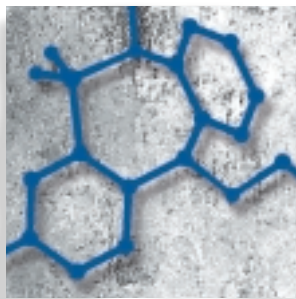


# Pharmacological aspects

## *Sleep disturbances, psychiatric disorders, and psychotropic drugs*

Luc Staner, MD



*Brain neurotransmitter dysfunctions involved in the pathophysiological processes of psychiatric disorders are likely to be reflected by concomitant alterations in sleep continuity and architecture. Since the corrective effects of psychotropic drugs on dysfunctional neurotransmission systems can be evidenced through polysomnographic recordings, one may consider sleep as a kind of “window” on the neurobiology of psychiatric disorders. During the last 10 years, major breakthroughs in our understanding of sleep-wake mechanisms have provided some indications on how psychotropic drugs could influence the sleep-wake cycle. In this review, recent inroads into the understanding of sleep regulatory neural mechanisms are introduced and discussed in terms of the effects of psychotropic drugs. The relationship between the pathophysiological process of a disease, its consequence on sleep, and the corrective effect of a psychotropic drug are exemplified by two psychopathological states: substance withdrawal and major depression. One may conclude that polysomnographic recordings are a unique noninvasive tool to analyze brain functioning, and are particularly well suited to evaluating the objective effects of new psychotropic drugs.*

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**A**s much as one third of the adult population reports difficulty sleeping<sup>1-3</sup> and the widespread use of prescribed hypnotic medication, as well as nonprescription remedies, is an indirect reflection of this high frequency of sleep complaints.<sup>2,4</sup> Sleep disturbance is considered as the second most common symptom of mental distress.<sup>5</sup> Individuals reporting disturbed sleep are more likely to report emotional distress and recurrent health problems.<sup>1</sup> In fact, disturbed sleep is a common finding in psychiatric illnesses. Some patients will even attribute their daytime psychiatric symptoms to abnormal sleep and believe that improved sleep will solve their problems. In some cases, the psychological symptoms associated with a primary sleep disorder could indeed improve with adequate therapy, for instance, the altered states of consciousness or depression encountered in some patients with sleep apnea could indeed improve with nasal continuous positive airway pressure treatment. In primary psychiatric disorders, the sleep complaint usually parallels the state of the disorder, and sleep improves when the psychiatric symptoms improve.

Another point is that alterations of sleep by psychiatric conditions are likely to have underlying brain neurotransmitter dysfunction directly involved in the pathophysiological process of the disease. Indeed, neurotransmission disturbances, such as those encountered in mental disorders, are reflected in spontaneous alteration of sleep continuity and architecture. The corrective effect

**Keywords:** *sleep disturbance; polysomnography; psychiatric disorder; sleep-wake mechanism; psychotropic drug; rapid eye movement sleep; non-rapid eye movement sleep; neurotransmitter*

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# Pharmacological aspects

## Selected abbreviations and acronyms

<b>DRN</b>	<i>dorsal raphe nucleus</i>
<b>GABA</b>	<i>γ-aminobutyric acid</i>
<b>LC</b>	<i>locus ceruleus</i>
<b>LDT</b>	<i>laterodorsal tegmental (nucleus)</i>
<b>NP</b>	<i>nicotine patch</i>
<b>NREM</b>	<i>non-rapid eye movement</i>
<b>PPT</b>	<i>pediculopontine tegmental (nucleus)</i>
<b>REM</b>	<i>rapid eye movement</i>
<b>SCN</b>	<i>suprachiasmatic nucleus</i>
<b>SWS</b>	<i>slow-wave sleep</i>
<b>TMN</b>	<i>tuberomammillary nucleus</i>
<b>VLPO</b>	<i>ventrolateral preoptic nucleus</i>

on dysfunctional neurotransmission systems of psychotropic drugs, such as antidepressants, is also evidenced through polysomnographic recordings. Sleep can thus be considered as a kind of window on the neurobiology of psychiatric disorders. The first section of this review will introduce recent inroads into understanding sleep-regulatory neural mechanisms. The following sections deal with the way psychotropic drugs interact with mechanisms involved in sleep-wake regulation. Finally, the relationship between the pathophysiological process of a disease, its consequence on sleep, and the corrective effect of a psychotropic drug will be exemplified.

## Sleep basics

Electrophysiological recordings of human brain reveal three distinct state of existence: wakefulness, rapid eye movement (REM) sleep, and non-REM (NREM) sleep. The distinction between sleep and wakefulness is attributed to the synchronization and desynchronization of thalamocortical circuits.<sup>6,7</sup> Wake-like or “desynchronized” (low-amplitude and high-frequency) electroencephalographic (EEG) activity with clusters of REM and very low levels of muscle tone characterize REM sleep. NREM sleep includes all sleep except REM sleep, and is by convention divided into four stages corresponding to increased depth of sleep as indicated by the progressive dominance of “synchronized” EEG activity (also known as low-voltage high-amplitude delta or slow-wave activity); in this respect, sleep stages 3 and 4 are collectively labelled as delta sleep or slow-wave sleep (SWS). Recurrent cycles of NREM and REM sleep of about 90 min characterize normal human sleep. In the successive cycles of the night, the duration of stages 3 and 4

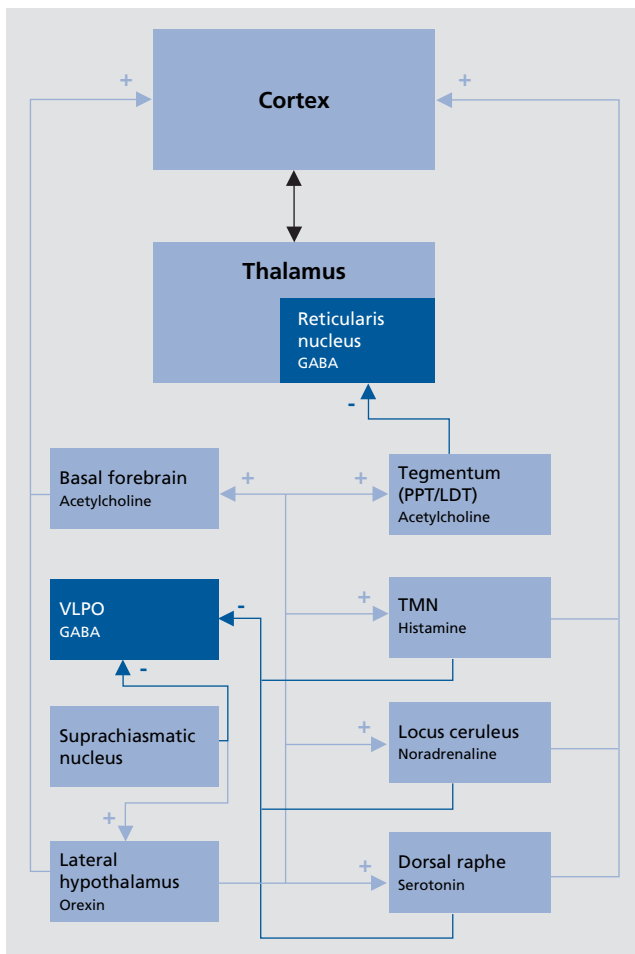
decrease, and the proportion of the cycle occupied by REM sleep tends to increase. The REM episodes occurring late in the night have more eye movement bursts than REM episodes occurring early in the night.<sup>8</sup> Sleep-wake alternation is classically viewed as resulting from the interaction of two regulating processes (circadian-C and homeostatic-S).<sup>9</sup> The propensity to sleep or be awake at any given time is a consequence of a sleep debt (process S) and its interaction with wake-promoting signals coming from the circadian clock (process C) located in the suprachiasmatic nucleus (SCN). This wake-promoting signal opposes the sleep need, which progressively increases from morning awakening, ensuring an even degree of alertness throughout the day.<sup>10</sup> At sleep onset, an imbalance between the two opposing influences favor sleep-promoting signals, and the sleep need and its electrophysiological signature, slow-wave activity, is at its highest level. Throughout sleep and up to final morning awakening, there is a progressive decline in slow-wave activity reflected by an increase in REM sleep proportion across successive REM/NREM cycles. During the last decade, research lent support to the idea that three interacting neuronal systems (a wake-promoting system, an NREM-promoting system, and a REM-promoting system) are involved in this complex regulation construct.

Different structures sending widespread cortical projection and located in the brain stem, the hypothalamus, and the basal forebrain constitute the wake-promoting or arousal system (*Figure 1*).<sup>11,12</sup> Glutamatergic brain stem reticular neurons, cholinergic neurons of the basal forebrain, and monoaminergic transmission are largely implicated in the arousal system.<sup>13</sup> It has been shown that serotonergic (dorsal raphe nuclei [DRN]), noreadrenergic (locus ceruleus [LC]) and histaminergic (tuberomammillary nucleus [TMN]) activity is high during wakefulness, decreases during NREM stages, and becomes almost silent during REM sleep.<sup>14</sup> The role of the dopaminergic system is less well established; however, recent studies indicated that lesions of wake-active dopaminergic cells in the ventral periaqueductal gray reduce waking<sup>15</sup> and that dopamine D<sub>1</sub>, D<sub>2</sub>, and D<sub>3</sub> receptor agonists increase waking and reduce REM and NREM sleep.<sup>16-18</sup> Orexin (also known as hypocretin) neurons located in the perifornical region of the lateral hypothalamus seem to play a particularly important role in arousal since they project not only over the entire isocortex, but also to additional arousal systems, including

the aforementioned monoaminergic and cholinergic systems.<sup>19,20</sup> The role of orexin in arousal regulation is further exemplified with narcolepsy, a sleep disorder characterized by excessive daytime sleepiness and deficiency of the orexin system.<sup>21-23</sup>

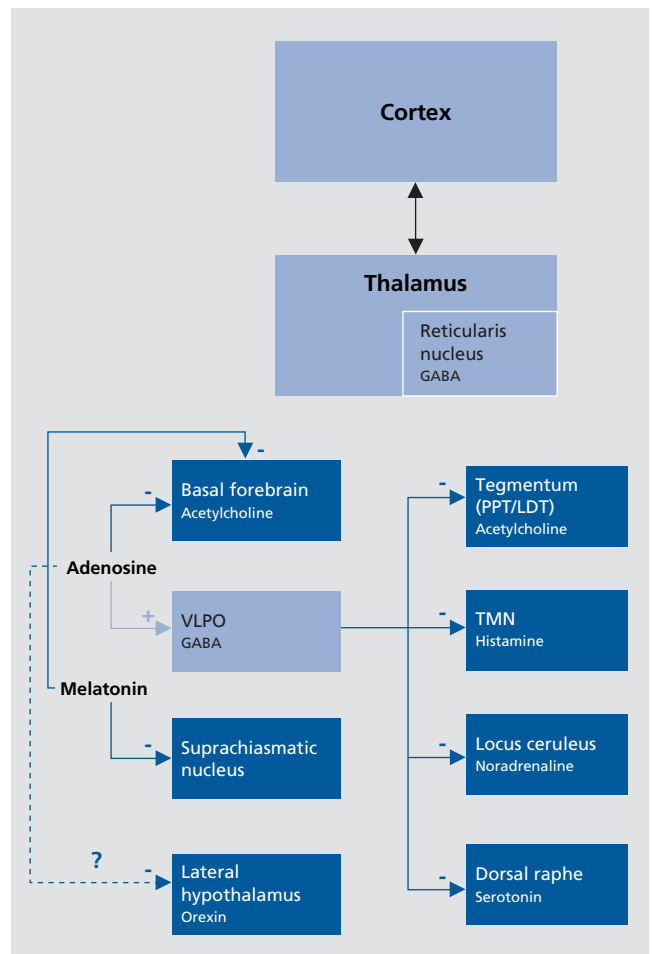
An NREM-promoting system has been evidenced in the hypothalamus (Figure 2). Electrophysiological recordings have identified GABAergic (GABA,  $\gamma$ -aminobutyric

acid) SWS-active neurons in a specific area, the ventrolateral preoptic nucleus (VLPO), where lesions produce insomnia in animals and humans.<sup>24</sup> These cells also contain galanin and project to all monoaminergic systems, inhibiting activity during NREM sleep, and receive inputs from multiple brain systems that regulate arousal and autonomic and circadian functions.<sup>25</sup> Recent research implicates adenosine in the homeostatic regulation of



**Figure 1.** Simplified representation of the various structures implicated in arousal mechanisms and their interrelationships. Light-blue boxes, activated structures; blue boxes, deactivated structures; light-blue arrows, excitatory influences; blue arrows, inhibitory influences. GABA,  $\gamma$ -aminobutyric acid; PPT/LDT pediclopontine tegmental/laterodorsal tegmental nuclei; TMN, tuberomammillary nucleus; VLPO, ventrolateral preoptic nucleus.

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**Figure 2.** Simplified representation of various structures implicated in non-rapid eye movement (NREM) mechanisms and their interrelationships. Light-blue boxes, activated structures; blue boxes, deactivated structures; light-blue arrows, excitatory influences; blue arrows, inhibitory influences. GABA,  $\gamma$ -aminobutyric acid; PPT/LDT pediclopontine tegmental/laterodorsal tegmental nuclei; TMN, tuberomammillary nucleus; VLPO, ventrolateral preoptic nucleus.

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# Pharmacological aspects

sleep via actions on the VLPO and other sleep regulatory regions such as the basal forebrain.<sup>26</sup> Adenosine functions as a natural sleep-promoting agent, accumulating during period of sustained wakefulness and decreasing during sleep; it has been shown to promote SWS through direct inhibitory effects on cholinergic neurons of the basal forebrain<sup>26</sup> and have indirect stimulatory effects on the VLPO.<sup>27,28</sup> A further inhibition of wake-promoting mechanism could occur through orexinergic neurons, since a study identified G<sub>i</sub> protein-coupled adenosine A<sub>1</sub> receptors on this group of neurons.<sup>29</sup>

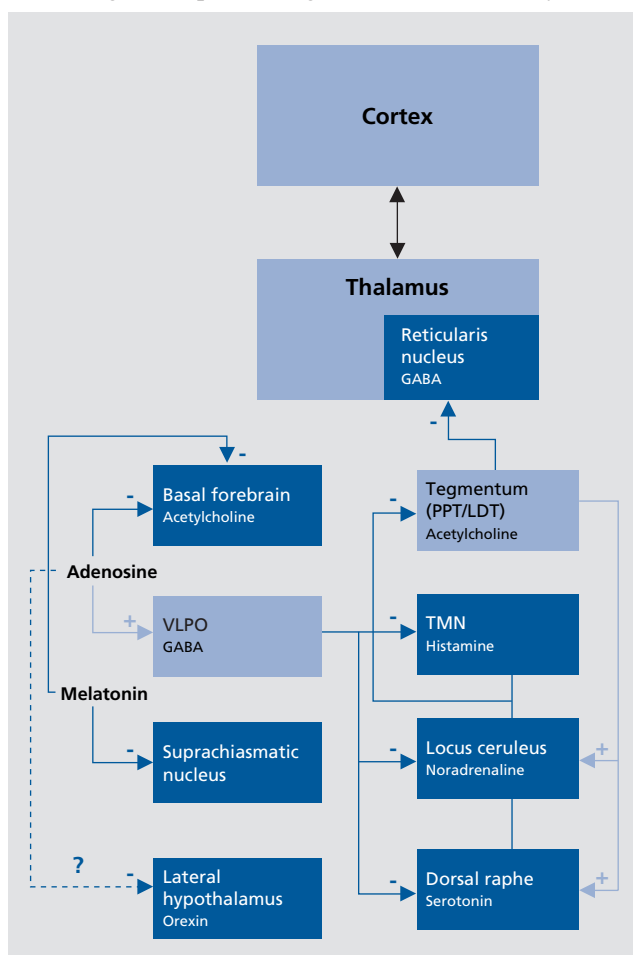
Regarding the circadian influence on the sleep-wake rhythm, recent studies suggested that the SCN regulates sleep-wake mechanisms through the dorsomedial hypothalamus, a key output nucleus of the SCN that inhibits VLPO and stimulates orexin-containing neurons in the lateral hypothalamus.<sup>30,31</sup> Melatonin, the hormone of the pineal gland secreted at night and concerned with biological timing, could mediate its sleep-inducing effect through inhibitory influence on SCN neurons<sup>32</sup> and cholinergic neurons of the basal forebrain.<sup>33</sup>

The REM-promoting system comprises “REM-on” cholinergic neurons located in the laterodorsal tegmental (LDT) and pediculopontine tegmental (PPT) nuclei (Figure 3). The McCarley and Hobson reciprocal interaction model, first proposed in 1975, and regularly revisited,<sup>14</sup> posits a bidirectional inhibitory influence between these REM-on neurons and both the serotonergic DRN and the noradrenergic LC, called “REM-off” neurons. Transition from NREM to REM occurs when activity in the aminergic REM-off neurons ceases. Cholinergic LDT/PPT REM-on neurons are then involved in the initiation of cortical desynchronization through excitatory inputs to the thalamus and in the occurrence of muscle atonia and REMs. During REM sleep, the excitatory input from the REM-on neurons to the DRN and LC leads to a gradual increase in the activity of the REM-off neurons, which in turn inhibit REM-on neurons until the REM episode ends. GABAergic and glutamatergic modulations of this aminergic-cholinergic interplay have been proposed in the revised version of the model.<sup>14</sup>

## The effects of drugs on wake- and sleep-inducing mechanisms

In the following sections, we will review the effects of psychotropic drugs on the three interacting neuronal systems that have been proposed to play a key role in

sleep-wake regulation (the wake-promoting system, the NREM-promoting system, and the REM-promoting system). The first four sections deal with drugs acting on wake- or NREM sleep-promoting neurons, while the following section concerns drugs acting on the REM-promoting system with special reference to antidepressant drugs. Whether drugs induce wakefulness (“waking drugs”) or sleep (“hypnotic drugs”) depend on their liability to stimulate or inhibit wake- or NREM sleep-promoting neurons. Before going further, it should be stressed that the net effects of a hypnotic drug inhibiting wake-promoting neurons will be very similar



**Figure 3.** Simplified representation of various structures implicated in rapid eye movement (REM) mechanisms and their interrelationships. Light-blue boxes, activated structures; blue boxes, deactivated structures; light-blue arrows, excitatory influences; blue arrows, inhibitory influences. GABA,  $\gamma$ -aminobutyric acid; PPT/LDT pediculopontine tegmental/laterodorsal tegmental nuclei; TMN, tuberomammillary nucleus; VLPO, ventrolateral preoptic nucleus.

to the effects of a drug stimulating NREM-promoting neurons. The converse is true for waking drugs: the effects of a drug inhibiting NREM-promoting neurons will parallel those induced by a drug stimulating wake-promoting neurons. Finally, it should be recognized that a distinction between drugs acting on wake- or NREM-promoting neurons is somewhat arbitrary, due to the close reciprocal negative feedback existing between these two groups of neurons.<sup>7</sup>

Some drugs directly influence both wake-promoting neurons and sleep-promoting neurons, but in an opposite way; this is the case for compounds influencing adenosine transmission such as caffeine. Caffeine is a psychoactive substance enhancing vigilance performance on psychomotor tasks and significantly affecting sleep at a dose of more than 100 to 150 mg.<sup>34,35</sup> It is now widely accepted that the vigilance mechanism of caffeine acts via the antagonism of adenosine receptors. The physiology of the adenosinergic transmission has been recently reviewed,<sup>36</sup> as well as its implication in sleep-wake mechanisms.<sup>26</sup> Adenosine, formed by breakdown of adenosine triphosphate (ATP), is present both intracellularly and extracellularly, and the balance is maintained by membrane transporters, but when energy expenditure exceeds energy production, adenosine levels increase in the extracellular space. In humans, adenosine exerts most of its effects through activation of two high-affinity receptors (the  $A_1$  coupled to "inhibitory"  $G_i$  proteins and the  $A_{2A}$  coupled to "stimulatory"  $G_s$  protein).  $A_1$  receptors are involved in the inhibitory effect of adenosine on the wake-active cholinergic neurons of the basal forebrain, while there are some indications that  $A_{2A}$  receptors could influence the dopaminergic control of wake-promoting mechanisms.<sup>37</sup> Adenosine may also disinhibit sleep-active VLPO neurons by removing GABAergic inhibitory inputs, possibly via  $A_1$  receptors.<sup>27,28</sup> The caffeine-induced increase in vigilance level results from the blockade of  $A_1$  and  $A_{2A}$  receptors. Accordingly, it is thought that caffeine exerts its effects through two complementary mechanisms: inhibition of wake-promoting cholinergic and dopaminergic influence and disinhibition of sleep-promoting neurons of the VLPO.

It thus emerges that there is a potential role of adenosine  $A_1$  and  $A_{2A}$  receptor antagonists as arousal stimulators and agonists as sleep promoters. Preclinical studies with such compounds have reported promising results,<sup>26</sup> but no clinical trials have been published to

date. Since direct adenosine agonists may have marked side effects such as hypotension and bradycardia,<sup>36</sup> the use of substances that indirectly modulate the level of endogenous adenosine, such as adenosine uptake inhibitor<sup>38</sup> or adenosine kinase inhibitor,<sup>39</sup> may be preferable to the use of direct adenosine agonists.

### Drugs enhancing the activity of wake-promoting neurons

Amphetamine-like drugs and modafinil are the two most popular wake-promoting medications used for the treatment of narcolepsy, a sleep disorder characterized by excessive daytime sleepiness. Amphetamine, methylphenidate, and cocaine are known to act pharmacologically by blocking the reuptake and enhancing the release of noradrenaline, dopamine, and serotonin within the synaptic cleft of monoamine synapses.<sup>40</sup> The exact mechanism by which amphetamine-like stimulants induce their wake-promoting effects remains to be elucidated, but there is growing evidence that the dopaminergic system is mostly implicated.<sup>41</sup> For instance, it has recently been demonstrated that dopamine transporter knockout mice were totally insensitive to the wake-promoting properties of classical stimulants suggesting that amphetamine-like compounds require the dopamine transporter for their wake-promoting effects.<sup>42</sup>

Despite numerous reports of its neuropharmacological action on the central nervous system (CNS), the wake-promoting mechanism of action of modafinil remains uncertain. Using c-Fos immunohistochemistry in cats, it has been shown that amphetamine-like drugs do not share with modafinil the same pattern of c-Fos activation in the brain. Amphetamine and methylphenidate activate neurons mainly in the cortex and the striatum, whereas modafinil-induced wakefulness was mainly associated with activated neurons in the hypothalamus.<sup>43,44</sup> Another study involving c-Fos labelling highlighted Fos activation mainly in the TMN and in orexin-containing neurons of the perifornical nucleus.<sup>45</sup> This suggests that modafinil induces wakefulness by mechanisms distinct from amphetamine-like drugs. It has been suggested that modafinil-induced arousal could be related to noradrenergic transmission, since modafinil affects the firing of the LC<sup>46</sup> and its arousal effects are blocked by  $\alpha_1$  and  $\beta$  adrenergic receptor antagonists.<sup>47</sup> One study shows that modafinil increases noradrenergic release in the hypothalamus, but also both dopaminergic and serotonergic transmission in the cortex, suggesting that the



# Pharmacological aspects

effects of modafinil are not entirely mediated through noradrenergic transmission.<sup>48</sup>

Besides amphetamine-like drugs and modafinil, the development of drugs acting through the histaminergic or orexinergic system is an area of active research in the field of new therapeutic approach for the treatment of major sleep-wake disorders, such as hypersomnia and narcolepsy.  $H_3$  receptors are an important target for arousal control and treatment of excessive daytime somnolence, since they are both autoreceptors controlling histamine-containing neuron activity and heteroreceptors, modulating the release of other neurotransmitters including acetylcholine, dopamine, and noradrenaline in brain regions that are crucial for the maintenance of wakefulness.<sup>49,50</sup> Administration of  $H_3$  receptor antagonists and inverse agonists induced a total suppression of slow-wave activity and spindles and a marked enhancement of fast rhythm, thus eliciting waking and increasing vigilance.<sup>51,52</sup> Moreover, recent studies have shown that  $H_3$  receptor blockade enhances cognition in rats.<sup>53</sup> These studies suggest that the potential benefit of  $H_3$  receptor antagonists and inverse agonists are not limited to promoting wakefulness because they could also improve general level of vigilance and cognitive responses in nonsomnolent individuals.<sup>50</sup> However, no clinical trials have yet been published showing that  $H_3$  receptor blockade promotes wakefulness in humans.

The pharmacology of the orexin system is, up to now, also limited to animal data. Orexins are a pair of neuropeptides, orexin-A and orexin-B, derived from a common precursor peptide, whose actions are mediated by two G protein-coupled receptors termed orexin receptor type 1 ( $OX_1R$ ) and orexin receptor type 2 ( $OX_2R$ ).<sup>54</sup> Both receptors are expressed in serotonergic neurons of the DRN, cholinergic neurons of the LDT/PPT, and the hypothalamus, while  $OX_1R$  is specific to the noradrenergic neurons of the LC and  $OX_2R$  to histaminergic neurons of the TMN.<sup>55,56</sup> Considering that canine narcolepsy results from a mutation of the  $OX_2R$  gene<sup>57</sup> and the phenotypic differences between  $OX_1R$  and  $OX_2R$  knockout mice, there are some indications that the lack of an orexin signal via  $OX_2R$  contributes to the pathogenesis of narcolepsy.<sup>58</sup> Since orexin is below detectable limits in the cerebrospinal fluid of human narcolepsy patients,<sup>21,22</sup> whose brains exhibit a nearly complete loss of neurons expressing orexin<sup>22,23</sup> an orexin agonist should be able to compensate for orexin deficiency, and therefore should be efficient in promoting wakefulness. However, no available clinical data so far support the effectiveness of this approach in treating sleep disorders.

## Sleep-inducing drugs that impair the activity of wake-promoting neurons

Many psychotropic drugs, known as sedatives, interfere with wake propensity mechanisms. Indeed, drugs inhibiting cholinergic, noradrenergic, dopaminergic, serotonergic, or histaminergic neurotransmission have shown various sedative effects. Potent sedative drugs used in psychiatry to treat psychomotor agitation, such as phenothiazine derivatives, often antagonize several of these systems. Antagonizing only one of these alerting systems, such as the histaminergic system with first-generation histamine  $H_1$  antagonists used for the treatment of allergies, procures merely mild-to-moderate sedation. However, as stated in the previous section, a renewed interest in histaminergic function, and more specifically in histamine  $H_3$  receptors, has grown during the last decade. Thus,  $H_3$  receptor agonists should lower histamine release in neuronal terminals as well as the release of other wake-promoting neurotransmitters, such as acetylcholine, dopamine, and nor-adrenaline. Preliminary results indicate that  $H_3$  agonists increase SWS in animals<sup>59,60</sup> and it can thus be expected that clinically suitable agonists will improve sleep in some types of insomnia.

In the same way, and according to the key involvement of the orexin system in the orchestration of arousal (see above), orexin antagonists could be potential sleep-inducing drugs. Moreover, some studies have suggested that the orexin neurotransmission may be associated with the high-arousal stress-like states<sup>61,62</sup> that typically characterize insomniac patients. Indeed, patients having complaints of insomnia show electrophysiological and psychomotor evidence of increased daytime arousal<sup>63-66</sup> as well as indications of other stress-related reactions such as increased hypothalamic-pituitary-adrenal axis (HPA) activity,<sup>67</sup> and increased sympathetic tone.<sup>68</sup> In a first attempt to record *in vivo* the activity of orexin neurons, Mileykovskiy et al<sup>69</sup> showed that, as expected, orexin neurons displayed very low discharge levels in both REM and NREM sleep, but that discharge rates were not significantly elevated during quiet waking, suggesting that orexin neurotransmission is not associated with waking *per se*. In contrast, high discharge rates were observed in active and/or alert waking. This further supports the potential clinical value of drugs antagonizing the orexin system in the treatment of stress-related sleep disorders, such as insomnia.

## Wake-promoting mechanisms and treatment of sleep disturbances in nicotine and alcohol withdrawal

Sleep disturbances following substance withdrawal, such as nicotine or alcohol, reflect complex hyperarousal states involving stress-related disturbances due to the craving phenomenon and peculiar substance-induced neurotransmission imbalance. For instance, polysomnographic recordings performed during the week following nicotine withdrawal in heavy cigarette smokers have shown increased sleep disruption.<sup>70,71</sup> It should, however, be stressed that even before withdrawal, current smokers subjectively complain of decreased sleep time and a fragmented sleep, mostly during the second part of the night.<sup>71-74</sup> These observations probably relate to the tobacco withdrawal state occurring each night in heavy smokers rather than to nicotine itself. Indeed, the cholinergic system is a major constituent of the wake-promoting system and it contributes to cortical arousal through its ascending components.<sup>13</sup> The involvement of nicotine acetylcholine receptors in these cholinergic effects is suggested by studies showing that nicotine injections increase waking,<sup>75</sup> and that mice lacking the  $\beta_2$  subunit gene of the nicotine acetylcholine receptor, a major component of high affinity nicotine-binding sites in the brain, exhibited a reduced fragmentation of NREM sleep through microarousals.<sup>76</sup> It is also worth noting that 24-h transdermal nicotine delivery system (nicotine patch [NP]), when administered in nonsmoking healthy volunteers has a sleep-disrupting effect.<sup>77,78</sup> However, during tobacco withdrawal, 24-h NP induced an improvement of sleep fragmentation and an increase in the proportion of SWS in cigarette smokers, thus reflecting the fact that nighttime nicotine administration decreases rather than increases arousal level in cigarette smokers.<sup>71</sup> This was further demonstrated by a study comparing a 16-h NP (applied only when awake) with a 24-h NP (applied continuously); the results show that microarousals were significantly more decreased by the 24-h NP compared with the 16-h NP, and only the former was found to increase SWS, suggesting a more potent protective effect of the 24-h NP on the tobacco-withdrawal-induced sleep fragmentation.<sup>79</sup> The sleep disturbances encountered with the 16-h NP were probably related to an insufficiently compensated withdrawal state (nicotine level is too low to balance tobacco withdrawal).

Postdetoxification sleep disturbances in alcohol dependence may reflect the alcohol-induced alterations of a number of neurochemical systems that are believed to regulate sleep.<sup>80</sup> Acute alcohol intake decreases neuronal excitability through its potentiation of inhibitory GABAergic mechanisms and its attenuation of excitatory glutamatergic mechanisms.<sup>80-82</sup> Over time, with chronic alcohol use, these neurotransmitter systems adapt, in order to maintain homeostasis and optimize brain functioning, and tolerance develops. However, with discontinuation of alcohol, a withdrawal-associated neural hyperexcitability occurs, favoring arousal and thus interfering with sleep-regulating mechanisms in addition to other negative symptoms.<sup>80-82</sup> Although the most commonly used strategy to renormalize neuronal excitability is to increase GABAergic transmission, influencing glutamatergic transmission could also reduce postwithdrawal neuronal hyperexcitability. Research on alcoholism has recently focused on the glutamatergic system as preclinical studies<sup>83,84</sup> and human laboratory studies,<sup>82</sup> provided compelling evidence for a role of the glutamate system in alcohol dependence. Moreover, drugs targeting the glutamatergic systems such as acamprostate are emerging as novel pharmacotherapeutic options for treating alcohol dependence.<sup>85-87</sup> Indeed, a magnetic resonance imaging study showed that acamprostate lowers glutamatergic neurotransmission in human subjects.<sup>88</sup> In a polysomnographic study, it was found that acamprostate treatment, initiated 1 week before alcohol withdrawal in alcohol-dependent subjects, enhanced sleep continuity during acute and protracted alcohol withdrawal by increasing time spent in sleep stage 3 and decreasing wakefulness after sleep onset (Staner L et al, unpublished data), while it prolonged REM sleep latency. Studies in healthy subjects have shown that acamprostate is devoid of any sedative effects per se.<sup>89</sup> Thus, the present results bring support to the idea that lowering the glutamate-related hyperarousal could influence postwithdrawal sleep disturbances. In accordance with this, in the same group of patients, daytime assessments by EEG and magnetoencephalography also indicate that acamprostate attenuates electrophysiological signs of CNS hyperexcitability.<sup>90</sup>

## Sleep-inducing drugs that enhance the activity of NREM sleep-promoting neurons

The most prescribed hypnotic drugs, benzodiazepines and benzodiazepine-related drugs such as zolpidem and zaleplon, have been shown to allosterically and posi-

# Pharmacological aspects

tively modulate the action of GABA via direct interaction with their recognition sites, ie, by increasing the affinity of GABA for its own GABA<sub>A</sub> sites. GABA<sub>A</sub> receptors are formed by the assembly of five protein subunits among the 18 subunits that have been identified by cloning techniques:  $\alpha$  (6 isoforms,  $\alpha_1$  to  $\alpha_6$ ),  $\beta$  (3 isoforms,  $\beta_1$  to  $\beta_3$ ),  $\gamma$  (3 isoforms,  $\gamma_1$  to  $\gamma_3$ ),  $\rho$  (3 isoforms,  $\rho_1$  to  $\rho_3$ ),  $\delta$  (1 isoform),  $\epsilon$  (1 isoform), and  $\theta$  (1 isoform).<sup>91</sup> However, most GABA<sub>A</sub> receptors are believed to be composed of two  $\alpha$ , one  $\beta$ , and two  $\gamma$  subunits. Receptors containing the  $\alpha_1$ ,  $\alpha_2$ ,  $\alpha_3$ , or  $\alpha_5$  subunits in combination with any of the  $\beta$  subunit and the  $\gamma_2$  are most prevalent in the brain, the  $\alpha_1\beta_2\gamma_2$  being the most prevalent subunit combination (60% of all GABA<sub>A</sub> receptors). Zolpidem and zaleplon are distinguished from classical benzodiazepine by binding selectively to GABA<sub>A</sub> receptors containing the  $\alpha_1$  subunit, a subtype of GABA<sub>A</sub> receptors thought to mediate sedative, anti-convulsive, and amnesic effects of benzodiazepine drugs, whereas  $\alpha_2$ -containing GABA<sub>A</sub> receptors relate to anxiolytic and myorelaxant effects.<sup>91</sup> Different mechanisms could explain the hypnotic effects of drugs enhancing GABA<sub>A</sub> neurotransmission. Firstly, GABA is the major inhibitory neurotransmitter system in the mammalian CNS, and GABA<sub>A</sub> receptors are ubiquitous in the CNS. Secondly, in the thalamus, these drugs could reinforce the inhibitory influence of GABAergic neurons of the reticular nucleus on the relay nuclei, which are the crossing points of all sensorimotor afferents going to the cortex. The reinforcement of inhibitory influence on relay nuclei has been proposed to underlie the decrease of high-amplitude delta slow-wave activity and the concomitant increase in sigma spindling activity during NREM sleep induced by drugs enhancing GABA<sub>A</sub> neurotransmission.<sup>92</sup> Thirdly, since VLPO sleep-promoting neurons are GABAergic, drugs enhancing GABA<sub>A</sub> neurotransmission will reinforce the VLPO inhibitory effects on all wake-promoting structures. Recent studies in a point-mutated mouse model have suggested that effects of benzodiazepines on sleep-onset latency and NREM sleep microstructure are mediated through different subtypes of GABA<sub>A</sub> receptors. Indeed,  $\alpha_2$ -containing GABA<sub>A</sub> receptors could relate to the reduction of NREM delta activity, while  $\alpha_1$ -containing GABA<sub>A</sub> receptors could be implicated in the shortening of sleep-onset latency induced by benzodiazepines.<sup>93-95</sup> Consequently, it may be suggested that sleep could be used a useful tool for the appraisal of  $\alpha_1$

GABA<sub>A</sub>-mediated sedative versus  $\alpha_2$  GABA<sub>A</sub>-mediated anxiolytic properties of a benzodiazepine drug. Other compounds enhancing GABAergic transmission could be valuable hypnotic drugs, some of which are currently in development. The drugs in question are another  $\alpha_1$ -containing GABA<sub>A</sub>-enhancing drug (indiplon), GABA analogues such as gabapentin, a GABA reuptake inhibitor (tiagabine), and a GABA<sub>A</sub> agonist (gaboxadol).<sup>96</sup> These agents, except gaboxadol, non-specifically enhance GABAergic transmission through GABA<sub>A</sub>, GABA<sub>B</sub>, and GABA<sub>C</sub> receptors. It should be stressed that the hypnotic effects of GABA<sub>B</sub> and GABA<sub>C</sub> ligands are not qualitatively similar to those obtained with GABA<sub>A</sub> ligands.<sup>97</sup>

## Major depression, REM sleep, and antidepressant drugs

More than 90% of depressed patients complain about difficulties in falling asleep, sleep disruption, or early-morning awakenings.<sup>98</sup> Well-established sleep EEG findings are disturbed sleep continuity (lengthening of sleep latency and increased wake after sleep onset resulting in decreased time spent asleep), deficit of SWS, especially during the first sleep cycle, and REM sleep disinhibition. The latter, also known as "increased REM sleep pressure," is described as a greater amount of REM sleep, mostly in the beginning of the night (also reflected by a shortened REM onset latency) and as an increase in the actual number of REMs during this sleep stage (REM density).<sup>99,100</sup> Many studies have suggested that the REM sleep disinhibition profile is not pathognomonic for major depression, but provides evidence of antidepressant-responsive conditions. Thus, beyond depression, shortened REM sleep latencies have been more reliably reported in conditions for which antidepressant drugs are recognized as effective, such as obsessive-compulsive disorder,<sup>101</sup> panic disorder,<sup>102</sup> generalized anxiety disorder,<sup>103</sup> or borderline personality disorder.<sup>104</sup> Polysomnographic recordings in some patients with anorexia nervosa<sup>105</sup> and alcohol dependence<sup>106</sup> could also demonstrate a shortened REM latency, but a depressive comorbidity was clearly present.

In 1982, McCarley posited that an imbalance between aminergic and cholinergic influences underlie REM sleep disinhibition in depressive disorder.<sup>107</sup> Conventional supports for the imbalance theory are based on the fact that the REM sleep suppressant effect of antidepressant



drugs might be attributed to facilitation of noradrenergic and/or serotonergic function or cholinergic blockade. In some cases, as with most tricyclic antidepressants, all three mechanisms may be involved. Antidepressant drugs devoid of clear-cut REM-suppressant effects (ie, bupropion, mirtazapine, nefazodone, tianeptine, trazodone, and trimipramine) share one characteristic: their potency to inhibit noradrenergic or serotonergic uptake is absent, doubtful, or moderate.<sup>108</sup>

There are several other arguments in favor of the aminergic/cholinergic imbalance theory. A recent [<sup>18</sup>F]deoxyglucose positron emission tomography (FDG-PET) study by Nofzinger et al<sup>109</sup> of waking to REM sleep changes reported that, compared with healthy subjects, depressed patients showed increased activation of the brain stem reticular formation limbic and anterior paralimbic cortex, and the executive cortex during REM sleep. The authors suggested that their findings could reflect the disinhibition of the REM-on cholinergic neurons either directly (brain stem activation) or indirectly (through cortical projections). Other evidence comes from studies administering different cholinergic-enhancing drugs (physostigmine, arecoline, RS86) in depressed patients. These compounds induced, to various degrees, stronger signs of REM sleep disinhibition than in healthy controls, as well as, for some of them, an increased rate of awakenings and arousals.<sup>110</sup> Other convincing arguments come from the monoamine depletion paradigms.  $\alpha$ -Methyl-para-

tyrosine, which inhibits catecholamine synthesis, provoked REM sleep abnormalities in humans.<sup>111</sup> Rapid tryptophan depletion induced by a tryptophan-free drink also disinhibited REM sleep without changing mood in individuals recovered from depression.<sup>112-115</sup> Bhatti et al<sup>116</sup> extended these observations to healthy volunteers (in these subjects, a tryptophan-free drink decreased REM latency, increased REM expressed as percentage of total sleep time, and increased REM density), findings that were only partially replicated by Voderholzer et al.<sup>117</sup>

## Conclusion

Polysomnographic recordings constitute a unique noninvasive tool to analyze brain function. Neurotransmission disturbances, such as those encountered in mental disorders, are reflected in alterations of sleep continuity and architecture. If we assume a neurobiological link between sleep and these disorders, the recent explosion of basic findings on the functional neuroanatomy of sleep-wake regulation and the cellular basis of the various sleep rhythms should raise new issues about our understanding of psychiatric disorders. Sleep laboratory investigations are a useful aid for the development of new psychotropic drugs, since their influence on a particular neurotransmission system could be reflected in the polysomnographic profile they induce. Moreover, this profile can be compared with the polysomnographic profiles of reference drugs. □

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# Pharmacological aspects

## Alteraciones del sueño, trastornos psiquiátricos y psicofármacos

Es probable que las disfunciones de la neurotransmisión cerebral involucradas en los procesos fisiopatológicos de los trastornos psiquiátricos se reflejen en alteraciones concomitantes de la continuidad y arquitectura del sueño. Ya que los efectos correctores de los psicofármacos en los sistemas de neurotransmisión disfuncionales pueden ser evidenciados a través de registros polisomnográficos, es posible considerar al sueño como un tipo de "ventana" hacia la neurobiología de los trastornos psiquiátricos. Durante los últimos diez años los principales progresos en nuestra comprensión de los mecanismos del sueño-vigilia han originado algunas sugerencias acerca de cómo los psicofármacos podrían afectar el ciclo sueño-vigilia. En esta revisión se presentan y discuten avances recientes en la comprensión de los mecanismos neurales reguladores del sueño a partir de los efectos de los psicofármacos. La relación entre los procesos fisiopatológicos de una enfermedad, su consecuencia en el sueño y los efectos correctores de un psicofármaco se ejemplifican en dos estados psicopatológicos: la privación de sustancias y la depresión mayor. Se puede concluir que los registros polisomnográficos constituyen una herramienta no invasora original para analizar el funcionamiento cerebral y son especialmente adecuados para evaluar los efectos objetivos de nuevos psicofármacos.

## Perturbations du sommeil, troubles psychiatriques, et psychotropes

Les dysfonctionnements de la neurotransmission impliqués dans la physiopathologie des troubles psychiatriques se reflètent très probablement dans les altérations concomitantes de la continuité et de l'architecture du sommeil. Comme les médicaments psychotropes corrigent les dysfonctionnements des systèmes de neurotransmission, leurs effets peuvent être mis en évidence par des enregistrements polysomnographiques. Le sommeil peut donc être considéré, en quelque sorte, comme un reflet de la neurobiologie des troubles psychiatriques. Au cours des 10 dernières années, des avancées majeures dans nos connaissances sur les mécanismes veille-sommeil ont permis d'apporter quelques éléments d'explication sur la manière dont les médicaments psychotropes pouvaient influencer sur le cycle veille-sommeil. Dans cette revue de la littérature, les découvertes récentes dans notre compréhension des mécanismes neuronaux impliqués dans la régulation du sommeil sont présentées et discutées en fonction des effets des médicaments psychotropes. Les relations entre le processus physiopathologique d'une maladie, ses conséquences sur le sommeil et les effets correcteurs d'un médicament psychotrope sont illustrés par deux exemples : le sevrage d'une substance et la dépression majeure. En conclusion, retenons que les enregistrements polysomnographiques représentent un outil unique, non invasif, permettant d'analyser le fonctionnement cérébral et particulièrement bien adapté pour l'évaluation des effets objectifs d'un nouveau médicament psychotrope.

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