Drugs for sleep disorders: mechanisms and therapeutic prospects

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Keywords:

Sleep disorders, neural mechanisms,
drug therapy, sleep-promoting
system, wakefulness-promoting
systems

The past decade has witnessed an explosion of knowledge about the neural mechanisms that control sleep and arousal, triggered by two discoveries relating to the sleep disorder narcolepsy. Narcolepsy is caused by the loss of orexin-containing neurons in the hypothalamus, and a novel nonstimulant wakefulness-promoting drug, modafinil, alleviates excessive day-time sleepiness associated with the disorder. The level of arousal is controlled by an intricate interplay between distinct wakefulness- and sleep-promoting nuclei situated in the hypothalamus and brainstem and the interconnections between the nuclei and the neurotransmitters involved have been mapped. Wakefulness-promoting nuclei include the orexinergic lateral hypothalamic/perifornical area, the histaminergic tuberomammillary nucleus, the cholinergic pedunculo-pontine tegmental nucleus, the noradrenergic locus coeruleus, the 5-hydroxytryptaminergic raphe nuclei and possibly the dopaminergic ventral tegmental area. The major sleep-promoting nucleus is the GABAergic ventrolateral preoptic nucleus of the hypothalamus. Currently available and future drugs exert their therapeutic effects in the three major classes of sleep disorder (insomnia, hypersomnia, parasomnia) by modifying neurotransmission at distinct sites within the arousal-controlling neuronal network. This enables classification of therapeutic drugs for sleep disorders on the basis of their modes of action: drugs that interact with the GABAergic sleep-promoting system, drugs that interact with different wakefulness-promoting systems and drugs that modulate the level of arousal by mechanisms that do not initially involve the basic network (e.g. melatonin, adenosine). The development of novel therapeutic drugs for sleep disorders is based on the synthesis of molecular/cellular mechanisms and the sites of action within the arousal-controlling neuronal network.

According to a simple classification, sleep disorders can be divided into insomnia, hypersomnia (excessive day-time sleepiness, EDS), and parasomnia (behavioural disturbance related to sleep). These disorders can occur in isolation (primary sleep disorders) or in association with mental or physical illnesses (secondary sleep disorders) [1]. Sleep disorders are common and can lead to significant disability and social and financial costs (for example, road traffic accidents, poor work performance) [2].

Narcolepsy and the orexins

The past decade has witnessed an explosion of knowledge of the neural mechanisms that control sleep and

arousal. This remarkable development was triggered by two unrelated discoveries, both concerning the rare, but severe, sleep disorder narcolepsy. The cardinal features of narcolepsy are excessive daytime sleepiness (EDS), cataplexy (episodes of sudden loss of muscle tone, usually triggered by emotions), a disrupted night-time sleep pattern, hypnagogic hallucinations and sleep paralysis [1, 2]. The cause of this disorder was unknown until the discovery of the orexins (or hypocretins), hitherto unknown neuropeptide transmitters, which are synthesized in a distinct neuronal group in the lateral hypothalamus. The brains of narcoleptic dogs, and also of patients suffering from narcolepsy, are deficient in orex-

ins [3, 4]. A large research effort about orexins ensued, establishing the connections of orexinergic neurons with other hypothalamic and brainstem nuclei involved in the regulation of sleep and wakefulness, appetite and feeding, autonomic and neuroendocrine regulation. It was also established that there are two variants of orexin: orexin A (hypocretin 1) and orexin B (hypocretin 2), which have excitatory effects at orexin A and orexin B receptors [3, 4].

Narcolepsy and modafinil

Another important development was the discovery of the wakefulness-promoting drug modafinil, which is now the first-line treatment for narcolepsy [5]. Before the advent of modafinil, narcolepsy was treated with psychostimulants, such as amphetamines and methylphenidate, which, although effective in alleviating excessive daytime sleepiness in narcolepsy, have adverse effects, such as psychomotor agitation, disruption of night-time sleep, inappropriate mood shifts and the potential for addiction [2]. Modafinil is not a psychostimulant and it does not cause psychomotor agitation, mood shifts or any sleep disruption [6]. Apart from alleviating excessive daytime sleepiness associated with narcolepsy, modafinil is effective in the treatment of excessive daytime sleepiness associated with a wide range of neurological disorders (multiple sclerosis, myotonic dystrophy, Parkinson's disease), psychiatric disorders (depression, schizophrenia) and other disorders (obstructive sleep apnoea, night-shift sleep disorder, drug-induced sedation) (for references see [7]). Modafinil has also been reported to be effective in treating pathological fatigue associated with multiple sclerosis [8], suggesting an overlap between sleepiness and fatigue. However, this finding is controversial [9]. The discovery of the clinical usefulness of modafinil was followed by a considerable research effort in an attempt to unravel its mode of action [10].

Wakefulness- and sleep-promoting neuronal systems

The level of arousal and alternation between states of wakefulness, nonrapid eye movement (NREM) sleep and rapid eye movement (REM) sleep is controlled by an intricate interplay between a number of wakefulness- and sleep-promoting hypothalamic and brainstem nuclei. These nuclei have been defined both anatomically and neurochemically (i.e. in terms of the neurotransmitter involved) [3, 4, 11–13] (Figure 1). The major wakefulness-promoting nuclei, apart from the orexin-containing neurons of the lateral hypothalamic/perifornical (LH/PF) area, include the histaminergic

tuberomammillary nucleus (TMN) of the posterior hypothalamus and a number of brainstem nuclei, such as the cholinergic pedunculopontine tegmental nucleus (PPT), the noradrenergic locus coeruleus (LC) and the 5-hydroxytryptaminergic raphe nuclei. The major sleep-promoting nucleus is the ventrolateral preoptic nucleus (VLPO) of the anterior hypothalamus, which uses γ -aminobutyric acid (GABA) and galanin as neurotransmitters.

Drugs that are used for the treatment of sleep disorders include sedative/hypnotic drugs to treat insomnia, alerting drugs to treat excessive daytime sleepiness and drugs that can alleviate the behavioural disturbance of parasomnia. Sedative drugs will increase the effectiveness of sleep-promoting systems and/or reduce the activity of wakefulness-promoting systems, whereas alerting drugs will act in a reciprocal fashion. However, drugs often affect more than one system, the observed effect reflecting the altered relation between different sleep- and wakefulness-promoting pathways.

Drugs that interact with the sleep-promoting system

Many sedative drugs act by enhancing the effectiveness of sleep-promoting GABAergic pathways. At the cellular/molecular level this is due to potentiation of the action of GABA at the ionotropic GABA_A receptor that regulates chloride channels. The GABA_A receptor is made up of several subunits and sedation is mediated by receptors that contain the α_1 subunit [14, 15]. These receptor subtypes can be found in the cerebral cortex, thalamus [15] and hypothalamus [16], target areas of sleep-promoting pathways. The GABA_A receptor is modulated by several sedative drugs, such as the benzodiazepines, barbiturates, neurosteroids, ethanol and general anaesthetics (e.g. isoflurane, propofol) [14]. GABAergic anaesthetics, including the barbiturates, selectively activate GABA_A receptors in the tuberomammillary nucleus, the target area of the GABAergic projection from the ventrolateral preoptic nucleus [17] (Figure 1). This observation shows that drugs traditionally regarded as 'nonselective central nervous system depressants' [18] have considerable neuroanatomical selectivity. It is likely that the sedative effects of other GABA_A receptor modulators, such as the benzodiazepines, are also mediated by the VLPO–TMN pathway. Nonbenzodiazepine compounds that interact with the benzodiazepine site on GABA_A receptors that contain the α_1 ('sedative') subunit have been developed. The so-called 'z' drugs (zolpidem, zopiclone, zaleplon) are available on prescription and new compounds with a similar action (e.g. indiplon, NG2-73) are in development [19, 20]. The novel hypnotic gaboxodol is an extra-

Figure 1

Schematic diagram of the connections within the arousal-controlling neuronal network. Wakefulness-promoting nuclei (yellow): TMN, tuberomammillary nucleus; LH/PF, lateral hypothalamic/perifornical area; LC, locus coeruleus; VTA, ventral tegmental area; PPT, pedunculopontine tegmental nucleus; R, raphe nucleus. Sleep-promoting nucleus (purple): VLPO, ventrolateral preoptic nucleus; (white): GABAergic interneurons. Neurotransmitters: ACh, acetylcholine; NA, noradrenaline; H, histamine; Ox, orexine; GABA, γ -aminobutyric acid; DA, dopamine; 5HT, 5-hydroxytryptamine. Receptors: α_1 , excitatory α_1 -adrenoceptors; α_2 , inhibitory α_2 -adrenoceptors; H_1 , excitatory H_1 histamine receptors; $5HT_{2A}$ and $5HT_{2C}$, excitatory 5HT receptors. Neuronal outputs: excitatory (red arrows) and inhibitory (blue arrows). The wakefulness-promoting nuclei exert a direct activating effect on the cerebral cortex; the VLPO promotes sleep by inhibiting the TMN. The LC promotes wakefulness by stimulating the cerebral cortex and the wakefulness-promoting neurons of the PPT, and by inhibiting the VLPO. The LC also inhibits the REM-sleep-promoting neurons of the PPT. The raphe nucleus promotes wakefulness by activating the cerebral cortex; this effect is attenuated by the stimulation of GABAergic interneurons, which inhibit the LC and the VTA. The VTA exerts its wakefulness-promoting effect largely via the activation of the LC, and the LH/PF largely via the activation of the TMN and the LC. Modified from [7] and [33].

synaptic nonbenzodiazepine GABA_A receptor agonist with a preferential action in the thalamus [21, 22]. Gammahydroxybutyrate (GHB, oxybate) is an old sedative drug with a considerable abuse potential [23]. It is licensed in the USA for the treatment of narcolepsy, especially cataplexy associated with narcolepsy [24, 25], and it is available from one designated pharmacy on a named-patient basis. GHB has recently received marketing authorization in the European Union, with the same indication as in the USA, and is available for specialist prescribing as a controlled substance. GABA_B receptors have been implicated in its sedative action [26], but the way in which it alleviates cataplexy remains to be elucidated.

Drugs that interact with wakefulness-promoting systems

Histaminergic system

The wakefulness-promoting histaminergic system [3, 4, 11–13] originates in the tuberomammillary nucleus, which sends a diffuse projection to the cerebral cortex,

where it interacts with excitatory H_1 histamine receptors [27]. First-generation antihistamines, which block these receptors in the brain, are highly sedative and some of them are used as hypnotics [28]. The release of histamine is modulated by inhibitory H_3 autoreceptors located on histaminergic nerve terminals; H_3 receptor agonists have sedative effects and antagonists alerting effects. It has been proposed that selective H_3 histamine receptor antagonists (e.g. ciproxifan, thioperamide) may be useful in the treatment of clinical conditions associated with excessive daytime sleepiness [29–31].

Noradrenergic system

The wakefulness-promoting effect of the locus coeruleus may be partly due to direct cortical activation via α_1 -adrenoceptors [32] and partly to the 'switching off' of the ventrolateral preoptic nucleus via activation of inhibitory α_2 -adrenoceptors [33] (Figure 1). Dexmedetomidine causes sedation by activating inhibitory α_2 -adrenoceptors (autoreceptors) on neurons in the locus coeruleus, leading to a cascade of events in the LC-

VLPO-TMN chain. Thus, reduction in locus coeruleus activity disinhibits the ventrolateral preoptic nucleus, which in turn leads to GABAergic inhibition of the tuberomammillary nucleus [33]. Other α_2 -adrenoceptor agonists, such as clonidine [7] and lofexidine, are also likely to exert their sedative effects in the same way. Modafinil, at least partly, may exert its wakefulness-promoting effect by activating the locus coeruleus [7], probably by potentiating tonic dopaminergic excitation (see below).

Dopaminergic system

Although it has been known for a long time that psychostimulants, such as amphetamines, methylphenidate and cocaine, increase the level of alertness by enhancing central dopaminergic neurotransmission, only more recent research has revealed the intricacies of the dopaminergic regulation of arousal. Dopaminergic neurons in the ventral tegmental area (VTA) of the midbrain have been implicated in the promotion of wakefulness. Both Parkinson's disease, which leads to the loss of some of these neurons, and, paradoxically, also antiparkinsonian D_2 dopamine receptor agonists cause excessive daytime sleepiness. This latter effect has been attributed to stimulation of inhibitory autoreceptors on VTA neurons, leading to a reduction in VTA activity [34]. The wakefulness-promoting effect of the VTA may be mediated, at least partly, by an excitatory connection to the locus coeruleus and modafinil may activate the locus coeruleus by blocking the uptake of dopamine, thereby potentiating its effect, at the 'meso-coerulear' synapse [10, 34, 35] (Figure 1). Furthermore, it has been proposed that the dopaminergic neurons may activate the orexinergic system [36]. Recently, reduced activity of dopaminergic neurons situated at the mesencephalic/hypothalamic border (area A11), which innervate the spinal cord via the diencephalospinal pathway, has been implicated in the pathogenesis of two parasomnic disorders, restless legs syndrome and periodic leg movements in sleep [34, 37]. Indeed, both syndromes respond favourably to treatment with dopaminergic drugs [34, 37].

5-hydroxytryptaminergic system

The 5-hydroxytryptaminergic (serotonergic) neurons that originate from the raphe nuclei of the brainstem also form a major arousal-enhancing system [38] (Figure 1). Both $5HT_{2A}$ and $5HT_{2C}$ receptors have been implicated in the regulation of arousal by serotonergic neurons. $5HT_{2A}$ receptor activation is likely to lead to enhancement of arousal, as shown by the sedative property of $5HT_{2A}$ receptor antagonists, such as ketanserin [39].

Several $5HT_{2A}$ receptor antagonists (eplivanserin, M-100907, pruvanserin) and an inverse agonist (APD125) are in development as potential hypnotic agents for the treatment of insomnia [19, 20]. On the other hand, activation of $5HT_{2C}$ receptors results in increased sedation: this is due to excitation of GABAergic interneurons in the brainstem which inhibit wakefulness-promoting neurons in the locus coeruleus and VTA [40]. Thus, $5HT_{2C}$ receptor antagonists, such as agomelatine, increase the activity of the locus coeruleus and VTA [40] and are expected to enhance the level of arousal.

Orexinergic system

Drugs that interact with orexin receptors may also offer therapeutic potential: agonists are expected to be alerting and antagonists to be sedative [13]. An orexin receptor antagonist (GW649868) is in pharmaceutical development [19].

Drugs that interact with other arousal-modulating mechanisms

Melatonin

Melatonin, the hormone of the pineal gland, is synthesized from 5-hydroxytryptamine under the influence of the suprachiasmatic nucleus (SCN) of the hypothalamus, the circadian 'clock' of the brain [41]. Melatonin interacts with two receptors (MT_1 and MT_2) at different sites in the brain and its action on the suprachiasmatic nucleus has been implicated in the initiation and maintenance of sleep. Melatonin has hypnotic properties and it has been used to alleviate 'jet lag' and milder forms of insomnia [41]. It is available commercially in the USA as a 'nutritional supplement' and can be obtained in other countries via the internet. Several synthetic melatonin receptor agonists (ramelteon, PD-6735, VEC-162) are in development for the treatment of insomnia [19]. Ramelteon has recently received a product licence in the USA. Although agomelatine is also a melatonin receptor agonist, its additional antagonistic effect at $5HT_{2C}$ receptors is likely to counteract the sedation that results from melatonin receptor activation.

Adenosine

Prolonged wakefulness results in an increase in the concentration of adenosine in the brain and this metabolic change has been implicated in the development of sleepiness and the 'pressure' to fall asleep. It has been proposed that adenosine may inhibit the activity of wakefulness-promoting neurons, such as cholinergic neurons in the basal forebrain [42]. Furthermore, antagonism of adenosine receptors at these sites may underlie the wakefulness-promoting effects of caffeine and theo-

phylline. Therefore, drugs that interact with these receptors may offer therapeutic potential in sleep disorders, agonists acting as hypnotics and antagonists as alerting agents.

Conclusion

In conclusion, dissection of the molecular and cellular mechanisms that underlie the actions of the neurotransmitters involved in the sleep–wakefulness neuronal network, together with unravelling the connections within the network, has already resulted in a better understanding of arousal and sleep and their disorders. As a result of these new insights, several therapeutic drugs have been developed, or are in development. Furthermore, these drugs can be exploited as research tools to further our knowledge about sleep/arousal mechanisms.

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