# Neuronal Networks Regulating Sleep and Arousal: Effect of Drugs

**Elemer Szabadi**

**Abstract** The three vigilance states (wakefulness [W], slow wave sleep [SWS], rapid eye movement sleep [REMS]) are controlled by distinct, but interconnected, networks of neurons. The sleep/arousal network consists of separate systems of W-promoting and SWS-promoting neurons, located in nuclei in the basal forebrain, diencephalon and brainstem. Each neuronal system operates via a distinct neurotransmitter, providing its unique "neurochemical signature". W-promoting neurons are active during W and quiescent during SWS, whereas SWS-promoting neurons are active during SWS and cease to fire during W. The level of arousal at any one time reflects the intricate balance between W-promoting and SWS-promoting systems. W is the result of cortical activation by W-promoting neurons; sleep ensues when SWS-promoting neurons switch off the W-promoting systems. REMS is regulated by a network of REMS-promoting and REMS-inhibiting neurons located in the brainstem and hypothalamus. A third network is responsible for the regulation of the circadian rhythmicity of the wakefulness/sleep cycle. The neurochemical signatures of W-promoting and SWS-promoting neurons make it possible to develop drugs that, by targeting specific neuroreceptors and synaptic mechanisms, have predictable effects on sleep and arousal. Arousal-modifying drugs act by tipping the balance between W-promoting and SWS-promoting neuronal activity. Thus a sedative drug, useful for the treatment of insomnia, may act by activating a SWS-promoting system (e.g. benzodiazepines, melatonin receptor agonists) or inhibiting a W-promoting system (e.g. H1-antihistamines, orexin receptor antagonists). Conversely, an alerting drug, useful for the treatment of excessive daytime sleepiness, may inhibit a SWS-promoting system or activate a W-promoting system (e.g. psychostimulants, H3 histamine receptor antagonists).

## Abbreviations

| | |
|---|---|
| BF | Basal forebrain |
| DMH | Dorsomedial hypothalamus |

E. Szabadi (✉)
Developmental Psychiatry, Queen's Medical Centre, E Floor, South Block, Nottingham NG7 2U, UK
e-mail: elemer.szabadi@nottingham.ac.uk



A. Guglietta (ed.), *Drug Treatment of Sleep Disorders*, Milestones in Drug Therapy,
DOI 10.1007/978-3-319-11514-6_2

| | |
|---|---|
| DR | Dorsal raphe nucleus |
| LC | Locus coeruleus |
| LDT | Laterodorsal tegmental nucleus |
| LGN | Lateral geniculate nucleus |
| LH | Lateral hypothalamic area |
| MCH | Melanin concentrating hormone |
| PBN | Parabrachial nucleus |
| PC | Precoeruleus nucleus |
| PF | Perifornical area |
| PPT | Pedunculopontine tegmental nucleus |
| PVN | Paraventricular nucleus |
| SCN | Suprachiasmatic nucleus |
| SLD | Sublaterodorsal nucleus |
| SPZ | Subparaventricular zone |
| Th | Thalamus |
| TMN | Tuberomamillary nucleus |
| TPR | Tegmentopontine reticular nucleus |
| vGC | Ventral gigantocellular nucleus |
| vlPAG | Ventrolateral periaquductal grey (matter) |
| VLPO | Ventrolateral preopic nucleus |
| VPAG | Ventral periaquductal grey (matter) |
| VTA | Ventral tegmental area |

## 1 Introduction

The mode of action of drugs used to treat the two major categories of sleep disorder (insomnia and hypersomnia) used to be interpreted on the basis that the level of arousal reflected the general excitability of the brain (Esplin 1970). Each level of general neuronal activity is reflected in the dominant frequency in the EEG and corresponds to a well-defined state of arousal along the "maximum depression (coma)" ↔ "maximum excitation (convulsions)" continuum. The drugs to treat insomnia (hypnotics) used to be regarded as general (nonselective) CNS depressants that depressed the activity of all neurons and shifted the levels of neuronal excitability and arousal downwards (towards sedation), whereas drugs to treat hypersomnia were classified as general (nonselective) CNS stimulants that increased the activity of all neurons and shifted the levels of excitability and arousal upwards (towards alertness). The effect of a given dose of a sedative or stimulant drug was dependent on the baseline (pre-treatment) level of activity of the CNS, a sedative drug causing a greater degree of sedation if the CNS was already depressed (Esplin 1970).

The lack of selectivity of sedative drugs (e.g. barbiturates, benzodiazepines) was supported by observations that, apart from hypnotic effects, they also possess some other actions (e.g. anaesthetic, anxiolytic, anticonvulsant) that can be related to

general CNS depression. However, on the other hand, it was also realized that even the nonselective drugs show some selectivity (e.g. different barbiturates have variable potencies as hypnotics, anaesthetics, anxiolytics and anticonvulsant). Furthermore, different groups of neurons show differential sensitivities: inhibitory interneurons are especially sensitive, leading to a paradoxical excitatory effect after the administration of relatively small doses of a sedative drug, whereas some neurons controlling vital functions (e.g. respiration) are relatively resistant (Esplin 1970).

It has been discovered over the past 20 years or so that arousal-modifying drugs are not nonselective, as used to be believed, but rather show a great degree of selectivity. This selectivity is both anatomical and neurochemical: the drugs act on specific neurochemically identified sites ("targets") in the brain that are critical for the regulation of sleep and wakefulness (Szabadi 2014). The functional significance of each target depends on its location within a well-defined arousal-modifying network (see Sect. 2).

Unravelling the sleep/arousal networks creates an opportunity for the classification of arousal-modifying drugs according to mechanism of action. The basis for this classification is the understanding that the level of arousal at any one time reflects the intricate balance between sleep-promoting and wake-promoting neuronal systems. Thus the level of arousal will be decreased by a drug that either activates a sleep-promoting system (e.g. benzodiazepines) or inhibits a wake-promoting system (e.g. antihistamines), whereas it will be increased by a drug that either activates a wake-promoting system (e.g. amphetamine, modafinil) or inhibits a sleep-promoting system. There are no therapeutically useful examples of alerting (stimulant) drugs that act by inhibiting a sleep-promoting system (e.g. the GABA receptor antagonists are also convulsants) (Szabadi 2014).

Targets of arousal-modifying drugs are specified both at the level of the arousal system and the cellular mechanism within that system. For example, a drug may be aimed at blocking release-inhibiting H3 receptors in the histaminergic wake-promoting system (see Sect. 4.1.3), or at stimulating melatonin receptors in the sleep-promoting suprachiasmatic nucleus/melatonin system (see Sect. 3.4.2).

## 2 Neuronal Networks Regulating Sleep and Arousal

On the basis of the level of arousal, it is possible to distinguish between three vigilance states (Fort et al. 2009): wakefulness (W), slow wave sleep (SWS) and rapid eye movement (REM) sleep (REMS). Each vigilance state is defined by the EEG: W and REMS are characterized by desynchronized, low amplitude, high frequency (alpha and beta) waves, whereas in SWS the EEG is synchronized with high amplitude low frequency (delta and theta) waves (Lin et al. 2011). The three vigilance states are regulated by distinct neuronal networks, consisting of neuronal groups (nuclei) and their connections, located in the basal forebrain, diencephalon and brainstem. Each neuronal group within a network has its unique

"neurochemical signature" derived from the neurotransmitter used. It is possible to distinguish between three separate, but interconnected, networks: the W/SWS network, the REMS network and the circadian network.

## *2.1 Sleep/Arousal Network*

The level of arousal at any one time reflects the intricate interplay between distinct W-promoting and SWS-promoting nuclei. Each of these nuclei is defined both anatomically and neurochemically, i.e. by the neurotransmitter utilized. The W-promoting nuclei are maximally active during wakefulness, show reduced activity during SWS and are quiescent during REMS. On the other hand, the SWS-promoting nuclei are maximally active during sleep and quiescent during wakefulness. The W-promoting and SWS-promoting nuclei, together with their major connections, are shown in Fig. 1. The W-promoting neurons send excitatory projections to the cerebral cortex and other W-promoting nuclei, and inhibitory outputs to SWS-promoting nuclei. The SWS-promoting neurons exert inhibitory influence on the W-promoting nuclei (Szabadi 2014).

W-promoting neurons can be found in the basal forebrain (BF), the diencephalon (thalamus and hypothalamus) and the brainstem. The BF contains W-promoting cholinergic neurons. There are W-promoting glutamatergic neurons in the thalamus. Hypothalamic W-promoting nuclei include the histaminergic tuberomamillary nucleus (TMN) and the orexinergic neurons of the lateral hypothalamic/perifornical are (LH/PF). W-promoting nuclei in the brainstem are the noradrenergic locus coeruleus (LC), the dopaminergic ventral tegmental area (VTA), the serotonergic dorsal raphe nucleus (DR) and the cholinergic pedunulopontine tegmental/laterodrosal tegmental nuclei (PPT/LDT). The PPT/LDT also contain REMS-promoting cholinergic neurons that are inhibited by the LC (see Sect. 2.2) (Szabadi 2014).

The basal forebrain contains some SWS-promoting GABAergic inhibitory neurons projecting to the cerebral cortex: these neurons are inhibited by a noradrenergic input from the LC (Fig. 5) (Szabadi 2013). The major SWS-promoting nucleus is the ventrolateral preoptic nucleus (VLPO) of the hypothalamus. GABAergic inhibitory neurons from the VLPO project to the TMN and LC. During wakefulness VLPO activity is switched off by an inhibitory input from the LC. Neurons containing the neuropeptide melanin concentrating hormone (MCH), located in the lateral hypothalamus, intermingled with orexinergic neurons, exert a SWS-promoting action by sending inhibitory projections to all W-promoting nuclei. There are also short-axon GABAergic inhibitory interneurons in the brainstem that exert a SWS-promoting effect by inhibiting W-promoting noradrenergic and dopaminergic neurons (Szabadi 2014).

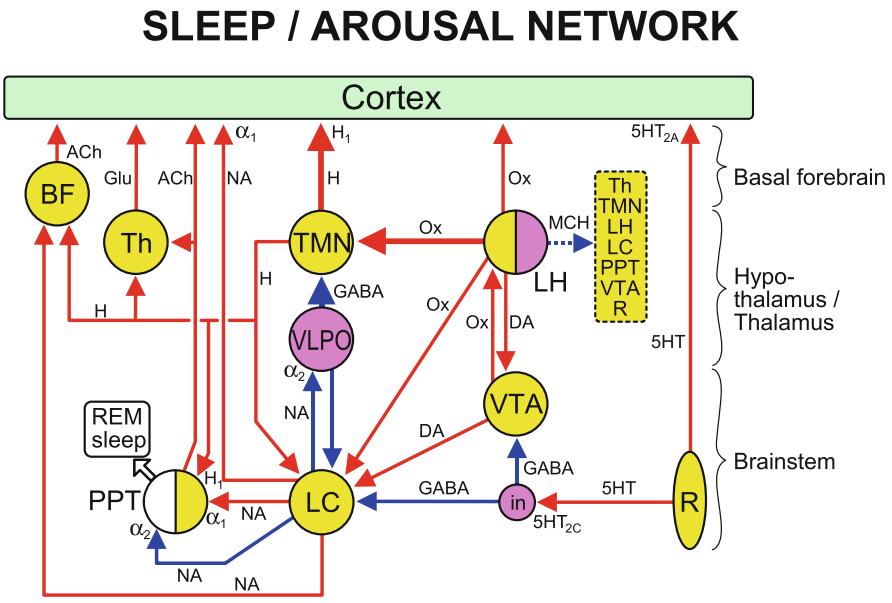


**Fig. 1** Schematic diagram of the connections within the neuronal network regulating slow wave sleep and wakefulness ("sleep/arousal network"). *Wake-promoting nuclei* (*yellow*): BF, basal forebrain; TMN, tuberomamillary nucleus; LH, lateral hypothalamic area; Th, thalamus; LC, locus coeruleus; VTA, ventral tegmental area; PPT, pedunculopontine tegmental nucleus; R, raphe nuclei. *Sleep-promoting nuclei* (*purple*): VLPO, ventrolateral preoptic nucleus; in, GABAergic interneurons; GABAergic interneurons; LH, lateral hypothalamic area. *REM sleep-promoting nucleus* (*white*): PPT, pedunculopontine tegmental nucleus. *Connections*: *arrows* (*red*: excitatory; *blue*: inhibitory). *Lettering next to arrow*: neurotransmitter (ACh: acetylcholine; NA: noradrenaline; H: histamine; Ox: orexin; GABA: γ-aminobutyric acid; DA: dopamine; 5HT: 5-hydroxytryptamine; Glu: glutamate; MCH: melanin-concentrating hormone). *Receptors*: $\alpha_1$, excitatory $\alpha_1$-adrenoceptors; $\alpha_2$, inhibitory $\alpha_2$-adrenoceptors; $H_1$, excitatory $H_1$ histamine receptors; $5HT_{2A}$ and $5HT_{2C}$, excitatory 5HT receptors. See text (Sect. 2.1) for details. Reproduced, with permission, from Szabadi (2014)

## 2.2 *REM-Sleep Network*

REM sleep is also called paradoxical or active sleep since, although the level of consciousness is restricted, the EEG is almost indistinguishable from that associated with W (McCarley 2007). REMS is also characterized, by definition, by the presence of phasic conjugate saccadic eye movements ("rapid eye movements") (Peigneux et al. 2001). In association with rapid eye movements electrical field potentials can be recorded in the pons, lateral geniculate bodies and occipital cortex (ponto-geniculo-occipital [PGO] spikes). PGO spikes are best recorded in experimental animals using deep electrodes, but they are also likely to occur in humans (McCarley 2007). Other features associated with REMS are muscle atonia (Chase 2013), penile erections (Hirshkowitz and Schmidt 2005) and dreaming (Hobson 2009).

The network regulating REMS consists of REMS-promoting and REMS-inhibiting nuclei, their interconnections and outputs to structures responsible for the somatic/behavioural changes characterizing REMS (Fig. 2). The neurotransmitters used by REMS-promoting nuclei are MCH (lateral hypothalamic area), acetylcholine (PPT/LDT) and glutamate (sublaterodorsal [SLD], precoeruleus [PC] and parabrachial [PBN] nuclei) (Saper et al. 2010; Luppi et al. 2011). REMS-inhibiting nuclei contain noradrenaline (LC), serotonin (DR), or GABA (ventrolateral periaqueductal grey matter [vlPAG]). The REMS-promoting neurons are active during REMS ("REM-on neurons") and quiescent during W and SWS, whereas the REMS-inhibiting neurons are active during W and SWS and quiescent during REMS ("REM-off neurons"). The REMS-inhibiting neurons of the brainstem inhibit the REMS-promoting neurons: the monoaminergic neurons, the cholinergic neurons, the GABAergic neurons and the glutamatergic neurons. In fact, there are reciprocal inhibitory links between the REMS-promoting and REMS-inhibiting nuclei (not shown in Fig. 2): this creates an unstable "flip-flop" situation allowing for switching in and out of REMS (Saper et al. 2010). The MCH-containing hypothalamic neurons can switch on REMS by inhibiting REMS-inhibiting monoaminergic and GABAergic neurons, and thus disinhibiting the cholinergic and glutamatergic REMS-promoting nuclei (Luppi et al. 2013; Jego et al. 2013).

Cortical activation during REMS is brought about by direct excitatory outputs from the cholinergic and glutamatergic REMS-promoting nuclei. The activation of the visual cortex, via an excitatory output from the lateral geniculate nucleus (LGN), originating from the PPT/LDT, underlies the generation of PGO spikes and dreams during REMS. Impairment of the balance between excitatory cholinergic and inhibitory serotonergic inputs to the LGN has been implicated in the generation of complex visual hallucinations (Manford and Andermann 1998).

Horizontal saccadic eye movements are controlled by premotor neurons in the tegmentopontine reticular nucleus (TPR) (Büttner-Ennever and Horn 1997). The activation of the TPR by a glutamatergic input from the SLD may be responsible for the rapid eye movements in REMS (Sánchez-López and Escudero 2011).

The activity of striated muscles is stimulated by a noradrenergic facilitatory influence on motoneurons originating from the LC, and is inhibited by a glycinergic/GABAergic influence on motoneurons originating from the ventral gigantocellular nucleus (vGC) of the medulla and a network of medullary and spinal interneurons (Saper et al. 2010). The atonia of the skeletal muscles and the relaxation of the facial (e.g. chin) muscles are due partly to the withdrawal of the noradrenergic stimulation of motoneurons (McGregor and Siegel 2010; Peever 2011) and partly to the activation of the glycinergic/GABAergic neurons in the vGC (Luppi et al. 2011; Chase 2013). Trigeminal motoneurons also cease their activity during REMS leading to the relaxation of the masseter muscle (Peever 2011). Recently a descending glutamatergic pathway from the SLD to the spinal inhibitory interneuron pool has been implicated in the causation of REMS-related atonia (Krenzer et al. 2011). In rapid-eye-movement-sleep behaviour disorder (RBD), a parasomnia associated with REMS, skeletal muscle atonia is absent

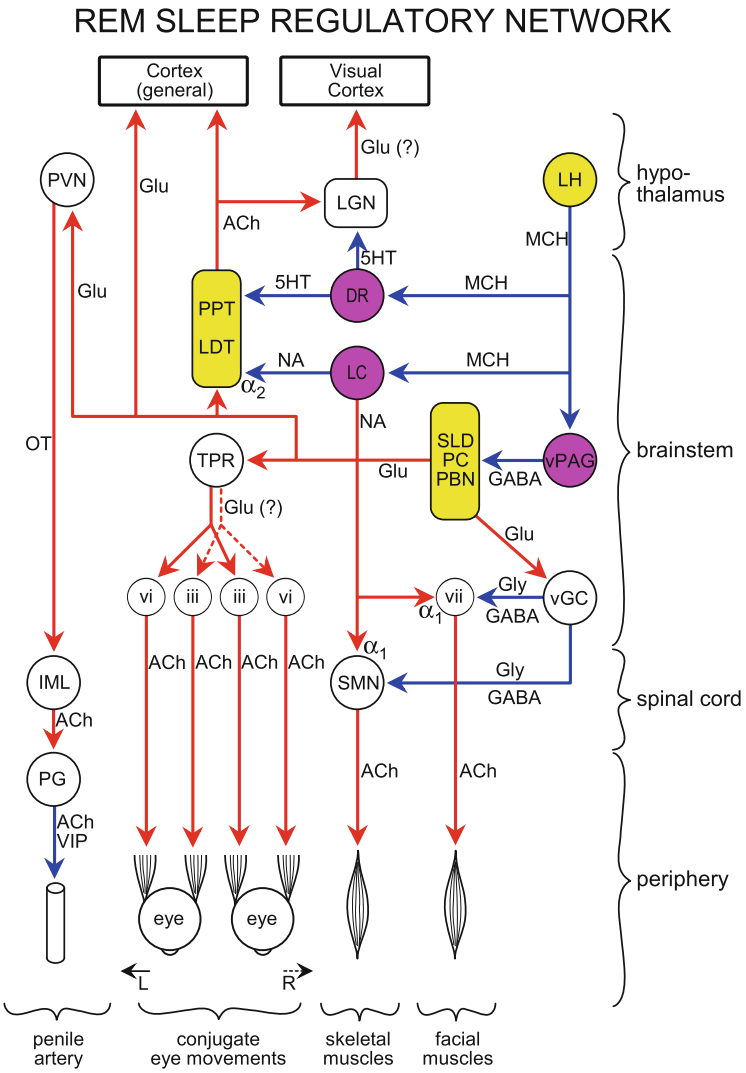


**Fig. 2** Schematic diagram of the connections within the neuronal network regulating REM sleep ("REM sleep network"). *REMS-promoting nuclei* (*yellow*): LH, lateral hypothalamic area; PPT/LDT, pedunculopontine/laterodrosal tegmental nuclei; SLD, sublaterodorsal nucleus; PC, precoeruleus nucleus; PBN: parabrachial nuclei. *REMS-inhibiting nuclei* (*purple*): vPAG, ventral periaqueductal grey matter; LC, locus coeruleus; DR, dorsal raphe nucleus). *Target nuclei* (*white*): LGN, lateral geniculate nucleus; PVN, paraventricular nucleus; TPR, tegmentopontine reticular nucleus; vGC, ventral gigantocellular nucleus; III, VI, VII, cranial nerve motor nuclei (III: oculomotor; VI: abducens; VII: facial); SMN, spinal motoneurons; IML, intermediolateral column of spinal cord; PG, pelvic ganglion. *Connections*: *arrows* (*red*: excitatory; *blue*: inhibitory). *Lettering next to arrow*: neurotransmitter (MCH: melanin concentrating hormone; GABA: γ-aminobutyric acid; Gly: glycine; Glu: glutamate; NA: noradrenaline; 5HT: 5-hydroxytryptamine [serotonin]; ACh: acetylcholine; OT: oxytocin; VIP: vasoactive intestine polypeptide). *Receptors*: $\alpha_1$, excitatory $\alpha_1$-adrenoceptors; $\alpha_2$, inhibitory $\alpha_2$-adrenoceptors. See text (Sect. 2.2) for details

during episodes of REMS and the patient may act out his/her dream experiences. RBD is due to brainstem lesions caused by neurodegenerative disorders (Luppi et al. 2011).

Penile erections are due to the engorgement of the cavernous body of the penis with blood as a result of the dilation of penile arteries and relaxation of the cavernous body. This response is mediated by the sacral parasympathetic outflow, which, in turn, is under the influence of the paraventricular nucleus (PVN) of the hypothalamus (Giuliano and Rampin 2004; Argiolas and Melis 2005). Penile erections associated with REMS (Hirshkowitz and Schmidt 2005) are likely to be due to the activation of parasympathetic premotor neurons in the PVN by a glutamatergic output from the SLD. Indeed, the PVN is rich in glutamatergic synapses (Argiolas and Melis 2005).

Our knowledge of the pharmacology of the REMS network is rather patchy compared to that of the W/SWS network. Interference with the cholinergic/monoaminergic REMS-promoting/REMS-inhibiting circuitry has predictable effects: cholinergic drugs, such as cholinesterase inhibitors, augment REMS (Schredl et al. 2006), whereas anticholinergic drugs (e.g. scopolamine) (Rao et al. 2004) and monoaminergic drugs (e.g. reuptake-inhibiting antidepressants) (Göder et al. 2011) suppress it. RBD can be treated with the GABAergic benzodiazepine clonazepam that can restore muscle atonia during episodes of REMS (Luppi et al. 2013), probably by potentiating the GABAergic inhibitory influence on motoneurons.

## *2.3 Circadian Network*

Many bodily functions (body temperature, locomotor activity, feeding, autonomic and endocrine activity, sleep/arousal) show rhythmic circadian (near-daily) fluctuations. The suprachiasmatic nucleus (SCN) of the hypothalamus is the central generator of circadian rhythms (Kalsbeek et al. 2006). A schematic diagram of the major outputs from the SCN, involved in circadian regulation, is shown in Fig. 3. The SCN, via excitatory output neurons using glutamate and the neuropeptides vasopressin and vasoactive intestinal polypeptide as transmitters (Mistlberger 2005), projects to two hypothalamic areas: the subparaventricular zone (SPZ) and the dorsomedial hypothalamus (DMH) (Fuller et al. 2006). The dorsal SPZ has been implicated in regulating the circadian rhythm of body temperature. The ventral SPZ projects to the DMH. The DMH is involved in the regulation of the rhythmicity of locomotor activity and sleep and arousal. Both glutamatergic excitatory and GABAergic inhibitory outputs from the DMH increase the level of arousal: the excitatory output by activating the LH and LC and the inhibitory output by inhibiting the VLPO. Light exerts its wake-promoting effect via this pathway: light stimulates the retina that sends a glutamatergic excitatory output to the SCN. This effect countermands the sleep-promoting effect of light arising from the direct stimulation of the VLPO (see also Sect. 4.5.1, Photomodulation).

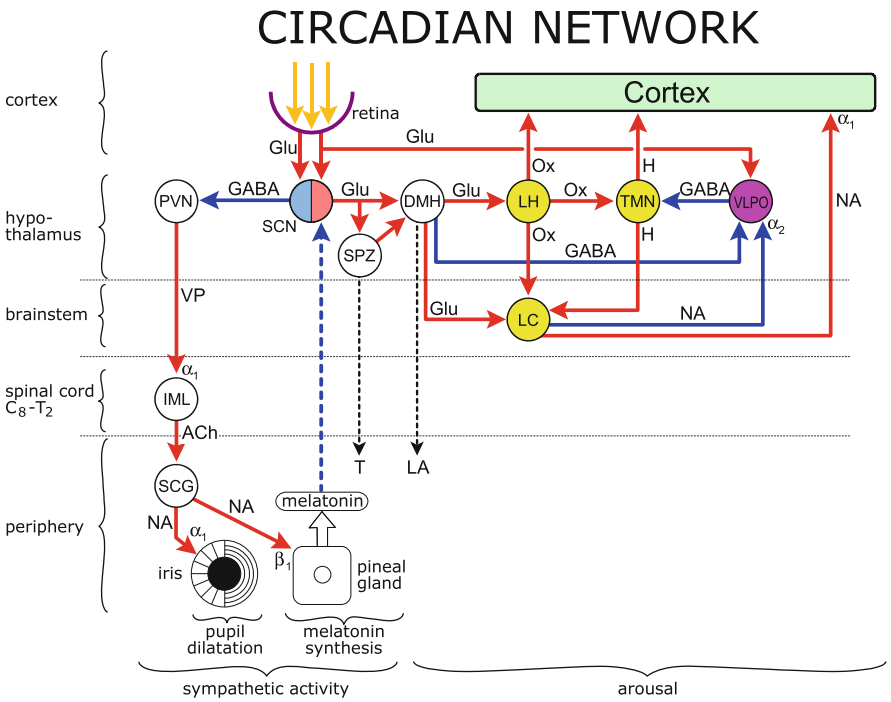


**Fig. 3** Schematic diagram of the connections within the neuronal network controlling circadian regulation ("circadian network"). *Wake-promoting nuclei* (*yellow*): LH, lateral hypothalamic area; TMN, tuberomamillary nucleus; LC, locus coeruleus). *Sleep-promoting nucleus* (*purple*): VLPO, ventrolateral preoptic nucleus. *SCN: suprachiasmatic nucleus* (*blue*: inhibitory output neurons; *red*: excitatory output neurons). *Target and relay nuclei* (*white*): DMH, dorsomedial hypothalamus; SPZ, subparaventricular zone; PVN, paraventricular nucleus; IML, intermediolateral column of spinal cord; SCG, superior cervical ganglion. *Target functions*: T, body temperature; LA, locomotor activity. *Connections*: *arrows* (*red*: excitatory, *blue*: inhibitory, *broken blue*: inhibitory hormonal; *broken black*: functional). *Lettering next to arrow*: neurotransmitter (Glu: glutamate, GABA: γ-aminobutyric acid; NA: noradrenaline; Ox: orexin; H: histamine; VP: vasopressin; ACh: acetylcholine). *Receptors*: $\alpha_1$, excitatory $\alpha_1$-adrenoceptors; $\beta_1$, excitatory $\beta_1$-adrenoceptors. See text (Sect. 2.3) for details

There is a GABAergic inhibitory output from the SCN to the premotor sympathetic neurons of the PVN that control sympathetic outflow from the lower cervical/upper thoracic spinal cord ($C_8$-$T_2$) to the dilator muscle of the iris and the pineal gland (Kalsbeek et al. 2000). The pineal gland synthesizes and secretes the "sleep hormone" melatonin. Melatonin has sleep-promoting propensity due to the stimulation of inhibitory $MT_1$ receptors on wake-promoting SCN neurons (Szabadi 2014). The GABAergic output neurons in the SCN control the circadian activity of melatonin secretion: during day time, when these neurons are maximally active, no melatonin is secreted, while during night time, when these neurons are quiescent, melatonin is synthesized and secreted. Light can switch off melatonin

secretion during night time ("melatonin suppression") by stimulating the light sensitive GABAergic inhibitory output neurons in the SCN.

Melatonin and/or light stimulation are used to treat sleep disorders arising from circadian dysregulation ("circadian rhythm sleep disorders") (Dodson and Zee 2010).

# 3 Drugs Interacting with Sleep-Promoting Systems

## *3.1 GABA*

### 3.1.1 The GABAergic Sleep-Promoting System

The amino acid GABA is the major inhibitory neurotransmitter in the brain. GABAergic neurons are widely distributed throughout the neuraxis (Niewenhuys 1985; Rudolph 2004). GABAergic neurons play an important role in the regulation of sleep and arousal: they promote SWS and inhibit REMS (Figs. 1 and 2). SWS-promoting GABAergic neurons are localized either in distinct nuclei from which they project to distinct targets ("projection neurons") or have a more diffuse distribution in the vicinity of their targets ("interneurons"). GABAergic neurons in the BF project to the cerebral cortex where they exert a sleep-promoting effect (Manns et al. 2003). These neurons, like the GABAergic neurons of the VLPO, are inhibited by the LC (Fig. 5). Paradoxically, the GABAergic neurons of the BF can also mediate a W-promoting effect by inhibiting inhibitory interneurons in the cerebral cortex, and thus disinhibiting cortical activity (Lin et al. 2011). GABAergic neurons in the VLPO, together with neurons containing the inhibitory neuropeptide galanin, project to the major W-promoting nuclei, such as the TMN and LC (España and Scammell 2011). There is a reciprocal inhibitory connection from the LC to the VLPO (Fig. 1). GABAergic interneurons in the brainstem, in the vicinity of the VTA and LC, exert an inhibitory influence on these catecholaminergic W-promoting nuclei. The activity of the GABAergic interneurons is facilitated by an excitatory serotonergic input from the DR stimulating $5HT_{2C}$ receptors (Gobert et al. 2000). Recently GABAergic neurons have been identified in the nucleus accumbens (ventral striatum): they project to W-promoting nuclei and thus may promote SWS (Lazarus et al. 2011).

### 3.1.2 GABA Receptors

GABA exerts its inhibitory effects by interacting with distinct receptors. Three GABA receptors have been identified: $GABA_A$, $GABA_B$ and $GABA_C$. Of these the $GABA_A$ receptor is the most important in the regulation of sleep and arousal, and most available GABAergic drugs act via $GABA_A$ receptors.

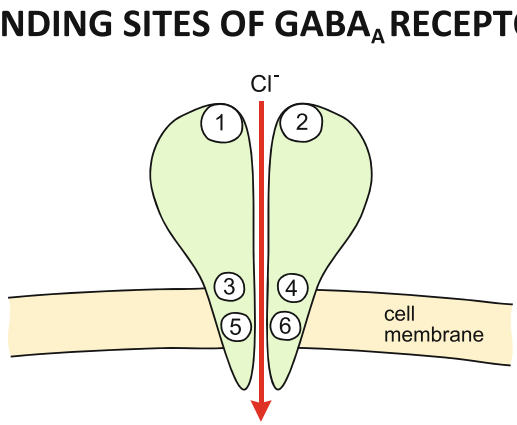


**Fig. 4** Schematic diagram of the $GABA_A$ receptor. The receptor is a chloride-gated ion channel that is opened when the receptor is activated by agonists. Numbers indicate binding sites for agonists. *1* orthosteric binding site for the natural transmitter (GABA); *2* to *6* binding sites for allosteric modulators (*2* for benzodiazepines; *3* for anaesthetics; *4* for ethanol; *5* for barbiturates; *6*: for neurosteroids). Positive allosteric modulators enhance the effect of GABA. See text (Sect. 3.1.2) for details. Modified, with permission, from Rudolph (2004)

The $GABA_A$ receptor is an ionotropic receptor: it mediates the passage of chloride ions into the cell leading to membrane hyperpolarization. In fact, the $GABA_A$ receptor is a ligand-gated chloride channel (Fig. 4). It has a pentameric structure corresponding to five subunits. $GABA_A$ receptors containing the $\alpha_1$ subunit are the most relevant for sedative drug action. The $GABA_A$ receptor, apart from a binding site for the natural neurotransmitter GABA ("orthosteric site"), also contains a number of binding sites for different drugs that modulate the activity of the receptor ("allosteric sites"). The positive allosteric $GABA_A$ receptor modulators, that include benzodiazepines, some anaesthetics, ethanol, barbiturates and neurosteroids, enhance the effect of endogenous GABA (Rudolph 2004; Sigel and Steinmann 2012). $GABA_A$ receptors occur both postsynaptically in close association with GABAergic nerve terminals and extrasynaptically on neurons located at some distance from the site of release. Extrasynaptic $GABA_A$ receptors mediate a slow tonic inhibitory response (Winsky-Sommerer 2009; Rudolph and Knoflach 2011).

The $GABA_B$ receptor is a metabotropic receptor that signals via G-proteins. These receptors also mediate neuronal inhibition (Pinard et al. 2010). $GABA_B$ receptors occur both presynaptically and postsynaptically. These receptors have been identified on W-promoting cholinergic neurons in the LDT and serotonergic neurons in the DR, mediating the sleep-promoting effect of GABA (Kohlmeier et al. 2013).

Relatively little is known about $GABA_C$ receptors. A number of ligands have been developed for these receptors with the aim of exploring their physiological role and the therapeutic potential of drugs interacting with them (Johnston et al. 2003).

### 3.1.3 Sleep-Promoting GABAergic Activators

$GABA_A$ Receptor Agonists

A number of orthosteric $GABA_A$ receptor agonists have been developed, of which gaboxadol (THIP) appears to be the most promising. Gaboxadol is selective for extrasynaptic $GABA_A$ receptors (Belelli et al. 2005). It has hypnotic effects and has reached the stage of clinical trial for the treatment of insomnia (Roth et al. 2010). However, further development has been halted due to unexpected side effects (hallucinations, disorientations) (Rudolph and Knoflach 2011).

$GABA_A$ Receptor Modulators

Drugs acting at the *benzodiazepine site* (also referred to as the "benzodiazepine receptor") include the benzodiazepines themselves (e.g. diazepam, temazepam) and the "Z" drugs (zolpidem, zopiclone/eszopiclone, zaleplon). These are the most commonly prescribed drugs for insomnia (Wilson et al. 2010; Proctor and Bianchi 2012). The adverse effects of the benzodiazepines (hangover effects causing daytime sedation, cognitive and psychomotor impairment, development of tolerance and dependence) are well recognized, and the Z drugs also share some of the disadvantages of benzodiazepines. However, it may be possible to improve the clinical usefulness of $GABA_A$ receptor modulators by fine-tuning the properties of new drugs according to the subtype (constellation of subunits) of $GABA_A$ receptor targeted (Winsky-Sommerer 2009; Nutt and Stahl 2010; Rudolph and Knoflach 2011).

The barbiturates act at the *barbiturate site*. These drugs, apart from acting as allosteric modulators of the $GABA_A$ receptor, also have some direct agonistic activity at the receptor. During the first half of the twentieth century, prior to the discovery of the benzodiazepines, these drugs were the most commonly used hypnotics. They are still used as anticonvulsants (phenobarbital) and anaesthetics (pentobarbital).

A number of intravenous (etomidate, propofol) and volatile (enflurane, isoflurane) anaesthetics produce sedation by enhancing GABAergic activity by binding to the *anaesthetic site* of the $GABA_A$ receptor. It should be noted, however, that the $GABA_A$ receptor may not be the only target of these drugs. It has been proposed that GABAergic anaesthetics, that also include the anaesthetic barbiturates (e.g. pentobarbital, thiopental), may act by stimulating $GABA_A$ receptors at the projection targets of VLPO neurons, such as the TMN. The increased inhibition of the wake-promoting histaminergic neurons of the TMN would lead to withdrawal of the histaminergic stimulation of the cerebral cortex, and this in turn would result in sedation (Nelson et al. 2002). It should be noted, however, that this model has been challenged recently (Zecharia et al. 2012).

There is an allosteric binding site on the $GABA_A$ receptor for *neurosteroids* (or neuroactive steroids) that can evoke rapid changes in neuronal excitability via the potentiation of GABAergic neurotransmission. Some steroids of the pregnane class, synthesized by neurons and glia cells, act as powerful endogenous regulators of $GABA_A$ receptor function (Lambert et al. 2009). There is evidence that neurosteroids (e.g. pregnalone, progesterone) have sleep-promoting effects both in experimental animals and humans (Steiger 2007). It is likely that synthetic steroid anaesthetics (e.g. alphaxolone) exert their sedative effects via this site (Lambert et al. 2009).

There is an allosteric binding site for *ethanol* that is different from the benzodiazepine and barbiturate sites. Ethanol has sleep-promoting effects (Dijk et al. 1992), and is often used as a hypnotic (Johnson et al. 1998).

#### $GABA_B$ Receptor Agonists

*Baclofen* is an orthosteric $GABA_B$ receptor agonist available for the treatment of spasticity. Drowsiness is one of its side effects, consistent with its sleep-promoting propensity (Bowery 2006).

*γ-Hydroxybutyric acid (GHB, sodium oxybate)* is an orthosteric partial agonist at $GABA_B$ receptors. In addition, it also interacts with some high-affinity binding sites ("GHB receptors") that have recently been identified as a subtype of the $GABA_A$ receptor (Bay et al. 2014). GHB is sleep promoting (Kohlmeier et al. 2013). It is licensed for the treatment of narcolepsy with cataplexy: there is evidence that GHB ameliorates all the cardinal symptoms of this disorder (i.e. it reduces cataplexy and EDS/daytime sleep attacks and improves sleep architecture) (Boscolo-Berto et al. 2012).

#### GABA Reuptake Inhibitors

Released GABA is removed from the synaptic cleft into GABAergic nerve terminals by an active transport mechanism operated by GABA transporter GAT-1 localized in the membrane of the nerve terminal. *Tiagabine* inhibits GAT-1 leading to the blockade of the reuptake of GABA: this leads to enhanced activation of $GABA_A$ and $GABA_B$ receptors (Winsky-Sommerer 2009). Tiagabine has well-documented sleep-promoting effects (Matthias et al. 2001).

### 3.1.4 Wake-Promoting GABAergic Inhibitors

Although inhibition of central GABAergic neurotransmission can increase the level of alertness, inhibition of the GABAergic system leads to a number of other changes (e.g. cognitive enhancement ["pro-cognitive effect"], anxiety, convulsions) that may mask a wake-promoting effect.

### $GABA_A$ Receptor Antagonists

The $GABA_A$ receptor antagonists bicuculline and gabazine, when administered systemically, are potent convulsants (Johnston 2013). However the wake-promoting effect of bicuculline is revealed when it is microinjected into the cholinergic wake-promoting nucleus PPT (Torterolo et al. 2002).

### Benzodiazepine Receptor Antagonists

Flumazenil is a *competitive antagonist* at the benzodiazepine binding site (Hoffman and Warren 1993). It has been shown to possess a procognitive effect in animal models of memory (Lal et al. 1988). It has no wake-promoting effect. Intravenously administered flumazenil is used as an antidote to benzodiazepine overdose and to reverse sedation after midazolam-induced anaesthesia (Hoffman and Warren 1993).

*Inverse agonists* of the benzodiazepine binding site (e.g. beta-carbolines) have procognitive, anxiogenic, proconvulsant (increased susceptibility to convulsions) and convulsant effects: these effects are observed as the dosage of the beta-carboline is increased from very low to high levels (Venault and Chapouthier 2007). The beta-carbolines also have wake-promoting effects, which, however, are superseded by convulsions (Massotti et al. 1985). Recently benzodiazepine receptor inverse agonists have been developed that are selective for the α5 subtype of the $GABA_A$ receptor. These drugs have marked procognitive effects without anxiogenic and (pro)convulsant propensities (Atack 2010), and thus may have a clinical potential for the treatment of cognitive disorders (Martinez-Cué et al. 2014).

### $GABA_B$ and $GABA_C$ Receptor Antagonists

Antagonists of both $GABA_B$ and $GABA_C$ receptors have wake-promoting effects (Gottesmann 2002). $GABA_B$ receptor antagonists also possess procognitive propensity (Stäubli et al. 1999), and some of these drugs have reached the stage of clinical trial for the treatment of cognitive disorders (Froestl et al. 2004).

### GABA Receptor Autoantibodies

In some autoimmune disorders neurotransmitter receptors can act as antigens leading to the generation of specific autoantibodies against the receptors (Bien et al. 2012). Autoantibodies have been identified against both $GABA_A$ (Petit-Pedrol et al. 2014) and $GABA_B$ (Lancaster et al. 2010) receptors in cases of autoimmune encephalitides. The autoantibodies close down the GABA receptors: this may explain the prevalence of seizures in these disorders. However, in a rare form of

autoimmune disorder, total insomnia ("agrypnia") was reported in association with $GABA_B$ receptor autoantibodies (Frisullo et al. 2007).

## *3.2 Melanin Concentrating Hormone*

### 3.2.1 The MCHergic Sleep-Promoting System

MCH is a cyclic neuropeptide localized mainly in neurons of the lateral hypothalamus. MCH-containing neurons are intermingled with orexin-containing neurons. There is a reciprocal discharge pattern of the two groups of neurons: orexinergic neurons are active during W and quiescent during SWS and REMS, whereas MCH neurons are quiescent during W, show some activity during SWS, and are maximally active during REMS (Hassani et al. 2009). MCH neurons, like the orexin-containing neurons, project diffusely to many structures of the brain. In particular, there are projections to the cholinergic and monoaminergic wake-promoting nuclei (Fig. 1) and the GABAergic REMS-inhibiting neurons of the midbrain (Fig. 2). There are two G-protein-coupled receptors (MCHR1 and MCHR2) stimulated by MCH; both receptors mediate neuronal inhibition. By inhibiting wake-promoting neurons, MCH promotes SWS, and by inhibiting REMS-inhibiting neurons, MCH promotes REMS (see Sect. 2; Monti et al. 2013; Tsunematsu et al. 2014). The main function of the MCH sleep-promoting system is likely to be to facilitate REMS (Jego et al. 2013). In fact, the optogenetic activation of MCH neurons can switch SWS into REMS (Tsunematsu et al. 2014).

### 3.2.2 Wake-Promoting MCH Inhibitors

MCHR1 receptor antagonists have been reported to increase wakefulness and suppress both SWS and REMS (Ahnaou et al. 2008), suggesting that these receptors may become a target for the development of wake-promoting drugs.

## *3.3 Galanin*

### 3.3.1 The Galaninergic Sleep-Promoting System

Galanin is a neuropeptide functioning both as an inhibitory neurotransmitter and a co-transmitter/neuromodulator. Galaninergic neurons have been identified in the VLPO where they are intermingled with GABAergic neurons (Gaus et al. 2002). These galaninergic neurons have the same projection targets as the GABAergic neurons. Galanin also occurs in other neurons, such as the noradrenergic neurons of the LC and serotonergic neurons of the DR, where it functions as a co-transmitter,

modulating (inhibiting) the release of the principal transmitter (Le Maître et al. 2013). Via synergism of the sleep-promoting GABAergic neurons of the VLPO and inhibition of the wake-promoting noradrenergic and serotonergic neurons, galanin exerts a sleep-promoting action.

Three galanin receptors (GalR1, GalR2, GalR3) have been identified, and agonists and antagonists have been developed for them (Webling et al. 2012).

#### 3.3.2 Sleep-Promoting Galanin Receptor Agonists

According to one report, galanin injected intravenously alters the sleep EEG consistent with promotion of both SWS and REMS (Murck et al. 1999). Like the GABA receptor agonists and positive allosteric modulators, galanin receptor agonists also possess anxiolytic (Rajarao et al. 2007) and anticonvulsant (Lerner et al. 2008) propensities. Galanin receptors are a promising target for the development of anticonvulsant drugs (Hoyer 2010).

#### 3.3.3 Wake-Promoting Galanin Receptor Antagonists

The development of these drugs is at an early stage. It is predicted that they would enhance the level of alertness. Furthermore, they may have antidepressant effects due to the disinhibition of central noradrenergic and serotonergic neurotransmission (Ögren et al. 2006).

### *3.4 Melatonin*

#### 3.4.1 The Melatoninergic Sleep-Promoting System

The hormone melatonin is secreted by the pineal gland. Its synthesis is under strict circadian control by the SCN, and is modulated by light (Sect. 2.3). Melatonin has a large number of targets where it stimulates $MT_1$ and $MT_2$ receptors (Pandi-Perumal et al. 2006). It has sleep-promoting and sleep-modulating (chronobiotic) effects by interacting with these receptors in the SCN. The sleep-promoting effect has been attributed to the stimulation of $MT_1$ receptors and the chronobiotic effect to the stimulation of $MT_2$ receptors (Hardeland 2012).

#### 3.4.2 Sleep-Promoting Melatoninergic Activators

Melatonin itself has sleep-promoting effect (Pandi-Perumal et al. 2006). This is likely to be due to the stimulation of inhibitory $MT_1$ receptors on wake-promoting glutamatergic output neurons in the SCN. This in turn would lead to dampening of

the activity of the wake-promoting "SCN → DMH → LC → cortex" circuit (Fig. 3), resulting in reduction in the level of arousal (Szabadi 2014).

Apart from a sustained release formulation of melatonin (Circadin®), a number of $MT_1/MT_2$ receptor agonists have been developed for the treatment of insomnia: ramelteon, tasimelteon and 6-chloromelatonin (LY156735) (Szabadi 2014).

### 3.4.3 Chronobiotic Melatoninergic Activators

$MT1/MT_2$ receptor agonists also exert chronobiotic effects that involve resetting the circadian clock and introducing phase shifts. These drugs are useful for the treatment of some circadian rhythm disorders, such as the initial insomnia of delayed sleep phase disorder and the free-running disorder of blind people (Dodson and Zee 2010).

### 3.4.4 Wake-Promoting Melatoninergic Inhibitors

The synthesis of melatonin is driven by the sympathetic outflow via the "PVN → spinal preganglionic neurons → postganglionic neurons in superior cervical ganglion" pathway. The postganglionic noradrenergic neurons innervate the pineal gland cells where they stimulate $\beta_1$-adrenoceptors (Fig. 3).

Inhibition of melatonin synthesis by β-adrenoceptor antagonists leads to wake-promoting and sleep-disrupting effects; this effect can be reversed by the administration of melatonin (Van den Heuvel et al. 1997). Melatonin has been recommended to treat insomnia associated with the use of beta-blockers (Fares 2011).

## *3.5 Adenosine*

### 3.5.1 The Adenosine-Mediated Sleep-Promoting System

Adenosine, a breakdown product of adenine nucleotides, accumulates in the brain during prolonged wakefulness (Huang et al. 2011). It is an endogenous sleep-inducing agent ("somnogen"): by increasing the tendency to fall asleep ("sleep propensity" or "sleep pressure"), it acts as a homoeostatic regulator of sleep (Porkka-Heiskanen 2013). The sleep-promoting effects of adenosine are mediated via the inhibition of wake-promoting neurons and the stimulation of sleep-promoting neurons.

### 3.5.2 Adenosine Receptors

Adenosine, released from metabolically active cells, interacts with specific cell surface receptors. Of the four adenosine receptors identified, two ($A_1$ and $A_{2A}$) are important for the promotion of sleep (Landolt 2008). The $A_1$ receptors mediate an inhibitory response. They are localized on wake-promoting cholinergic neurons of the BF, noradrenergic neurons of the LC, serotonergic neurons of the DR, and orexinergic neurons of the LH/PF. These receptors are located partly on the cell bodies and partly on the nerve terminals of these neurons where they inhibit the release of the neurotransmitter. The $A_{2A}$ receptors mediate an excitatory response, either directly (Gallopin et al. 2005) or indirectly by inhibiting inhibitory interneurons and thus disinhibiting the target neuron (Morairty et al. 2004). $A_{2A}$ receptors have been identified on or near GABAergic sleep-promoting neurons in the VLPO (Scammell et al. 2001; Gallopin et al. 2005). Recently, $A_{2A}$ receptors have been detected on putative GABAergic sleep-promoting neurons in the nucleus accumbens (ventral striatum): these neurons may inhibit the activity of wake-promoting neurons via their widespread projections (Zhang et al. 2013).

### 3.5.3 Sleep-Promoting Adenosine Receptor Agonists

Agonists of both $A_1$ (Benington et al. 1995) and $A_{2A}$ (Scammell et al. 2001) receptors have sleep-inducing effects in experimental animals. However, these drugs have not been studied in humans.

### 3.5.4 Wake-Promoting Adenosine Receptor Antagonists

The psychostimulant *caffeine* exerts its wake-promoting effect via antagonizing adenosine receptors (Landolt 2008). Although caffeine has affinity for both $A_1$ and $A_{2A}$ receptors, recent evidence indicates that its alerting effect is mediated primarily via the $A_{2A}$ receptor (Huang et al. 2005). Furthermore, $A_{2A}$ receptors in the nucleus accumbens have been implicated in this effect (Lazarus et al. 2011).

*SYN115* is a synthetic $A_{2A}$ adenosine receptor antagonist developed for the treatment of movement disorders resulting from dopaminergic deficiency (e.g. Parkinson's disease) (Kulisevsky and Poyurovsky 2012). The basis for this is that $A_{2A}$ receptors are co-localized with $D_2$ dopamine receptors in the basal ganglia where they modulate (inhibit) dopamine receptor function. As expected, SYN115 possesses marked wake-promoting effects (Lane et al. 2012).

# 4 Drugs Interacting with Wake-Promoting Systems

## *4.1 Histamine*

### 4.1.1 The Histaminergic Wake-Promoting System

Histaminergic neurons are localized in the TMN of the posterior hypothalamus and send diffusely arborizing projections to most areas of the brain and spinal cord. The histaminergic neurons, like most other wake-promoting neurons, are maximally active during wakefulness and quiescent during sleep (Ko et al. 2003). These neurons, via their precisely targeted connections within the W/SWS network (Fig. 1), play an essential role in the maintenance of wakefulness (Haas and Lin 2012; Szabadi 2014). The importance of the posterior hypothalamus, including the TMN, in the maintenance of wakefulness was first highlighted by von Economo who correlated lesions in this area with the hypersomnia in encephalitis lethargica (Triarhou 2006). Central histaminergic neurons are activated by an excitatory orexinergic input from the lateral hypothalamus, and inhibited by a GABAergic input from the VLPO. In fact, the sleep-promoting effect of the VLPO is mediated largely by the switching off of TMN activity. VLPO activity is kept in check during wakefulness by an inhibitory output from the LC. Histaminergic outputs from the TMN mediate an excitatory effect via stimulation of H1 histamine receptors at their target areas, including the cerebral cortex and a number of wake-promoting nuclei (LC, PPT/LDT, BF and thalamus). The activation of cortically projecting cholinergic neurons in the BF may play a major role in mediating the wake-promoting effect of histamine (Zant et al. 2012).

### 4.1.2 Histamine Receptors

There are four types of histamine receptor, of which three (H1, H2 and H3) occur in the central nervous system. H1 and H2 receptors are excitatory postsynaptic receptors, whereas H3 receptors are inhibitory autoreceptors located on the histaminergic neuron itself (Szabadi 2014). In a somatodendritic location, H3 receptors suppress neuronal firing, whereas located on presynaptic terminals they inhibit transmitter synthesis and release. H3 receptors also occur on the nerve terminals of other neurons ("heteroreceptors") where they inhibit the release of the neurotransmitter (monoamines, acetylcholine, glutamate, GABA, peptides) (Haas and Lin 2012). Interestingly, the H3 receptor can signal on its own without an agonist ("constitutive activity") (Arrang et al. 2007). This may explain why inverse agonists are more effective than neutral antagonists in suppressing H3 receptor signalling (Haas and Lin 2012).

### 4.1.3 Wake-Promoting Histaminergic Activators

H1 Receptor Agonists

Currently available agonists are of little therapeutic significance. Histamine itself injected into the brain of experimental animals has wake-promoting effects (Lin et al. 1988). However, systemically administered histamine cannot pass the blood–brain barrier and can trigger allergic reactions. Betahistine, a derivative of histamine, is a partial H1 receptor agonist that has some central histaminergic effects in humans when administered orally. However, these effects may have been, at least partly, mediated by H3 receptor blockade (Reynolds 2012). At present there are no selective and potent H1 receptor agonists available (Taberan 2013). Although it may be possible to develop more effective centrally acting H1 receptor agonists, recent effort has concentrated on the development of H3 receptor antagonists for the stimulation of the central histaminergic system.

H3 Receptor Antagonists

H3 receptor antagonists and inverse agonists increase histaminergic activity by disinhibiting autoreceptors, thus leading to a wake-promoting effect. This effect is enhanced by the disinhibition of heteroreceptors modulating the release of wake-promoting transmitter substances (monoamines, acetylcholine). There is a large body of evidence demonstrating the wake-promoting propensity of H3 receptor antagonists and inverse agonists (Parmentier et al. 2007). Furthermore, these drugs also have potential cognitive-enhancing effects (Brioni et al. 2011). A large number of H3 receptor antagonists/inverse agonists have been developed over the past 25 years for the treatment of excessive daytime sleepiness (EDS), cognitive disorders and obesity (Gemkow et al. 2009; Berlin et al. 2011). Some early compounds have been superseded by more novel molecules that are at various stages of development. Pitolisant (formerly BF2.649, tiprolisant) has reached the stage of clinical trial for the treatment of EDS in narcolepsy (Schwartz 2011).

### 4.1.4 Sleep-Promoting Histaminergic Inhibitors

H1 Receptor Antagonists

H1 receptor antagonists are referred to as antihistamines, or more precisely as H1-antihistamines (Church and Church 2013). H1-antihistamines have been used since the 1930s for the treatment of allergic disorders. *First-generation H1-antihistamines* (e.g. diphenhydramine, promethazine, chlorpheniramine, cyclizine) readily cross the blood–brain barrier and have potent sedative/hypnotic effects. These drugs have poor receptor selectivity and often interact with muscarinic

cholinoceptors, α-adrenoceptors and serotonin (5HT) receptors, leading to side effects resulting from the blockade of these various receptors. Some of the first-generation H1-antihistamines (e.g. diphenhydramine) are available as over-the-counter hypnotics (Proctor and Bianchi 2012). Some antipsychotic drugs (e.g. chlorpromazine, thioridazine, levomepromazine) and antidepressants (amitriptyline, trazodone, mirtazapine, doxepin) have sedative propensities and prescribed for the treatment of insomnia. Although these drugs interact with a number of receptors, their sleep-promoting effects are likely to be due primarily to the blockade of H1 histamine receptors (Proctor and Bianchi 2012). *Second-generation H1-antihistamines* are chemically different from the first-generation H1-anthistamines, and are more selective for the H1 histamine receptor. These drugs (e.g. desloratadine, levocetirizine, fexofenadine) have an important role in the treatment of allergic disorders: as they do no penetrate into the brain, unwanted sedation is not a problem.

H3 Receptor Agonists

A number of potent and selective H3 histamine receptor agonists (e.g. imetit, R-(α) methylhistamine, BP294) have been developed (Leurs et al. 1998). These drugs, by stimulating release-inhibiting presynaptic H3 histamine receptors, exert an antihistaminergic effect. There is evidence that they promote SWS in experimental animals (Thakkar 2011) and thus have therapeutic potential for the treatment of insomnia. However, they have not reached the stage of clinical development.

## *4.2 Orexin*

### 4.2.1 The Orexinergic Wake-Promoting System

The orexins (orexin A and orexin B, also known as hypocretin-1 and hypocretin-2) are neuropeptides localized in distinct groups of neurons (LH/PF, DMH) in the hypothalamus. Orexinergic neurons of the LH/PF constitute an important wake-promoting system via their projections to the cerebral cortex and other wake-promoting nuclei (TMN, LC, VTA) (Fig. 1). At their projection targets, orexinergic neurons interact with excitatory orexin receptors (OX1 and OX2) (Ohno and Sakurai 2008). The orexinergic neurons of the DMH are involved in circadian regulation and in mediating the effect of light on arousal (Fig. 3).

### 4.2.2 Narcolepsy: An Orexin-Deficiency State

The loss of orexinergic neurons is responsible for the sleep disorder narcolepsy. The symptoms of narcolepsy are complex and can be related to the intrusion of sleep-

related vigilance states into wakefulness. Intrusion of SWS into W leads to EDS and sleep attacks, whereas intrusion of REMS into W results in cataplexy (loss of muscle tone in response to emotions), hypnagogic hallucinations (dream-like visions before falling asleep) and sleep paralysis (inability to move before falling asleep) (Ohno and Sakurai 2008; Sakai 2013).

#### 4.2.3 Wake-Promoting Orexinergic Activators

It would be of great therapeutic importance to replace orexinergic function in narcolepsy. Unfortunately, there are no non-peptide orexin receptor agonists available to date, and the orexin peptides do not readily penetrate into the brain. Administration of orexin peptides into the lateral cerebral ventricle (Mieda et al. 2004) or transplantation of orexin neurons into the LH (Arias-Carrión and Murillo-Rodriguez 2014) have reversed the symptoms of narcolepsy in experimental animals. Furthermore, the administration of orexin A as a nasal spray to narcoleptic patients has been reported to alleviate narcoleptic symptoms (Weinhold et al. 2014).

#### 4.2.4 Sleep-Promoting Orexinergic Inhibitors

A number of orexin receptor antagonists have been developed for the treatment of insomnia (Hoyer and Jacobson 2013). Development has reached the stage of clinical trial with some of these drugs (e.g. almorexant, SB-649868, suvorexant, filorexant) that all antagonize both orexin A and orexin B receptors ("dual orexin receptor antagonists, DORAs"). The first one of these, almorexant, has been withdrawn following Phase III trials, while suvorexant has been submitted for registration. The possible usefulness of selective orexin receptor antagonists is being explored: while OX1 antagonists are probably not good candidates as insomnia drugs, OX2 antagonists have some promise (Hoyer and Jacobson 2013).

An important consideration with the clinical use of orexin receptor antagonists is the risk of provoking the symptoms of narcolepsy, and in particular cataplexy (Tafti 2007). However, clinical trials with DORAs so far have failed to support this possibility (Hoyer and Jacobson 2013).

### *4.3 Glutamate*

#### 4.3.1 The Glutamatergic Wake-Promoting System

The thalamus contains both specific (sensory relay) and non-specific glutamatergic neurons that project diffusely to the cerebral cortex (Brown et al. 2012). The non-specific neurons, located in the intralaminar and reticular nuclei, are wake-

promoting and constitute an integral part of the "ascending arousal system" (McCormick and Bal 1997). These neurons receive excitatory inputs from wake-promoting cholinergic and histaminergic neurons (Fig. 1), and their activity is modulated by GABA. The hypnotic effect of gaboxadol has been attributed to the stimulation of extrasynaptic inhibitory $GABA_A$ receptors on thalamocortical neurons (Belelli et al. 2005).

Recently a second glutamatergic wake-promoting system has been identified: glutamatergic neurons in the upper brainstem (parabrachial nucleus and precoeruleus area) evoke wakefulness via an excitatory output to the BF. In fact, in rats, this second system appears to be more important in maintaining alertness than the cortico-thalamic system (Fuller et al. 2011).

Glutamatergic neurons are also involved in the regulation of REMS: they exert a REMS-promoting effect (Sect. 2.2 and Fig. 2).

### 4.3.2 Glutamate Receptors

There are two classes of glutamate receptor: ionotropic receptors (ligand-gated ion channels) and metabotropic receptors. There are three inotropic receptors defined by their selectivities to some prototype ligands: NMDA, AMPA and kainite receptors (Dingledine et al. 1999). The ionotropic receptors mediate excitatory responses. There are eight metabotropic receptors (mGluR1-8) divided into three groups: I (mGluR1, 5), II (mGluR2, 3), III (mGluR4, 6, 7, 8). The Group I receptors are excitatory, whereas the Group II and Group III receptors are inhibitory. The Group II receptors are mainly release-inhibiting presynaptic receptors (Niswender and Conn 2010).

### 4.3.3 Wake-Promoting Glutamatergic Activators

An antagonist (negative allosteric modulator) of inhibitory metabotropic mGluR2 glutamate receptors has been reported to increase wakefulness in experimental rats (Ahnaou et al. 2014).

### 4.3.4 Sleep-Promoting Glutamatergic Inhibitors

Some antiepileptic drugs that act by inhibiting central glutamatergic neurotransmission (Gitto et al. 2012) also possess sedative properties. Thus *topiramate*, an AMPA/kainite receptor antagonist (Poulsen et al. 2004), is a highly sedative drug (Berigan 2002), and *levetiracetam*, a drug that reduces glutamate release by blocking calcium channels (Lee et al. 2009), has marked sleep-promoting effects (Cicolin et al. 2006).

AMN082, a positive allosteric modulator of mGlu7 inhibitory metabotropic glutamate receptors, increases SWS in experimental rats (Cavas et al. 2013b).

### 4.3.5 REMS-Suppressing Glutamatergic Inhibitors

Stimulation of inhibitory metabotropic mGluR2 (Ahnaou et al. 2009) and mGluR7 (Cavas et al. 2013b) glutamate receptors or antagonism of excitatory mGluR5 metabotropic receptors (Cavas et al. 2013a) have been reported to suppress REMS in experimental animals.

## *4.4 Acetylcholine*

### 4.4.1 The Cholinergic Wake-Promoting System System

There are two major cholinergic arousal systems, one originating in the LD/PPT and another one in the BF. The wake-promoting cholinergic neurons of the LD/PPT project to the cerebral cortex both directly and indirectly via thalamic glutamatergic neurons. The wake-promoting cholinergic neurons of the BF project to the cortex. The wake-promoting cholinergic neurons of both the LD/PPT and the BF receive a facilitatory noradrenergic input from the LC and a facilitatory histaminergic input from the TMN (Sect. 2.1, Fig. 1). Cholinergic neurons are also involved in the regulation of REMS (Sect. 2.2, Fig. 2).

### 4.4.2 Acetylcholine Receptors (Cholinoceptors)

At their targets, cholinergic neurons interact with two types of receptor: muscarinic and nicotinic receptors. Muscarinic cholinoceptors are G-protein-coupled metabotropic receptors, whereas nicotinic cholinoreceptors are ionotropic receptors (ligand-gated ion channels). There are five types ($M_1$–$M_5$) of muscarinic receptor (Brown 2010) and a large number of "subtype assemblies" of the nicotinic receptor (Gotti et al. 2009). Both muscarinic and nicotinic cholinoceptors are present both in the thalamus and the cerebral cortex (McCormick 1992).

### 4.4.3 Wake-Promoting Cholinergic Activators

Cholinesterase Inhibitors

These drugs, by inhibiting the enzyme responsible for the degradation of acetylcholine, increase cholinergic neurotransmission. *Physostigmine* has marked alerting effect (Votava et al. 1968), and is able to reverse anaesthesia (Meuret et al. 2000). Physostigmine also increases REMS and dreaming (Sitaram et al. 1978), probably due to potentiation of cholinergic mechanisms in the REMS network.

*Donepezil*, a cholinesterase inhibitor used to improve cognitive function in dementia, increases wakefulness in rats (Abe et al. 2003) and causes insomnia in patients. It also increases REMS (Schredl et al. 2006).

Muscarinic Receptor Agonists

*Milameline*, a muscarinic receptor agonist, developed for the treatment of dementia, has been reported to increase alertness in experimental animals (Schwarz et al. 1999).

Nicotinic Receptor Agonists

*Nicotine* is widely used, in the form of inhaled tobacco smoke, for its cognitive-enhancing effect. It increases arousal (Fisher et al. 2012). The enhancement of attention by nicotine is likely to reflect its alerting effect (Myers et al. 2013).

*TC-1734*, a synthetic nicotinic receptor agonist, has been shown to possess alerting effects (Dunbar et al. 2007).

### 4.4.4 Sleep-Promoting Cholinergic Inhibitors

Muscarinic cholinoceptor antagonists (e.g. atropine: Santucci et al. 1981; scopolamine: Ebert and Kirch 1998) are sedative. Anticholinergic drugs used to treat overactive bladder cause drowsiness (Scheife and Takeda 2005). The sedative propensities of H1-antihistamines (Church and Church 2013), phenothiazine antipsychotics and tricyclic antidepressants (Proctor and Bianchi 2012) are likely to reflect, to some extent, muscarinic cholinoceptor blockade. In extreme cases, such as administration during anaesthesia (Moos 2007) and poisoning (Parissis et al. 2003), anticholinergic drugs may lead to coma. Physostigmine has proved to be an effective antidote in these cases.

### 4.4.5 REMS-Suppressing Cholinergic Inhibitors

Anticholinergic drugs, such as scopolamine, suppress REMS (Rao et al. 2004).

## *4.5 Noradrenaline*

### 4.5.1 The Noradrenergic Wake-Promoting System

Central noradrenergic neurons are clustered in seven brainstem nuclei, labelled A1–A7, of which the locus coeruleus (A6) is the largest one (Samuels and Szabadi 2008a; Szabadi 2013). The locus coeruleus (LC) occupies a central position in the sleep-arousal network, collating arousal-related information from all wake-promoting and sleep-promoting nuclei (Fig. 1).

The LC, apart from functioning as a major wake-promoting nucleus, has three additional functions that are intimately linked to its arousal-enhancing effect: autonomic regulation, motor regulation and modulation of the effect of light on arousal ("photomodulation").

#### Regulation of Arousal

The LC exerts its wake-promoting effect via excitatory projections to the cerebral cortex and some other wake-promoting nuclei (e.g. cholinergic wake-promoting neurons of the PPT/LDT and the BF, serotonergic neurons of the DR) and inhibitory projections to the sleep-promoting GABAergic neurons of the VLPO and BF. The LC also suppresses REM sleep by inhibiting REMS-promoting cholinergic neurons in the PPT/LDT (Figs. 1 and 5; Szabadi 2013). The excitatory projections operate via stimulation of excitatory $\alpha_1$-adrenoceptors and the inhibitory projections via stimulation of inhibitory $\alpha_2$-adrenoceptors (Szabadi 2013).

#### Autonomic Regulation

The LC functions as a premotor autonomic nucleus, sending excitatory projections to sympathetic preganglionic neurons and inhibitory projections to preganglionic parasympathetic neurons (Figs. 1 and 5). LC activation leads to increased arousal, sympathetic activation and parasympathetic deactivation, whereas the opposite pattern occurs as LC activity diminishes. This is beautifully illustrated by the regulation of the diameter of the pupil. It has been shown that fluctuations in pupil diameter, that is under dual sympathetic/parasympathetic control (Szabadi 2013), are closely paralleled by fluctuations in LC activity (Aston-Jones and Cohen 2005; Murphy et al. 2014). Furthermore, both fluctuations in pupil diameter (Wilhelm et al. 2001) and LC activity (Sterpenich et al. 2006; Minzenberg et al. 2008) are related to the level of arousal. Recording pupillary fluctuations forms the basis of the Pupillographic Sleepiness Test (PST) that has been widely used for the assessment of level of arousal in humans (Wilhelm et al. 2001; Samuels et al. 2006).

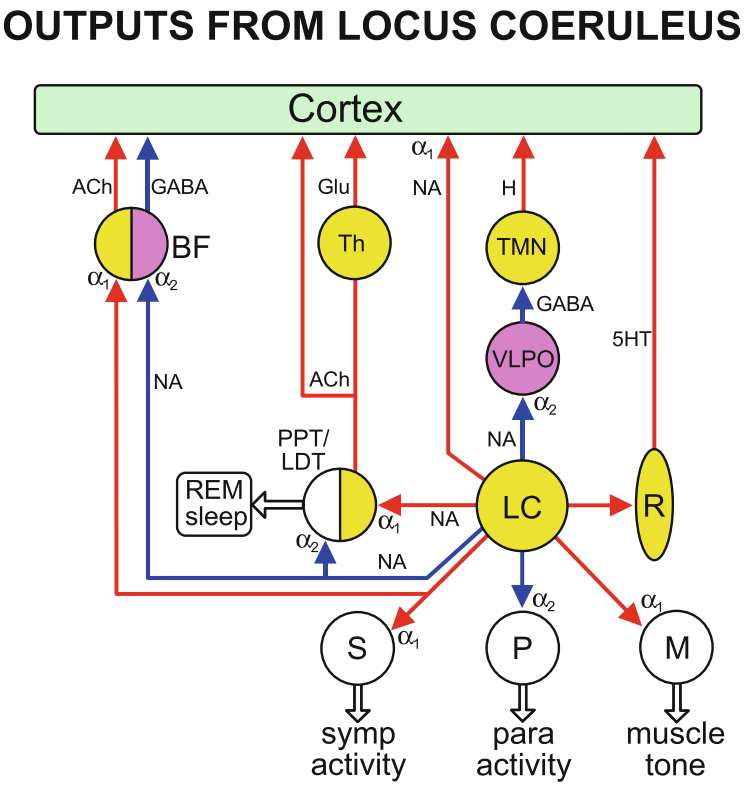


**Fig. 5** Schematic diagram of outputs from the noradrenergic locus coeruleus (LC), in relation to the regulation of sleep and arousal. *Wake-promoting nuclei* (*yellow*): BF, basal forebrain; Th, thalamus; TMN, tuberomamillary nucleus; PPT/LDT, pedunculopontine/laterodorsal tegmental nuclei; R, raphe nuclei. *Sleep-promoting nuclei* (*purple*): VLPO, ventrolateral preoptic nucleus; BF, basal forebrain. *Targets outside the sleep/arousal network* (*white*): S, sympathetic preganglionic neurons; P, parasympathetic preganglionic neurons; M, motoneurons. *Connections*: *arrows* (*red*: excitatory; *blue*: inhibitory). *Lettering next to arrow*: neurotransmitter (ACh: acetylcholine; NA: noradrenaline; H: histamine; GABA: γ-aminobutyric acid; 5HT: 5-hydroxytryptamine; Glu: glutamate). *Receptors*: $\alpha_1$, excitatory $\alpha_1$-adrenoceptors; $\alpha_2$, inhibitory $\alpha_2$-adrenoceptors. See text (Sect. 4.5.1) for details

## Motor Regulation

The LC modulates motor activity via excitatory projections to motoneurons (Fig. 5) both in the brainstem and the spinal cord (Szabadi 2013). There is a close link between the modulation of arousal and muscle tone by the LC (McGregor and Siegel 2010). LC activity is reduced during SWS while in REMS there is near complete cessation of LC activity (Gottesmann 2011). The reduction in LC activity during sleep is associated with reduced muscle tone. There is complete cessation of LC activity during attacks of cataplexy in the sleep disorder narcolepsy (Wu et al. 1999), leading to total atonia (Peever 2011). The reduction in the

facilitatory drive from the LC to brainstem motor nuclei may be responsible for the loss of the tone of the muscles of the upper airway (pharynx, tongue, jaw muscles) during sleep (Lo et al. 2007), that may contribute to the genesis of sleep-related obstructive breathing disorders (Heinzer and Sériès 2011).

Photomodulation

Light has a direct acute effect on the level of arousal via the photomodulation network (Szabadi 2013). The effect of light consists of two mutually antagonistic components: it is both sleep-promoting and wake-promoting. The sleep-promoting effect is mediated via a direct excitatory output from the retina to the VLPO (Fig. 3; Lu et al. 1999): activation of the VLPO leads to dampening of the activity of major wake-promoting nuclei (LC, TMN, LH/PF). The wake-promoting effect is channelled via a multi-synaptic pathway in which the LC plays a key role: retina → SCN → DMH → LC → cerebral cortex (Fig. 3; Aston-Jones 2005). Indeed, it has been shown by fMRI that light evokes LC activation (Vandewalle et al. 2007). The overall response to light reflects the relationship between the two opposing effects: in nocturnal animals the prevalent effect of light is stimulation of the VLPO, leading to sleep-promotion, whereas in diurnal animals, this effect is likely to be superseded by the consequence of LC activation, leading to wake promotion (Szabadi 2012, 2013).

### 4.5.2 Cellular Targets of Noradrenergic Drugs

There are three classes of adrenoceptor ($\alpha_1$, $\alpha_2$, $\beta$): they all have been identified on follower cells ("postsynaptic receptors"). In general, the $\alpha_1$-adrenoceptors mediate excitatory effects, the $\alpha_2$-adrenoceptors inhibitory effects and the β-adrenoceptors either excitatory or inhibitory effects. Inhibitory $\alpha_2$-adrenoceptors have also been identified on the noradrenergic neuron itself ("presynaptic receptors" or "autoreceptors"): in a somato-dendritic location they inhibit the firing of the neuron, whereas located on the nerve terminal they inhibit transmitter release.

Somatodendritic autoreceptors are stimulated by noradrenaline released either from dendrites ("dendritic release") or from recurrent axon collaterals, whereas terminal autoreceptors ("release-modulating receptors") are stimulated by noradrenaline released from the noradrenergic nerve terminals. Stimulation of inhibitory somatodendritic $\alpha_2$-adrenoceptors dampens the firing of the neuron as activity increases (Huang et al. 2012), providing a mechanism for the autoregulation of central noradrenergic neurons. This mechanism may be responsible for the "switching off" of the central noradrenergic neuron at very high rates of firing (Carter et al. 2010).

Somatodendritic inhibitory $\alpha_2$-autoreceptors on LC neurons are co-localized with μ opioid receptors: the activation of each receptor leads to cellular inhibition

via a shared potassium channel (Christie 1991). Morphine, like the $\alpha_2$-adrenoceptor agonist clonidine, reduces LC activity (Seutin et al. 1990).

Drugs can also interfere with the release and the reuptake of the transmitter into the nerve terminal or synaptic vesicles. The reuptake of noradrenaline into nerve terminals (Mandela and Ordway 2006) and its accumulation in synaptic vesicles (Zheng et al. 2006) are controlled by specific transporter proteins.

### 4.5.3 Wake-Promoting Noradrenergic Activators

$\alpha_2$-Adrenoceptor Antagonists

It is well documented that $\alpha_2$-adrenoceptor antagonists (yohimbine: Phillips et al. 2000; idazoxan: Glue et al. 1991; atipamezole: Pertovaara et al. 2005) have alerting effects. The alerting effects of these drugs are relatively mild: this is in contrast with the powerful sedative effects of the $\alpha_2$-adrenoceptor agonists (see Sect. 4.5.4.1).

Noradrenaline Reuptake Inhibitors

These drugs, by impeding the removal of noradrenaline from the synaptic cleft, enhance the effect of noradrenaline. *Selective noradrenaline reuptake inhibitors (NARI)* include the antidepressant reboxetine (Szabadi and Bradshaw 2000) and atomoxetine, a drug indicated for the treatment of attention deficit hyperactivity disorder (ADHD) (Kratochvil et al. 2003). These drugs have relatively mild alerting effects, and insomnia is one of their adverse effects. The NARI have distinct sympathomimetic and parasympatholytic effects, due to the potentiation of the effects of noradrenaline on preganglionic sympathetic and parasympathetic neurons (Szabadi and Bradshaw 2000). *Nonselective catecholamine reuptake inhibitors* (e.g. amphetamine, modafinil), although they also block the reuptake of noradrenaline, act primarily at the dopamine uptake site (see Sect. 4.6.3).

### 4.5.4 Sleep-Promoting Noradrenergic Inhibitors

$\alpha_2$-Adrenoceptor Agonists

$\alpha_2$-Adrenoceptor agonists (e.g. clonidine, medetomidine and dexmedetomidine) are potent sedatives in humans (Hossmann et al. 1980; Scheinin et al. 1987). Dexmedetomidine is used as an anaesthetic (Nelson et al. 2003). The sedative effect of these drugs can be attributed to the stimulation of inhibitory autoreceptors on noradrenergic neurons in the LC leading to the "switching off" of the LC (Abercrombie and Jacobs 1987). The sedation is accompanied by pupil constriction (miosis): this is due to the removal of the excitatory influence of the LC on

sympathetic preganglionic neurons and of its inhibitory influence on preganglionic parasympathetic neurons ("disinhibition") (Samuels and Szabadi 2008b). These drugs also cause sedation and miosis in other diurnal species (dog, rabbit); however, they have the opposite effects (i.e. increases in alertness and pupil diameter) in nocturnal animals (cat, rat, mouse). This species difference is likely to reflect the preponderance of the stimulation of $\alpha_2$-adrenoceptors on LC neurons ("autoreceptors") in diurnal animals versus the stimulation of these receptors on follower neurons ("postsynaptic receptors") in nocturnal animals (Samuels and Szabadi 2008b).

### μ Opioid Receptor Agonists

These drugs, including morphine (Paqueron et al. 2002), oxycodone (Verster et al. 2006), tramadol (Lewis and Han 1997) and codeine (Max et al. 1988) are highly sedative in man. The sedation caused by these drugs can be attributed, at least partly, to the inhibition of LC activity via the stimulation of inhibitory μ opioid receptors on the noradrenergic neurons (Seutin et al. 1990). As there is a close association between $\alpha_2$-adrenoceptors and μ opioid receptors (Sect. 4.5.1), there is a parallelism between the effects of clonidine and morphine on the level of arousal and the diameter of the pupil. Morphine, like clonidine, causes sedation and pupil constriction in diurnal animals (man, dog, rabbit) and increases in alertness and pupil diameter in nocturnal species (cats, rats, mice) (Samuels and Szabadi 2008b).

Apart from its soporific effect, morphine also reduces REM sleep (Cronin et al. 1995). This effect is likely to be due to a decrease in acetylcholine release from central cholinergic neurons involved in REM sleep regulation (Lydic and Baghdoyan 2007).

### Monoamine Depletors

Noradrenaline, dopamine and serotonin are accumulated in presynaptic storage vesicles by vesicular monoamine transporter 2, (VMAT2) (Zheng et al. 2006). VMAT2 is inhibited by reserpine and tetrabenazine. Reserpine affects all three monoamines, whereas tetrabenazine shows some selectivity for dopamine. The blockade of VMAT2 leads to emptying ("depletion") of the storage vesicles, resulting in cessation of transmitter release (Shore 1962). The depletion of central noradrenaline stores results in sedation and pupil constriction. Reserpine also depletes peripheral noradrenaline stores leading to a sympatholytic effect (hypotension) (Sulser and Bass 1968). Reserpine is not used clinically any longer. Tetrabenazine is prescribed for the treatment of hyperkinetic movement disorders (e.g. chorea) (Kenney and Jankoovic 2006).

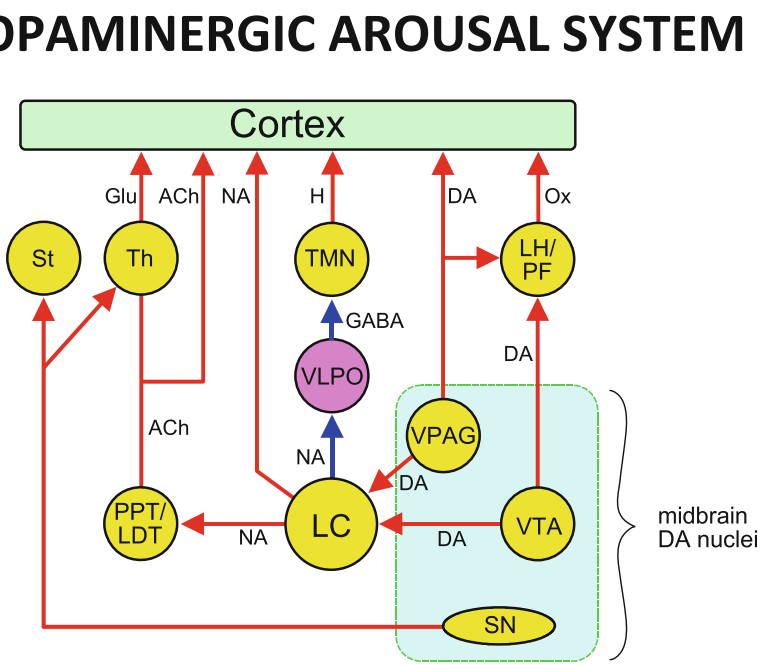


**Fig. 6** Schematic diagram of the connections of the midbrain dopaminergic nuclei underlying their wake-promoting propensity. *Wake-promoting nuclei* (*yellow*): midbrain dopaminergic nuclei (SN, substantia nigra; VTA, ventral tegmental area, VPAG: ventral periaqueductal grey matter); TMN, tuberomamillary nucleus; LH/PF, lateral hypothalamic/perifornical area; Th, thalamus; LC, locus coeruleus; PPT/LDT, pedunculopontine/laterodorsal tegmental nuclei; St, striatum. *Sleep-promoting nucleus* (*purple*): VLPO, ventrolateral preoptic nucleus. *Connections*: *arrows* (*red*: excitatory; *blue*: inhibitory). *Lettering next to arrow*: neurotransmitter (ACh: acetylcholine; NA: noradrenaline; H: histamine; Ox: orexin; GABA: γ-aminobutyric acid; DA: dopamine; Glu: glutamate. See text (Sect. 4.6.1). Reproduced, with permission, from Niepel et al. (2013)

## *4.6 Dopamine*

### 4.6.1 The Dopaminergic Wake-Promoting System

Dopaminergic neurons are localized in distinct nuclei in the midbrain, hypothalamus and olfactory bulb (Niewenhuys 1985). The three nuclei in the midbrain (substantia nigra, VTA, ventral periaqueductal grey matter) are involved in the regulation of motor activity (locomotion), motivation/reward and arousal, whereas the hypothalamic nuclei play a role in neuroendocrine secretion. All three midbrain nuclei make a contribution to the wake-promoting effect of the dopaminergic system, via their direct and indirect projections to the cerebral cortex and other wake-promoting nuclei (Fig. 6; Niepel et al. 2013).

The *substantia nigra (pars compacta)* regulates motor activity via its projection to the striatum (nigrostriatal pathway). This pathway sends excitatory collaterals to the wake-promoting neurons in the thalamus, thus contributing to the wake-

promoting influence of the dopaminergic system (Freeman et al. 2001). The loss of the dopaminergic input to the thalamus, resulting from the degeneration of nigrostriatal neurons, has been implicated in the genesis of EDS in Parkinson's disease (Keating and Rye 2003).

The *VTA* is involved in the regulation of motivation/reward via the mesolimbic pathway. It also exerts a wake-promoting influence via excitatory outputs to the LC (Deutch et al. 1986) and LH/PF (Bubser et al. 2005) (Figs. 1 and 6).

The *ventral periaqueductal grey matter (VPAG)* contains dopaminergic neurons that mediate a wake-promoting effect via projections to the cerebral cortex, LC and LH/PF (Lu et al. 2006).

Dopaminergic neurons, unlike other wake-promoting neurons, do not vary their firing rate across the sleep-wakefulness cycle. However, they rather display a cycle-dependent modulation of their firing pattern: they fire in bursts during W and REMS (Monti and Monti 2007).

### 4.6.2 Dopamine Receptors

There are five G-protein-coupled metabotropic dopamine receptors (D1–D5) that are divided into two subfamilies: D1-like (D1 and D5) and D2-like (D2, D3, D4) receptors. The D1-like receptors mediate excitatory and the D2-like receptors inhibitory cellular responses. The D1-like receptors are post-synaptic, whereas the D2-like receptors are both post-synaptic and presynaptic. The presynaptic receptors inhibit the firing of the neuron and the release of the transmitter (Beaulieu and Gainetdinov 2011).

As D2 receptors occur both presynaptically and postsynaptically, and the presynaptic receptors are more sensitive than the postsynaptic ones, D2 receptor agonists display a dose-dependent dual effect: lower doses decrease and higher doses increase dopamine-mediated functions (Beaulieu and Gainetdinov 2011). It has been proposed that the stimulant effects of D2 receptor agonists on some functions (e.g. locomotion, arousal) may be mediated via inhibition of GABAergic interneurons ("disinhibition") (Monti and Monti 2007).

### 4.6.3 Wake-Promoting Dopaminergic Activators

Dopamine Reuptake Inhibitors

Blockade of the dopamine transporter (DAT) leads to inhibition of the reuptake of dopamine from the extracellular space, resulting in potentiation of dopaminergic functions. The psychostimulants *amphetamine*, *cocaine* and *methylphenidate* are potent blockers of DAT (Zhu and Reith 2008), and also have marked wake-promoting effects (Nishino et al. 1998). Amphetamine is used to treat EDS/daytime sleep attacks in narcolepsy, and methylphenidate is used for the treatment of ADHD. These drugs also have pro-cognitive effects and a potential for addiction.

*Modafinil* is a wake-promoting drug licensed for the treatment of EDS in narcolepsy. It also has some procognitive effects (Müller et al. 2013). There is evidence that modafinil, like the psychostimulants amphetamine and cocaine, inhibits dopamine uptake. However, it also differs from the psychostimulants (Wisor 2013). Whereas nonselective psychostimulants (amphetamine, cocaine) enhance all dopaminergic function, including motor activity and motivation/reward, modafinil seems to be relatively selective for the dopaminergic arousal system. This may explain its relatively low addiction potential (Wisor 2013). It has recently been suggested that modafinil may promote wakefulness by selectively potentiating the dopaminergic inhibition of putative sleep-promoting neurons in the nucleus accumbens (Qiu et al. 2012).

#### Dopamine Release Promoters

The accumulation of monoamines, including dopamine, in presynaptic vesicles is mediated by vesicular monoamine transporter-2 (VMAT-2). Psychostimulants (amphetamine, cocaine, methylphenidate), apart from inhibiting DAT (Sect. 4.6.3.1), also inhibit VMAT-2, thus enhancing the release of dopamine (Riddle et al. 2005).

*Nicotine*, by stimulating nicotinic receptors on dopaminergic nerve terminals, enhances the release of dopamine (Zhu and Reith 2008). This effect contributes to the wake-promoting propensity of nicotine (see Sect. 4.4.3.3).

#### Postsynaptic D1 and D2 Dopamine Receptor Agonists

D1 receptor agonists (e.g. SKF 38393) increase wakefulness in experimental animals. D2 receptor agonists (e.g. apomorphine) have a biphasic effect: lower doses decrease alertness, due to stimulation of presynaptic receptors, whereas higher doses increase it, due to the stimulation of postsynaptic receptors (Monti and Monti 2007).

#### Presynaptic D2 Dopamine Receptor Antagonists

Lower doses of D2 receptor antagonists (e.g. amisulpride) can increase alertness (Patat et al. 1999).

### 4.6.4 Sleep-Promoting Dopaminergic Inhibitors

Presynaptic D2 Receptor Agonists

D2 receptor agonists (pergolide, pramipexole, ropinirole, bromocriptine) are used to treat Parkinson's disease: they are believed to improve motor deficits through an action at postsynaptic D2 receptors in the striatum. In therapeutic doses these drugs are highly sedative consistent with the stimulation of presynaptic D2 receptors of the wake-promoting dopaminergic neurons in the VTA and VPAG (Samuels et al. 2006). Thus the same dosage of a D2 receptor agonist may stimulate postsysnaptic receptors in the striatum, a structure that is partially denervated in Parkinson's disease, and presynaptic receptors on the anatomically intact wake-promoting neurons of the VTA and VPAG.

Postsynaptic D1 and D2 Receptor Antagonists

D1 receptor antagonists (e.g. SCH 23390) and high doses of D2 receptor antagonists (e.g. haloperidol) have sedative effects (Monti and Monti 2007). The sedation caused by most antipsychotic drugs is only partially attributable to the blockade of postsynaptic D2 dopamine receptors, since many antipsychotics also block other wake-promoting neuroreceptors, such as H1-histamine receptors (Sect. 4.1.4) and cholinoceptors (Sect. 4.4.4)

Monoamine Depletors

Long-term or irreversible blockade of VMAT-2, by reserpine or tetrabenazine, leads to the depletion of monoamine stores, resulting in impairment of central monoaminergic neurotransmission. One of the consequences of central monoamine depletion is sedation (see Sect. 4.5.4).

## *4.7 Serotonin*

### 4.7.1 The Serotonergic Wake-Promoting System

Serotoninergic neurons are located in nine nuclei (B1–B9) in the midline (raphe) of the brainstem (Niewenhuys 1985). Of these B7 (dorsal raphe nucleus, DR) is involved in the regulation of sleep and arousal (Monti 2010). Serotonergic DR neurons project diffusely to the same areas as LC neurons, including the cerebral cortex, BF and subcortical arousal-modulating nuclei. These neurons vary their activity across the sleep-wakefulness cycle: they are maximally active during W, show reduced activity during SWS and stop firing during REMS. However, mainly

due to the distribution of a complex receptor system (Sect. 4.7.2), the serotonergic system does not play a uniform role in the regulation of sleep and arousal: apart from promoting W and SWS, it also initiates SWS (Datta and McLean 2007).

### 4.7.2 Serotonin Receptors

There are seven classes of serotonin (5-hydroxytryptamine, 5-HT) receptors: 5-$HT_{1–7}$, with a number of subtypes yielding 16 receptors (Hoyer et al. 2002). 5-$HT_3$ receptors are ligand-gated ion channels, whereas all other 5-HT receptors signal via G-proteins. 5-$HT_1$ receptors are negatively, and 5-$HT_{2,4–7}$ receptors are positively coupled to G-proteins. 5-$HT_1$ receptors are inhibitory, and occur both in presynaptic and postsynaptic locations. 5-$HT_2$ and 5-$HT_3$ receptors are excitatory and located mainly postsynaptically. 5-$HT_{2A}$ and 5$HT_{2C}$ receptors are often located on GABAergic interneurons where their activation would mediate an inhibitory influence ("disinhibition") (Monti 2010). In the cerebral cortex, 5-$HT_{2A}$ receptors are co-localized with $\alpha_1$-adrenoceptors on the same neurons (Santana et al. 2013), indicating synergism between noradrenergic and serotonergic excitatory mechanisms.

### 4.7.3 Wake-Promoting Serotonergic Activators

Serotonin Receptor Agonists

Systemically administered agonists of 5-$HT_{1A}$ (flesinoxan, 8-OH-DPAT, buspirone), 5-$HT_{1B}$ (GCS 12066B), 5-$HT_{2A/2C}$ (DOI), 5-$HT_3$ (mCPG), 5-$HT_6$ 9SB-399665) and 5-$HT_7$ (LP-44) receptors all increase wakefulness in experimental animals (Monti 2011). In humans, buspirone, used as an anxiolytic, has wake-promoting effects (Manfredi et al. 1991). The mode of action of these different drugs is not known: they are likely to act at different sites in the sleep/arousal network.

Serotonin Reuptake Inhibitors

Released serotonin is removed from the synaptic cleft by the serotonin transporter (SERT): its blockade leads to the potentiation of serotonergic functions (Ramamoorthy et al. 1993). A group of antidepressants (selective serotonin reuptake inhibitors, SSRIs), as their name indicates, act by blocking SERT. These drugs would increase neurotransmission at every serotonergic synapse: in the cerebral cortex increased 5-$HT_{2A}$ receptor stimulation would lead to a wake-promoting effect, whereas in the brainstem 5-$HT_{2C}$ receptor stimulation on GABAergic interneurons, that inhibit wake-promoting noradrenergic neurons in the LC and dopaminergic neurons in the VTA, would lead to a sleep-promoting effect

(Sect. 3.1.1, Figs. 1 and 5). This dual action of the SSRIS may explain their mixed effects on the level of arousal: while they disrupt SWS and cause insomnia, they have little effect on daytime alertness and may even cause sedation (Winokur et al. 2001).

### 4.7.4 Sleep-Promoting Serotonergic Inhibitors

Serotonin Receptor Antagonists

Since antagonists of 5-$HT_{2A}$ receptors (e.g. ritanserin, ketanserin) increase SWS (Monti 2011), the $5HT_{2A}$ receptor has become a target for the development of anti-insomnia drugs. A number of 5-$HT_{2A}$ receptor antagonists (e.g. volinanserin, eplivanserin) and inverse agonists (e.g. primavanserin) have been developed and are undergoing clinical assessment (Vanover and Davis 2010).

Monoamine Depletors

Inhibitors of VMAT-2, the vesicular membrane pump transporter (Sects. 4.5.4 and 4.6.4), such as reserpine and tetrabenazine, also inhibit the storage of serotonin and lead to the depletion of presynaptic serotonin stores. This leads to a serotonergic contribution to the sleep-promoting effect of these drugs.

### 4.7.5 REMS-Suppressing Serotonergic Activators

Central serotonergic activation by serotonin receptor agonists and uptake inhibitors leads to the suppression of REMS (Datta and McLean 2007; Monti 2011).

**Conclusions**
The level of arousal at any one time reflects the intricate interplay between distinct, anatomically and neurochemically defined, wake-promoting and sleep-promoting neuronal systems. These neuronal systems can be grouped into three distinct networks, the sleep/arousal network, the REMS network and the circadian network. In each network there are pharmacologically sensitive sites, such as neuroreceptors and the synaptic machinery: by targeting these sites, drugs can be developed with selective and predictable effects on sleep and arousal. There is complexity at the levels of neuronal connections (e.g. projections to targets via interneurons), cellular localization of neuroreceptors (presynaptic vs postsynaptic) and their signalling mechanisms (excitatory vs inhibitory), and the molecular pharmacology of the drug/

(continued)

receptor interaction (orthosteric vs allosteric). Unravelling the networks at anatomical, cellular and molecular levels has already provided dividends, such as the development of orexin receptor antagonists, $5HT_{2A}$ receptor antagonists and melatonin receptor agonists to treat insomnia and histamine H3 receptor antagonists to treat EDS. The molecular dissection of the $GABA_A$ receptor has already provided subunit selective allosteric modulators with clinical selectivities as hypnotics or anxiolytics. And this is only the beginning of a new area for sleep pharmacology: drugs interacting with the cholinergic, glutamatergic and galaninergic systems provide a hitherto untapped resource.

There is a two-way relationship between the sleep/arousal networks and drugs: while the networks can provide the impetus for the development of novel drugs, drugs can be used as tools for further dissection of the networks. An example for this is modafinil: efforts to discover its mode of action have resulted in important insights into sleep/arousal mechanisms (Qiu et al. 2012).

Finally, new knowledge about the operation of the networks can be obtained from clinical neuropsychiatry and neuropathology. The discovery of the biological bases of the sleep disorders in narcolepsy, RBD and auto-immune encephalitides (Rye 2014), and of the relationship between visual hallucinations and REMS (Manford and Andermann 1998), have yielded valuable insights.

**Acknowledgement** I am grateful to Rob Langley for drawing the figures.

## References

Abe Y, Aoyagi A, Hara T et al (2003) Pharmacological characterization of RS-1259, an orally active dual inhibitor of acetylcholinesterase and serotonin transporter, in rodents: possible treatment of Alzheimer's disease. J Pharmacol Sci 93:95–105

Abercrombie ED, Jacobs BL (1987) Microinjected clonidine inhibits noradrenergic neurons of the locus coeruleus in freely moving cats. Neurosci Lett 76:203–208

Ahnaou A, Drinkenburg WHIM, Bouwknecht JA et al (2008) Blocking melanin-concentrating hormone MCH1 receptor affects rat sleep-wake architecture. Eur J Pharmacol 579:177–188

Ahnaou A, Dautzenberg FM, Geys H et al (2009) Modulation of group II metabotropic glutamate receptor ($mGlu_2$) elecits common changes in rat and mice sleep-wake architecture. Eur J Pharmacol 603:62–72

Ahnaou A, Ver Donck L, Drinkenburg WHIM (2014) Blockade of the metabotropic glutamate (mGluR2) modulates arousal through vigilance states transitions: evidence from sleep-wake EEG in rodents. Behav Brain Res 270:56–67

Argiolas A, Melis MR (2005) Central control of penile erection: role of the paraventricular nucleus of the hypothalamus. Prog Neurobiol 76:1–21

Arias-Carrión O, Murillo-Rodriguez E (2014) Effects of hypocretin/orexin cell transplantation on narcoleptic-like sleep behavior in rats. PLoS One 9:e95342

Arrang JM, Morisset S, Gbahou F (2007) Constitutive activity of the histamine H3 receptor. Trends Pharmacol Sci 28:350–357
Aston-Jones G (2005) Brain structures and receptors involved in alertness. Sleep Med 6(Suppl 1): S3–S7
Aston-Jones G, Cohen JD (2005) An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance. Annu Rev Neurosci 28:403–450
Atack JR (2010) Preclinical and clinical pharmacology of the $GABA_A$ receptor α5 subtype inverse agonist α5IA. Pharmacol Ther 125:11–26
Bay T, Eghorn L, Klein AB et al (2014) GHB receptor targets in the CNS: focus on high-affinity binding sites. Biochem Pharmacol 87:220–228
Beaulieu J-M, Gainetdinov RR (2011) The physiology, signaling, and pharmacology of dopamine receptors. Pharmacol Rev 63:182–217
Belelli D, Peden DR, Rosahl TW et al (2005) Extrasynaptic $GABA_A$ receptors of thalamocortical neurons: a molecular target for hypnotics. J Neurosci 25:11513–11520
Benington JH, Kodali SK, Heller HC et al (1995) Stimulation of $A_1$ adenosine receptors mimics the electroencephalographic effects of sleep deprivation. Brain Res 692:79–85
Berigan TR (2002) Modafinil treatment of excessive daytime sedation and fatigue associated with topiramate. Prim Care Companion J Clin Psychiatry 4:249–250
Berlin M, Boyce CW, Ruiz Mde L (2011) Histamine H3 receptor as a drug discovery target. J Med Chem 54:26–53
Bien CG, Vincent A, Barnett MH et al (2012) Immunopathology of autoantibody-associated encephalitides: clues for pathogenesis. Brain 135:1622–1638
Boscolo-Berto R, Viel G, Montagnese S et al (2012) Narcolepsy and effectiveness of gamma-hydroxybutyrate (GHB): a systematic review and meta-analysis of randomized controlled trials. Sleep Med Rev 16:431–443
Bowery NG (2006) $GABA_B$ receptor: a site of therapeutic benefit. Curr Opin Pharmacol 6:37–43
Brioni JD, Esbenshade TA, Garrison TR et al (2011) Discovery of histamine $H_3$ antagonists for the treatment of cognitive disorders and Alzheimer's disease. J Pharmacol Exp Ther 336:38–46
Brown DA (2010) Muscarinic acetylcholine receptors (mAChRs) in the nervous system: some functions and mechanisms. J Mol Neurosci 41:340–346
Brown RE, Basheer R, McKenna JT et al (2012) Control of sleep and wakefulness. Physiol Rev 92:1087–1187
Bubser M, Fadel JR, Jackson LL et al (2005) Dopaminergic regulation of orexin neurons. Eur J Neurosci 21:2993–3001
Büttner-Ennever JA, Horn AKE (1997) Anatomical substrates of oculomotor control. Curr Opin Neurobiol 7:872879
Carter ME, Yizhar O, Chikahisha S et al (2010) Tuning arousal with optogenetic modulation of locus coeruleus neurons. Nat Neurosci 13:1526–1533
Cavas M, Scesa G, Navarro JF (2013a) Effects of MPEP, a selective metabotropic glutamate mGlu5 ligand, on sleep and wakefulness in the rat. Prog Neuropsychopharmacol Biol Psychiatry 40:18–25
Cavas M, Scesa G, Navarro JF (2013b) Positive allosteric modulation of mGlu7 receptors by AMN082 affects sleep and wakefulness in the rat. Pharmacol Biochem Behav 103:756–763
Chase MH (2013) Motor control during sleep and wakefulness: clarifying controversies and resolving paradoxes. Sleep Med Rev 17:299–312
Christie MJ (1991) Mechanisms of opioid actions on neurons of the locus coeruleus. Prog Brain Res 88:197–20
Church MK, Church DS (2013) Pharmacology of antihistamines. Indian J Dermatol 58:219–224
Cicolin A, Magliola U, Giordano A et al (2006) Effects of levetiracetam on nocturnal sleep and daytime vigilance in healthy volunteers. Epilepsia 47:82–85
Cronin A, Keier JC, Baghdoyan HA et al (1995) Opioid inhibition of rapid eye movement sleep by a specific mu receptor agonist. Br J Anaesth 74:188–192

Datta S, McLean RR (2007) Neurobiological mechanisms for the regulation of mammalian sleep-wake behavior: reinterpretation of historical evidence and inclusion of contemporary cellular molecular evidence. Neurosci Biobehav Rev 31:775–824

Deutch AY, Goldstein M, Roth RH (1986) Activation of the locus coeruleus induced by selective stimulation of the ventral tegmental area. Brain Res 363:307–314

Dijk DJ, Brunner DP, Aeschbach D et al (1992) The effects of ethanol on human sleep EEG power spectra differ from those of benzodiazepine receptor agonists. Neuropsychopharmacology 7:225–232

Dingledine R, Borges K, Bowie D et al (1999) The glutamate receptor ion channels. Pharmacol Rev 51:7–61

Dodson ER, Zee PC (2010) Therapeutics for circadian rhythm sleep disorders. Sleep Med Clin 5:701–771

Dunbar G, Boeijinga PH, Demazières A et al (2007) Effects of TC-1734 (AZD3480), a selective neuronal nicotinic receptor agonist, on cognitive performance and the EEG of young healthy male volunteers. Psychopharmacology 191:919–929

Ebert U, Kirch W (1998) Scopolamine model of dementia: electroencephalogram findings and cognitive performance. Eur J Clin Invest 28:944–949

España RA, Scammell TE (2011) Sleep neurobiology from a clinical perspective. Sleep 34:845–858

Esplin DW (1970) Drugs acting on the central nervous system – introduction. In: Goodman LS, Gilman A (eds) The pharmacological basis of therapeutics, 4th edn. Macmillan, New York, pp 36–42

Fares A (2011) Night-time exogenous melatonin administration may be a beneficial treatment for sleeping disorders in beta blocker patients. J Cardiovasc Dis Res 2:153–155

Fisher DJ, Daniels R, Jaworska N et al (2012) Effects of acute nicotine administration on resting EEG in nonsmokers. Exp Clin Psychopharmacol 20:71–75

Fort P, Bassetti CL, Luppi PH (2009) Alternating vigilance states: new insights regarding neuronal networks and mechanisms. Eur J Neurosci 29:1741–1753

Freeman A, Ciliax B, Bakay R et al (2001) Nigrostriatal collaterals to thalamus degenerate in parkinsonian animal models. Ann Neurol 50:321–329

Frisullo G, Della Marca G, Mirabella M (2007) A human anti-neuronal autoantibody against $GABA_B$ receptor induces experimental autoimmune agrypnia. Exp Neurol 204:808–818

Froestl W, Gallagher M, Jenkins H et al (2004) SGS742: the first $GABA_B$ receptor antagonist in clinical trials. Biochem Pharmacol 68:1479–1478

Fuller PM, Gooley JJ, Saper CB (2006) Neurobiology of the sleep-wake cycle: sleep architecture, circadian regulation, and regulatory feedback. J Biol Rhythms 21:482–493

Fuller P, Sherman D, Pedersen NP et al (2011) Reassessment of the structural basis of the ascending arousal system. J Comp Neurol 519:933–956

Gallopin T, Luppi PH, Cauli B et al (2005) The endogeneous somnogen adenosine excites a subset of sleep-promoting neurons via $A_{2A}$ receptors in the ventrolateral preoptic nucleus. Neuroscience 134:1377–1390

Gaus SE, Strecker E, Tate BA et al (2002) Ventrolateral preoptic nucleus contains sleep-active, galaninergic neurons in multiple mammalian species. Neuroscience 115:285–294

Gemkow MJ, Davenport AJ, Harich S et al (2009) The histamine H3 receptor as a therapeutic target for CNS disorders. Drug Discov Today 14:9–10

Gitto R, De Luca L, De Grazia S et al (2012) Glutamatergic neurotransmission as molecular target of new anticonvulsants. Curr Top Med Chem 12:971–993

Giuliano F, Rampin O (2004) Neural control of erection. Physiol Behav 83:189–201

Glue P, Wilson S, Lawson C (1991) Acute and chronic idazoxan in normal volunteers: biochemical, physiological and psychological effects. J Psychopharmacol 5:396–403

Gobert A, Rivet J-M, Lejeune F et al (2000) $Serotonin_{2C}$ receptors tonically suppress the activity of mesocortical dopaminergic and adrenergic, but not serotonergic, pathways: a combined dialysis and electrophysiological analysis in the rat. Synapse 36:205–221

Göder R, Seeck-Hirschner M, Stingele K (2011) Sleep and cognition at baseline and the effects of REM sleep diminution after 1 week of antidepressive treatment in patients with depression. J Sleep Res 20:544–551

Gottesmann C (2002) GABA mechanisms and sleep. Neuroscience 111:231–239

Gottesmann C (2011) The involvement of noradrenaline in rapid eye movement sleep mentation. Front Neurol 2:1–10 (Article 81)

Gotti C, Clementi F, Fornari A et al (2009) Structural and functional diversity of native brain neuronal nicotinic receptors. Biochem Pharmacol 78:703–711

Haas HL, Lin J-S (2012) Waking with the hypothalamus. Pflugers Arch Eur J Physiol 463:31–42

Hardeland R (2012) Melatonin in aging and disease – multiple consequences of reduced secretion, options and limits of treatment. Aging Dis 3:194–225

Hassani OK, Lee MG, Jones BE (2009) Melanin-concentrating hormone neurons discharge in a reciprocal manner to orexin neurons across the sleep-wake cycle. Proc Natl Acad Sci USA 106:2418–2422

Heinzer RC, Sériès F (2011) Normal physiology of the upper and lower airways. In: Kryger MH, Roth T, Dement WS (eds) Principles and practice of sleep medicine, 5th edn. Elsevier, St Louis, pp 259–268

Hirshkowitz M, Schmidt MH (2005) Sleep-related erections: clinical perspectives and neural mechanisms. Sleep Med Rev 9:311–329

Hobson JA (2009) REM sleep and dreaming: towards a theory of protoconsciousness. Nat Rev Neurosci 10:803–813

Hoffman EJ, Warren EW (1993) Flumazenil: a benzodiazepine antagonist. Clin Pharm 12:641–656

Hossmann V, Maling TJ, Hamilton CA et al (1980) Sedative and cardiovascular effects of clonidine and nitrazepam. Clin Pharmacol Ther 28:167–176

Hoyer D (2010) Neuropeptide receptor positive allosteric modulation in epilepsy: galanin modulation revealed. Proc Natl Acad Sci USA 107:14943–1494

Hoyer D, Jacobson LH (2013) Orexin in sleep, addiction and more: is the perfect insomnia drug at hand? Neuropeptides 47:477–488

Hoyer D, Hannon JP, Martin GR (2002) Molecular, pharmacological and functional diversity of 5-HT receptors. Pharmacol Biochem Behav 71:533–554

Huang Z-L, Qu W-M, Eguchi N (2005) Adenosine $A_{2A}$, but not $A_1$, receptors mediate the arousal effect of caffeine. Nat Neurosci 8:858–859

Huang Z-L, Urade Y, Hayaishi O (2011) The role of adenosine in the regulation of sleep. Curr Top Med Chem 11:1047–1057

Huang H-P, Zhu F-P, Chen X-W et al (2012) Physiology of quantal norepinephrine release from somatodendritic sites of neurons in locus coeruleus. Front Mol Neurosci 5:1–5 (Article 29)

Jego S, Glasgow SD, Gutierrez Herrera C et al (2013) Optogenetic identification of a rapid eye movement sleep modulatory circuit in the hypothalamus. Nat Neurosci 16:1637–1643

Johnson EO, Roehrs T, Roth T et al (1998) Epidemiology of alcohol and medication as aids to sleep in early adulthood. Sleep 21:178–186

Johnston GAR (2013) Advantages of an antagonist: bicuculline and other GABA antagonists. Br J Pharmacol 169:328–336

Johnston GA, Chebib M, Hanrahan JR et al (2003) GABA(C) receptors as drug targets. Curr Drug Targets CNS Neurol Disord 2:260–268

Kalsbeek A, Garidou ML, Palm IF et al (2000) Melatonin sees the light: blocking GABA-ergic transmission in the paraventricular nucleus induces daytime secretion of melatonin. Eur J Neurosci 12:3146–3154

Kalsbeek A, Palm IF, La Fleur SE et al (2006) SCN outputs and the hypothalamic balance of life. J Biol Rhythms 21:458–469

Keating GL, Rye DB (2003) Where you least expect it: dopamine in the pons and modulation of sleep and REM-sleep. Sleep 26:788–789

Kenney C, Jankoovic J (2006) Tetrabenazine in the treatment of hyperkinetic movement disorders. Mov Disord 22:193–197

Ko EM, Eastbrooke IV, McCarthy M et al (2003) Wake-related activity of tubermammillary neurons in rats. Brain Res 992:220–226

Kohlmeier KA, Vardar B, Christensen MH (2013) γ-Hydroxybutyric acid induces actions via the $GABA_B$ receptor in arousal and motor control-related nuclei: implication for therapeutic actions in behavioural state disorders. Neuroscience 248:261–277

Kratochvil CJ, Vaughan BS, Harrington MJ et al (2003) Atomoxetine: a selective noradrenaline reuptake inhibitor for the treatment of attention-deficit/hyperactivity disorder. Expert Opin Pharmacother 4:1165–1174

Krenzer M, Anaclet C, Vetrivelan R et al (2011) Brainstem and spinal cord circuitry regulating REM sleep and muscle atonia. PLoS One 6(10):e24998

Kulisevsky J, Poyurovsky M (2012) Adenosine $A_{2A}$-receptor antagonism and pathophysiology of Parkinson's disease and drug-induced movement disorders. Eur Neurol 67:4–11

Lal H, Kumar B, Forster MJ (1988) Enhancement of learning and memory in mice by a benzodiazepine antagonist. FASEB J 2:2707–2711

Lambert JL, Cooper MA, Simmons RDJ et al (2009) Neurosteroids: endogenous allosteric modulators of $GABA_A$ receptors. Psychoneuroendocrinology 34S:S48–S58

Lancaster E, Lai M, Peng X et al (2010) Antibodies to the $GABA_B$ receptor in limbic encephalitis with seizures: case series and characterisation of antigen. Lancet Neurol 9:67–76

Landolt H-P (2008) Sleep homeostasis: a role for adenosine in humans? Biochem Pharmacol 75:2070–2079

Lane SD, Green CE, Steinberg JL et al (2012) Cardiovascular and subjective effects of the novel adenosine $A_{2A}$ receptor antagonist SYN115 in cocaine dependent individuals. J Addict Res Ther Suppl 1:1–15

Lazarus M, Shen H-Y, Cherasse Y et al (2011) Arousal effect of caffeine depends on adenosine $A_{2A}$ receptors in the shell of the nucleus accumbens. J Neurosci 31:10067–10075

Le Maître E, Barde SS, Palkovits M et al (2013) Distinct features of neurotransmitter systems in the brain with focus on the galanin system in locus coeruleus and dorsal raphe. Proc Natl Acad Sci USA 110:E536–545

Lee C-Y, Chen C-C, Liou H-H (2009) Levetiracetam inhibits glutamate transmission through presynaptic P/Q-type calcium channels on the granule cells of the dentate gyrus. Br J Pharmacol 158:1753–1762

Lerner JT, Sankar R, Mazarati AM (2008) Galanin and epilepsy. Cell Mol Life Sci 65:1864–1871

Leurs R, Blanidan P, Tedford C (1998) Therapeutic potential of histamine $H_3$ receptor agonists and antagonists. Trends Pharmacol Sci 19:177–183

Lewis KS, Han NH (1997) Tramadol: a new centrally acting analgesic. Am J Health Syst Pharm 54:643–652

Lin JS, Sakai K, Jouvet M (1988) Evidence for histaminergic arousal mechanisms in the hypothalamus of cat. Neuropharmacology 27:111–122

Lin J-S, Anaclet C, Sergeeva OA et al (2011) The waking brain: an update. Cell Mol Life Sci 68:2499–2512

Lo YL, Jordan AS, Malhorra A et al (2007) The influence of wakefulness on pharyngeal muscle activity. Thorax 62:799–805

Lu J, Shiromani P, Saper CB (1999) Retinal input to the sleep-active ventrolateral preoptic nucleus in the rat. Neuroscience 93:209–214

Lu J, Jhou TC, Saper CB (2006) Identification of wake-active dopaminergic neurons in the ventral periaqueductal gray matter. J Neurosci 26:193–202

Luppi P-H, Clément O, Sapin E et al (2011) The neuronal network responsible for paradoxical sleep and its dysfunctions causing narcolepsy and rapid eye movement (REM) behavior disorder. Sleep Med Rev 15:153–163

Luppi P-H, Clément O, Fort P (2013) Paradoxical (REM) sleep genesis by the brainstem is under hypothalamic control. Curr Opin Neurobiol 23:786–792

Lydic R, Baghdoyan HA (2007) Neurochemical mechanisms mediating opioid-induced REM sleep disruption. In: Lavigne G, Sessle B, Choinière M et al (eds) Sleep and pain. IASP Press, Seattle, pp 99–122
Mandela P, Ordway GA (2006) The norepinephrine transporter and its regulation. J Neurochem 97:310–333
Manford M, Andermann F (1998) Complex visual hallucinations – clinical and neurobiological insights. Brain 121:1819–1840
Manfredi RL, Kales A, Vgontzas AN et al (1991) Buspirone: sedative or stimulant effect? Am J Psychiatry 148:1213–1217
Manns ID, Lee MG, Modirrousta M et al (2003) Alpha 2 adrenergic receptors on GABAergic, putative sleep-promoting basal forebrain neurons. Eur J Neurosci 18:723–727
Martinez-Cué C, Delatour B, Potier M-C (2014) Treating enhanced GABAergic inhibition in Down syndrome: use of GABA α5-selective inverse agonists. Neurosci Biobehav Rev. doi:10.1016/j.neurobiorev.2013.12.008
Massotti M, Lucantoni D, Caporali MG et al (1985) Supraspinal convulsions induced by inverse benzodiazepine agonists in rabbits. J Pharmacol Exp Ther 234:274–279
Matthias S, Wetter TC, Steiger A et al (2001) The GABA uptake inhibitor tiagabine promotes slow wave sleep in normal elderly subjects. Neurobiol Aging 22:247–253
Max MB, Schafer SC, Culnane M et al (1988) Association of pain relief with drug side effects in postherpetic neuralgia: a single-dose study of clonidine, codeine, ibuprofen, and placebo. Clin Pharmacol Ther 43:363–371
McCarley RW (2007) Neurobiology of REM and NREM sleep. Sleep Med 8:302–330
McCormick DA (1992) Neurotransmitter actions in the thalamus and cerebral cortex and their role in neuromodulation of thalamocortical activity. Prog Neurobiol 39:37–388
McCormick DA, Bal T (1997) Sleep and arousal: thalamocortical mechanisms. Annu Rev Neurosci 20:185–215
McGregor R, Siegel JM (2010) Illuminating the locus coeruleus: control of posture and arousal. Nat Neurosci 13:1448–1449
Meuret P, Backman SB, Bonhomme V et al (2000) Physostigmine reverses propofol-induced unconsciousness and attenuation of the auditory steady state response and bispectral index in human volunteers. Anesthesiology 93:708–717
Mieda M, Willie JT, Hara J et al (2004) Orexin peptides prevent cataplexy and improve wakefulness in an orexin neuron-ablated model of narcolepsy in mice. Proc Natl Acad Sci USA 101:4649–4654
Minzenberg MJ, Watrous AJ, Yoon JH et al (2008) Modafinil shifts human locus coeruleus to low-tonic, high-phasic activity during functional MRI. Science 322:1700–1702
Mistlberger RE (2005) Circadian regulation of sleep in mammals: role of the suprachiasmatic nucleus. Brain Res Rev 49:429–454
Monti JM (2010) The structure of the dorsal raphe nucleus and its relevance to the regulation of sleep and wakefulness. Sleep Med Rev 14:307–317
Monti JM (2011) Serotonin control of sleep-wake behavior. Sleep Med Rev 15:269–281
Monti JM, Monti D (2007) The involvement of dopamine in the modulation of sleep and waking. Sleep Med Rev 11:113–133
Monti JM, Torterolo P, Lagos P (2013) Melanin-concentrating hormone control of sleep-wake behaviour. Sleep Med Rev 17:293–298
Moos DD (2007) Central anticholinergic syndrome: a case report. J Perianesth Nurs 22:309–321
Morairty S, Rainnie D, McCarley R et al (2004) Disinhibition of ventrolateral preoptic area sleep-active neurons by adenosine: a new mechanism for sleep promotion. Neuroscience 123:451–457
Müller U, Rowe JB, Rittman T et al (2013) Effects of modafinil on non-verbal cognition, task enjoyment and creative thinking in healthy volunteers. Neuropharmacology 64:490–495
Murck H, Antonijevic IA, Frieboes RM et al (1999) Galanin has REM-sleep deprivation-like effects on the sleep EEG in healthy young men. J Psychiatr Res 33:225–232

Murphy PR, O'Connell RG, O'Sullivan M et al (2014) Pupil diameter covaries with BOLD activity in human locus coeruleus. Hum Brain Mapp. doi:10.1002/hbm.22466
Myers CS, Taylor RC, Salmeron BJ et al (2013) Nicotine enhances alerting, but not executive, attention in smokers and nonsmokers. Nicotine Tob Res 15:277–281
Nelson LE, Guo TZ, Lu J et al (2002) The sedative component of anesthesia is mediated by $GABA_A$ receptors in an endogenous sleep pathway. Nat Neurosci 5:979–984
Nelson LE, Lu J, Guo TZ et al (2003) The α2-adrenoceptor agonist dexmedetomidine converges on an endogenous sleep-promoting pathway to exert its sedative effects. Anesthesiology 98:428–436
Niepel G, Bibani RH, Vilisaar J et al (2013) Association of a deficit of arousal with fatigue in multiple sclerosis: effect of modafinil. Neuropharmacology 64:380–388
Niewenhuys R (1985) Chemoarchitecture of the brain. Springer, Berlin
Nishino S, Mao J, Sampathkumaran R et al (1998) Increased dopaminergic transmission mediates the wake-promoting effects of CNS stimulants. Sleep Res Online 1:49–61
Niswender CM, Conn PJ (2010) Metabotropic glutamate receptors: physiology, pharmacology, and disease. Annu Rev Pharmacol Toxicol 50:295–322
Nutt DJ, Stahl SM (2010) Searching for perfect sleep: evolution of $GABA_A$ receptor modulators as hypnotics. J Psychopharmacol 24:1601–1612
Ögren SO, Kuteeva E, Hökfelt T et al (2006) Galanin receptor antagonists: a potential novel pharmacological treatment for mood disorders. CNS Drugs 20:633–654
Ohno K, Sakurai T (2008) Orexin neuronal circuitry: role in the regulation of sleep and wakefulness. Front Neuroendocrin 29:70–87
Pandi-Perumal SR, Srinivasan V, Mastroni GJM et al (2006) Melatonin: nature's most versatile signal? FEBS J 273:2813–2838
Paqueron X, Lumbroso A, Mergoni P et al (2002) Is morphine-induced sedation synonymous with analgesia during intravenous morphine titration? Br J Anaesth 89:697–701
Parissis D, Mellidis C, Boutis A et al (2003) Neurological findings in a case of coma secondary to *Datura stramonium* poisoning. Eur J Neurol 10:745–746
Parmentier AC, Guhennec C et al (2007) The brain $H_3$ receptor as a novel therapeutic target for vigilance and sleep-wake disorders. Biochem Pharmacol 73:1157–1171
Patat A, Rosenzweig P, Miget N et al (1999) Effects of 50 mg amisulpride on EEG, psychomotor and cognitive functions in healthy sleep-deprived subjects. Fundam Clin Pharmacol 13:582–594
Peever J (2011) Control of motoneuron function and masseter muscle tone during REM sleep, REM sleep behaviour disorder and cataplexy/narcolepsy. Arch Ital Biol 149:454–466
Peigneux P, Laureys S, Fuchs S et al (2001) Generation of rapid eye movements during paradoxical sleep in humans. NeuroImage 14:701–708
Pertovaara A, Haapaalinna A, Sirviö J et al (2005) Pharmacological properties, central nervous system effects, and potential therapeutic application of atipamezole, a selective alpha2-adrenoceptor antagonist. CNS Drug Rev 11:273–288
Petit-Pedrol M, Armangue T, Peng X et al (2014) Encephalitis with refractory seizures, status epilepticus, and antibodies to the $GABA_A$ receptor: a case series, characterisation of the antigen, and analysis of the effects of antibodies. Lancet Neurol 13:276–286
Phillips MA, Szabadi E, Bradshaw CM (2000) Comparison of the effects of clonidine and yohimbine on spontaneous pupillary fluctuations in healthy human volunteers. Psychopharmacology 150:85–89
Pinard A, Seddick R, Bettler B (2010) $GABA_B$ receptors: physiological functions and mechanisms of diversity. Adv Pharmacol 58:231–255
Porkka-Heiskanen T (2013) Sleep homeostasis. Curr Opin Neurobiol 23:799–805
Poulsen CF, Simeone TA, Mar TE et al (2004) Modulation by topiramate of AMPA and kainite mediated calcium influx in cultured cerebral cortical, hippocampal and cerebellar neurons. Neurochem Res 29:275–282

Proctor A, Bianchi MT (2012) Clinical pharmacology in sleep medicine. ISRN Pharmacol (Article ID 914168). doi:10.5402/2012/914168

Qiu M-H, Liu W, Qu W-M (2012) The role of nucleus accumbens core/shell in sleep-wake regulation and their involvement in modafinil-induced arousal. PLoS One 7:e45471

Rajarao SJ, Platt B, Sukoff SJ et al (2007) Anxiolytic-like activity of the non-selective galanin receptor agonist, galnon. Neuropeptides 41:307–320

Ramamoorthy S, Bauman AL, Moore KR et al (1993) Antidepressant- and cocaine-sensitive human serotonin transporter: molecular cloning, expression, and chromosomal localization. Proc Natl Acad Sci USA 90:2542–2546

Rao U, Lin KM, Schramm P et al (2004) REM sleep and cortisol responses to scopolamine during depression and remission in women. Int J Neuropsychopharmacol 7:265–274

Reynolds GP (2012) Histamine and antipsychotic drug-induced weight gain. J Psychopharmacol 26:1608–1609

Riddle EL, Fleckenstein AE, Hanson GR (2005) Role of monoamine transporters in mediating psychostimulant effects. AAPS J 7:E847–851

Roth T, Lines C, Vandormael K et al (2010) Effect of gaboxadol on patient-reported measures of sleep and waking function in patients with primary insomnia: results from two randomized, controlled, 3-month studies. J Clin Sleep Med 6:30–39

Rudolph U (2004) GABAergic system. In: Offermanns S, Rosehthal W (eds) Encyclopedic reference of molecular pharmacology. Springer, Berlin, pp 373–378

Rudolph U, Knoflach F (2011) Beyond classical benzodiazepines: novel therapeutic potential of $GABA_A$ receptor subtypes. Nat Rev Drug Discov 10:685–697

Rye D (2014) Paralysis lost: a new cause for a common parasomnia? Lancet Neurol 13:531–532

Sakai T (2013) Orexin deficiency and narcolepsy. Curr Opin Neurobiol 23:760–766

Samuels ER, Szabadi E (2008a) Functional neuroanatomy of the noradrenergic locus coeruleus: its roles in the regulation of arousal and autonomic function. Part I: principles of functional organisation. Curr Neuropharmacol 6:235–253

Samuels ER, Szabadi E (2008b) Functional neuroanatomy of the noradrenergic locus coeruleus: its roles in the regulation of arousal and autonomic function. Part II: physiological and pharmacological manipulations and pathological alterations of locus coeruleus activity in humans. Curr Neuropharmacol 6:254–285

Samuels ER, Hou RH, Langley RW et al (2006) Comparison of pramipexole and modafinil on arousal, autonomic and endocrine functions in healthy volunteers. J Psychopharmacol 20:756–770

Sánchez-López A, Escudero M (2011) Tonic and phasic components of eye movements during REM sleep in the rat. Eur J Neurosci 33:2129–2138

Santana N, Mengod G, Artigas F (2013) Expression of $\alpha_1$-adrenergic receptors in rat prefrontal cortex: cellular co-localization with $5\text{-}HT_{2A}$ receptors. Int J Neuropsychopharmacol 16:1139–1151

Santucci V, Glatt A, Demieville H et al (1981) Quantification of slow wave EEG induced by atropine: effects of physostigmine, amphetamine and haloperidol. Eur J Pharmacol 73:113–122

Saper CB, Fuller PM, Pedersen NP et al (2010) Sleep state switching. Neuron 68:1023–1042

Scammell TE, Gershchenko DY, Mochizuki T et al (2001) An adenosine A2a agonist increases sleep and induces Fos in ventrolateral preoptic neurons. Neuroscience 107:653–663

Scheife R, Takeda M (2005) Central nervous system safety of anticholinergic drugs for the treatment of overactive bladder in the elderly. Clin Ther 27:144–153

Scheinin M, Kallio A, Koulu M (1987) Sedative and cardiovascular effects of medetomidine, a novel selective alpha 2-adrenoceptor agonist, in healthy volunteers. Br J Clin Pharmacol 24:443–451

Schredl M, Hornung O, Regen F (2006) The effect of donepezil on sleep in elderly, healthy persons: a double-blind placebo-controlled study. Pharmacopsychiatry 39:205–208

Schwartz J-C (2011) The histamine H3 receptor: from discovery to clinical trials with pitolisant. Br J Pharmacol 163:713–721
Schwarz RD, Callahan MJ, Coughenour LL (1999) Milameline (Cl-979/RU35926): a muscarinic receptor agonist with cognition-activating properties: biochemical and in vivo characterization. J Pharmacol Exp Ther 291:812–822
Seutin V, Franchimont N, Massotte L et al (1990) Comparison of the effect of morphine on locus coeruleus noradrenergic and ventral tegmental area dopaminergic neurons *in vitro*. Life Sci 46:1879–1885
Shore PA (1962) Release of serotonin and catecholamines by drugs. Pharmacol Rev 14:531–550
Sigel E, Steinmann ME (2012) Structure, function, and modulation of $GABA_A$ receptors. J Biol Chem 287:40224–40231
Sitaram N, Moore AM, Gillin JC (1978) The effect of physostigmine on normal human sleep and dreaming. Arch Gen Psychiatry 35:1239–1243
Stäubli U, Scafidi J, Chun D (1999) $GABA_B$ receptor antagonism: facilitatory effects on memory parallel those on LTP induced by TBS but not HFS. J Neurosci 19:4609–4615
Steiger A (2007) Neurochemical regulation of sleep. J Psychiatr Res 41:537–552
Sterpenich V, D'Argembeau A, Desseilles M et al (2006) The locus ceruleus is involved in the successful retrieval of emotional memories in humans. J Neurosci 26:7416–7423
Sulser F, Bass AD (1968) Pharmacodynamic and biochemical considerations on the mode of action of reserpine-like drugs. In: Efron DH, Cole JO, Levine J et al (eds) Psychopharmacology: a review of progress 1957–1967. Public Health Service Publication No 1836. Washington, DC, pp 1093–1100
Szabadi E (2012) Modulation of physiological reflexes by pain: role of the locus coeruleus. Front Integr Neurosci 6:1–15 (Article 94)
Szabadi E (2013) Functional neuroanatomy of the central noradrenergic system. J Psychopharmacol 27:659–693
Szabadi E (2014) Selective targets for arousal-modifying drugs: implications for the treatment of sleep disorders. Drug Discov Today 19:701–708
Szabadi E, Bradshaw CM (2000) Mechanisms of action of reboxetine. Rev Contemp Pharmacother 11:267–282
Taberan IV (2013) Functional pharmacology of histamine $H_1$ receptors expressed in mouse preoptic/anterior hypothalamic neurons. Br J Pharmacol 170:415–425
Tafti M (2007) Reply to 'Promotion of sleep by targeting the orexin system in rats, dogs and humans'. Nat Med 13:525–526
Thakkar MM (2011) Histamine in the regulation of wakefulness. Sleep Med Rev 15:65–74
Torterolo P, Morales FR, Chase MH (2002) GABAergic mechanisms in the pedunculopontine tegmental nucleus of the cat promote active (REM) sleep. Brain Res 944:1–9
Triarhou LC (2006) The percipient observations of Constantin von Economo on encephalitis lethargica and sleep disruption and their lasting impact on contemporary sleep research. Brain Res Bull 69:244–258
Tsunematsu T, Ueno T, Tabuchi S et al (2014) Optogenetic manipulation of activity and temporally controlled cell-specific ablation reveal a role for MCH neurons in sleep/wake regulation. J Neurosci 34:6896–6909
Van den Heuvel CJ, Reid KJ, Dawson D (1997) Effect of atenolol on nocturnal sleep and temperature in young men: reversal by pharmacological doses of melatonin. Physiol Behav 61:795–802
Vandewalle G, Schmidt C, Albouy G et al (2007) Brain responses to violet, blue and green monochromatic light exposures in humans: prominent role of blue light and the brainstem. PLoS One 2(11):e1247
Vanover KE, Davis RE (2010) Role of $5\text{-}HT_{2A}$ receptor antagonists in the treatment of insomnia. Nat Sci Sleep 2:139–150
Venault P, Chapouthier G (2007) From behavioural pharmacology of beta-carbolines to seizures, anxiety, and memory. ScientificWorldJournal 7:204–223

Verster JC, Veldhuijzen DS, Volkerts ER (2006) Effects of an opioid (oxycodone/paracetamol) and an NSAID (bromfenac) on driving ability, memory functioning, psychomotor performance, pupil size, and mood. Clin J Pain 22:499–504

Votava Z, Benesová O, Bohdanecký Z et al (1968) Influence of atropine, scopolamine and benactyzine on the physostigmine arousal reaction in rabbits. Prog Brain Res 28:40–47

Webling KE, Runesson J, Bartfai T et al (2012) Galanin receptors and ligands. Front Endocrinol (Lausanne) 3:146

Weinhold SL, Seeck-Hirschner NA et al (2014) The effect of intranasal orexin-A (hypocretin-1) on sleep, wakefulness and attention in narcolepsy with cataplexy. Behav Brain Res 262:8–13

Wilhelm B, Giedke H, Lödtke H et al (2001) Daytime variations in central nervous system activation measured by a pupillographic sleepiness test. J Sleep Res 10:1–7

Wilson SJ, Nutt DJ, Alford C et al (2010) British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders. J Pschopharmacol 24:1577–1600

Winokur A, Gary KA, Rodner S et al (2001) Depression, sleep physiology, and antidepressant drugs. Depress Anxiety 14:19–28

Winsky-Sommerer R (2009) Role of $GABA_A$ receptors in the physiology and pharmacology of sleep. Eur J Neurosci 29:1779–1794

Wisor J (2013) Modafinil as a catecholaminergic agent: empirical evidence and unanswered questions. Front Neurol 4:139 (eCollection 2013)

Wu MF, Gulyani SA, Yau E et al (1999) Locus coeruleus neurons: cessation of activity during cataplexy. Neuroscience 91:1389–1399

Zant JC, Rozov S, Wigren HK et al (2012) Histamine release in the basal forebrain mediates cortical activation through cholinergic neurons. J Neurosci 32:13244–13254

Zecharia AY, Yu X, Götz T et al (2012) GABAergic inhibition of histaminergic neurons regulates active waking but not the sleep-wake switch or propofol-induced loss of consciousness. J Neurosci 32:13062–13075

Zhang J-P, Qi X, Yuan X-S et al (2013) Projections of nucleus accumbens adenosine $A_{2A}$ receptor neurons in the mouse brain and their implications in medicating sleep-wake regulations. Front Neuroanat 7:1–15 (Article 43)

Zheng G, Dwoskin LP, Crooks PA (2006) Vesicular monoamine transporter 2: role as a novel target for drug development. AAPS J 8:E682–E692

Zhu J, Reith MEA (2008) Role of dopamine transporter in the action of psychostimulants, nicotine, and other drugs of abuse. CNS Neurol Disord Drug Targets 7:393–409

http://www.springer.com/978-3-319-11513-9

Drug Treatment of Sleep Disorders

Guglietta, A. (Ed.)

2015, VIII, 297 p. 23 illus., 14 illus. in color., Hardcover
ISBN: 978-3-319-11513-9