19). Many benzodiazepines have a long half-life (20+ h) and a similar spectrum of activity, being both anxiolytic and sedative, and unless these effects are actually required during the day after the hypnotic action (as would occur with nitrazepam and flurazepam) it is important to use those benzodiazepines with a short half-life: e.g. temazepam, lorazepam

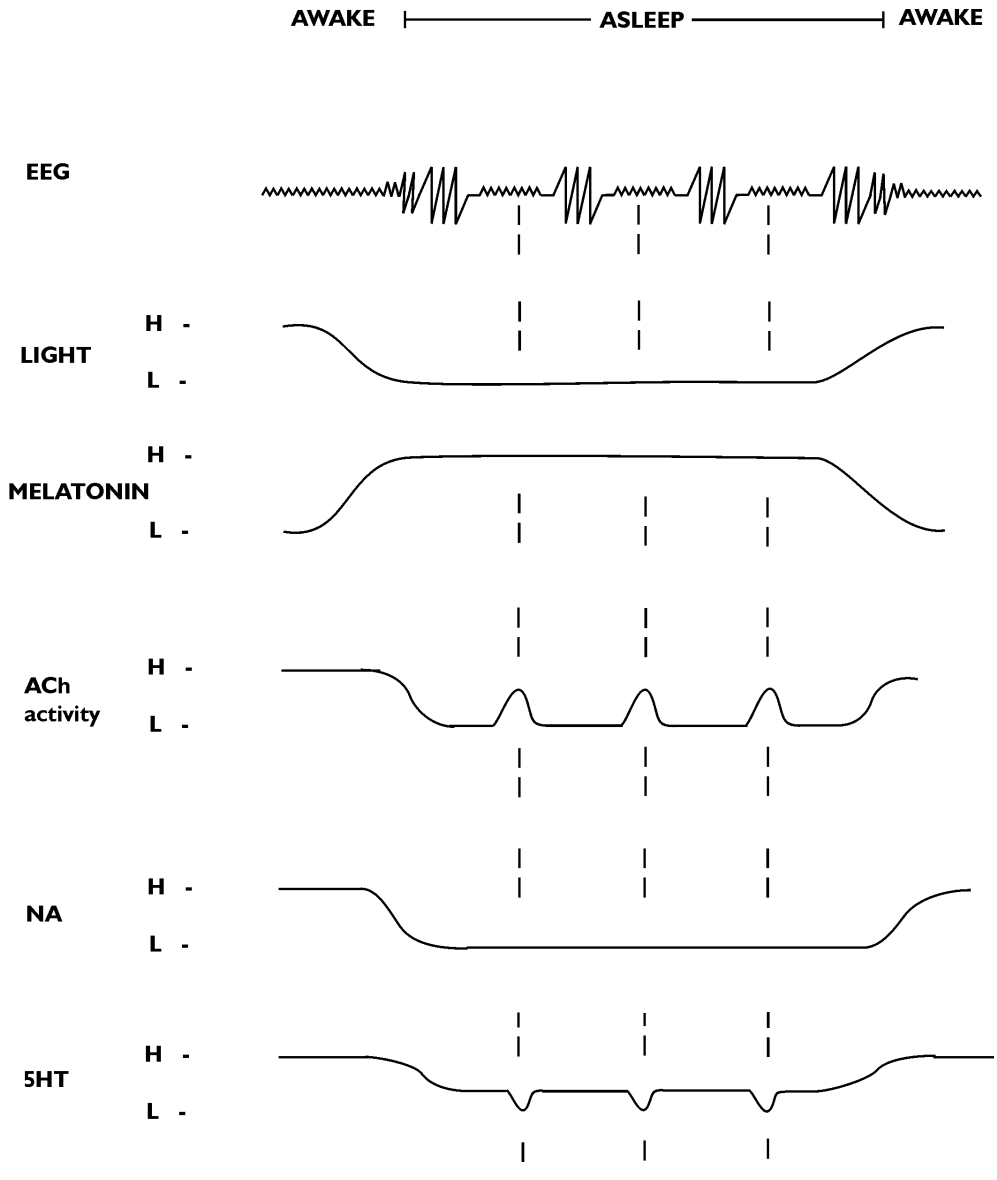

Figure 22.9 Summary of the influence of varying factors on sleep and waking. The EEG is shown diagramatically in the typical arousal (awake) state and in both non-REM (slow wave) and REM sleep. Appropriate activity levels, high or low, are shown for the different factors such as light input, melatonin secretion or ACh, NA, and 5-HT function in the different phases

and lormetazepam ($T^{1/2}$ s = 6–10 h). All hypnotics appear to increase SWS at the expense of REM sleep and this has been suggested as a cause of irritability and possibly even the cognitive deficits claimed to be associated with use of these drugs.

That hypnotic drugs do not produce a natural sleep should not be surprising in view of the fact that they merely augment GABA and depress neuronal function, when sleep is clearly a very complex phenomenon involving the integrated activity of a number of neurotransmitters. To what extent it might be possible to induce sleep by simultaneously blocking the action of ACh, noradrenaline, 5-HT and histamine is not known. It would be an interesting experiment but the peripheral and other central effects are too numerous and dangerous to contemplate its trial.

SUMMARY

Sleep appears to rely on synchrony in cortico-thalamic reciprocal pathways in which GABA plays an important part such that sleep can be enhanced by augmenting GABA function. Probably such synchrony is the state to which the nervous system and our bodies return unless it can be disrupted as a result of stimulation by appropriate afferent inputs. Some of this information may come from the SCN, which is activated simply by the reception of light, but other diffuse, ascending inputs from the reticular activating system certainly cause EEG arousal also. In turn, activation of this system depends on normal sensory inputs to the body since it receives collaterals from classical sensory axons projecting to specific thalamic nuclei. Part of this activating effect appears to be mediated by cholinergic neurons of the nucleus basalis but other ascending projections from brainstem nuclei utilising acetylcholine, noradrenaline and histamine also disrupt the cortical synchrony thereby causing EEG desynchronisation and behavioural arousal.

To what extent we depend on these neuronal projections to stay awake is uncertain but it seems clear that noradrenaline, histamine, 5-HT and cholinergic ones all become less active, or quiescent, when sleep starts except that, periodically, certain cholinergic neurons in the prepontine nucleus discharge and initiate REM sleep while the neurons releasing the classical monoamines generally cease firing (Fig. 22.9). The role of other chemicals in sleep induction is even less clear, although melatonin release is certainly increased during sleep.

This, of course, is only an outline of what has been observed during sleep and waking. It is evident that, over the last 50 years, a great deal has been learned about the sleep pattern and its underlying neurobiology. Indeed, it is now clear that the induction and regulation of sleep and arousal involves the concerted influences of a wide range of neurotransmitters and, possibly, non-neuronal factors. However, we still cannot explain how sleep occurs or how these neurotransmitter systems are actually activated, inhibited or coordinated to control our sleep and waking. Also, we still do not know why sleep is necessary at all. The challenge of these questions still remains.

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