

# Awakening to the Psychopharmacology of Sleep and Arousal: Novel Neurotransmitters and Wake-Promoting Drugs

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**Issue:** *Unique neurotransmitters acting at specific hypothalamic neurons promote either wakefulness or sleep. Drugs and diseases that modify neurotransmission at these sites can produce both desirable and undesirable changes in wakefulness.*

**N**ew developments in the psychopharmacology of sleep and wakefulness are leading to enhanced clinical insight into disorders of sleep and arousal and to the development of novel treatments for sleepiness and fatigue. A glimpse into the neuroanatomical substrates and chemical mediators of arousal is now possible.

## Getting Wired

Recent advances in neuroanatomy are now providing a picture of how neuronal pathways mediate sleep and wakefulness, allowing us to better understand how the brain's wires keep us awake or "wired." Several interesting sites within the hypothalamus are at work here, including brain "pacemakers," sleep promoters, and wake promoters.<sup>1,2</sup> The brain's pacemaker is the well-known suprachiasmatic nucleus that serves as an internal clock for regulating circadian rhythms, especially the sleep-wake cycle, in part by alternating the activation of either sleep-promoting neurons (in the ventrolateral preoptic area) or wake-promoting neurons (in the tuberomammillary nucleus and lateral hypothalamus). Activation of cerebral cortex is essential for achieving wakefulness. Two pathways provide

such activation: a newly characterized projection from the hypothalamus and the classical ascending reticular activating system (ARAS) that arises from the brainstem.

## Getting Juiced

Numerous neurotransmitter "juices" arise from these various neurons and mediate aspects of both sleep and arousal. Particularly interesting are the recently discovered peptides hypocretin 1 and 2 (named for their hypothalamic origin and homology to secretin), also called orexin A and B (because they also stimulate appetite).<sup>3,4</sup> Orexin/hypocretin neurons are located in the lateral hypothalamus and are critical for maintaining normal wakefulness. In fact, when they malfunction or are destroyed, they cause narcolepsy with daytime sleepiness and sleep attacks. These neurons apparently regulate monoaminergic and cholinergic components of the ARAS known to mediate important dimensions of arousal. They may also regulate both sleep-promoter and wake-promoter neurons in the hypothalamus. Wake-promoter neurons in the tuberomammillary nucleus project to cortex and use the neurotransmitter histamine.<sup>1</sup> Thus, boosting histamine causes arousal and blocking

histamine output causes sedation or sleep (e.g., antihistamines that block H<sub>1</sub> receptors). Sleep-promoter neurons in the ventrolateral preoptic area use the neurotransmitters  $\gamma$ -aminobutyric acid and galanin.<sup>1</sup>

## Eyes Wide Open:

### Stimulation Versus Wakefulness

The neuroanatomy and psychopharmacology of arousal suggest that 2 types of arousal, each mediated by separate pathways and neurotransmitters, may exist: stimulated vigilance and normal wakefulness.<sup>1-6</sup> The former may involve external vigilance, with tense hyperarousal, putting the individual on the lookout for threats from the environment. Arousal of this type may be mediated by the monoamines dopamine, norepinephrine, serotonin, and acetylcholine via the ARAS. The ability to activate the ARAS may enhance the

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survival of an individual in a hostile environment. The other form of arousal may be a more reflective type of calm wakefulness, in which there is internal vigilance to executive functions as the individual focuses on cognitive tasks. Such wakefulness may be mediated by the ascending histaminergic neurons arising from the hypothalamus. The ability to activate this system would lead to problem solving, learning, and creativity.

### Flip-Flopping the Sleep-Wake Switch

Normal wakefulness may be something akin to an all-or-nothing phenomenon, with the hypothalamus providing a reciprocal switching circuit so that the brain can either be “on” (calm wakefulness) or “off” (asleep). Such an arrangement would limit intermediate states, allowing relatively brief times to be spent in transitions between the wake or sleep states. One model of the normal sleep-wake cycle proposes that wake-promoter and sleep-promoter neurons inhibit each other, thus causing oscillation between wakefulness and sleep in a rhythm determined by the brain’s internal clock (located within the suprachiasmatic nucleus).<sup>1</sup>

Disruption of wake- and sleep-promoting pathways or their neurotransmitters would therefore result in problems with wakefulness and arousal and could lead to fatigue and cognitive and executive deficiencies in problem solving. Specifically, unstable on-off switches could lead to insomnia or to unwanted transitions into sleep during wakefulness, e.g., narcolepsy. In fact, patients with narcolepsy have lost their orexin/hypocretin signaling in

the hypothalamus, perhaps due to an autoimmune process that destroys the lateral portion of the hypothalamus.<sup>4,5</sup> Furthermore, drugs that compensate for such disruptions by acting on specific neurotransmitters within these various neuroanatomical systems may have therapeutic actions on disorders of sleepiness and fatigue.<sup>5,7</sup> Stimulants (e.g., amphetamine) and nonstimulants (e.g., modafinil) can treat narcolepsy, the former by activating both arousal systems, and the latter by selectively activating normal wakefulness.

### Psychopharmacologic Wakefulness on Demand

What is so interesting about the new developments in this field is that it may now be possible to activate the normal wakefulness pathway selectively and on demand with novel wake-promoting drugs. Theoretically, a person with the wakefulness system “on” is experiencing the cognitive chemistry of a normal, well-rested state.<sup>1</sup> By contrast, so-called stimulants (e.g., amphetamine, caffeine) seem to nonselectively activate both external and internal vigilance arousal systems. Theoretically, a person with the external vigilance system “on” may have motor hyperactivity, jitteriness, overconfidence, and a

### Take-Home Points

- ◆ The neuroanatomy of wakefulness appears to involve activation of neuronal projections to cerebral cortex and is regulated by several key hypothalamic nuclei.
- ◆ The psychopharmacology of wakefulness is mediated by numerous neurotransmitters acting in hypothalamus and cortex, including the newly identified neurotransmitters known as both orexins and hypocretins, the classical monoamine histamine, and several others.
- ◆ A new wake-promoting drug, modafinil, activates the cerebral cortex by increasing neuronal activity in wake-promoting hypothalamic neurons and by decreasing neuronal activity in sleep-promoting hypothalamic neurons, which appears to be useful in treating conditions associated with sleepiness and fatigue.

negative rebound effect of nonrestorative sleep once it is turned off.

Selective activation of wakefulness could lead to improvement in the cognitive decrements normally associated with sleep deprivation in anyone from a shift worker to a jet-lagged international traveler or fighter pilot flying halfway around the world.<sup>8</sup> In addition, activating internal vigilance systems may reduce the sense of fatigue in patients with depression and physical illnesses

such as multiple sclerosis and might even enhance cognitive symptoms in attention deficit disorder as well as cognitive and negative symptoms of schizophrenia.

### Summary

Exciting new developments in the psychopharmacology of wakefulness are clarifying the neurotransmitters, pathways, and drugs that impact this important physiologic state. Selectively inducing normal wakefulness without stimulating external vigilance may lead to therapeutic benefits not only in sleep disorders but also in cognitive disorders and conditions associated with fatigue. ◆

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