

# The Neurotransmitters of Sleep

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The part of the brain most important in regulating sleep duration is the hypothalamus. Certain groups of hypothalamic neurons and adjacent groups of basal forebrain neurons produce the neurotransmitter  $\gamma$ -aminobutyric acid (GABA). Projections of these GABA neurons inhibit the firing of cells involved in wakefulness. Several groups of neurons have been shown to be inhibited by this action—including neurons containing histamine, norepinephrine, serotonin, hypocretin, and glutamate—and this inhibition promotes sleep. Hypocretin (also called orexin) was discovered in 1998, and its role in sleep and narcolepsy was identified in 2001. Other as-yet undiscovered transmitters are undoubtedly involved in sleep control. The transmitters discussed in this article have been the most thoroughly studied, and many aspects of the role of each of these transmitters in relation to sleep are reasonably well understood.

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The most rostral neurons in the brain with a major role in sleep control are  $\gamma$ -aminobutyric acid (GABA)-ergic cells located in the basal forebrain and in the anterior hypothalamus. These GABAergic cells are unique: while most neurons tend to have minimal activity during non-rapid eye movement (NREM) sleep, these cells are more active during NREM sleep than they are in rapid eye movement (REM) sleep or in waking.<sup>1–5</sup> They also increase discharge rates with sleep onset and continue to release GABA at a high level while sleep continues. In some cases, GABA neurons continue firing during REM sleep. In other cases, neurons are active in relation to NREM sleep in particular.

GABAergic cells induce sleep by inhibiting cells that are involved in arousal functions. Cholinergic neurons in the basal forebrain are directly inhibited by GABAergic sleep-active neurons (Figure 1), and since the cholinergic system is one of the main forebrain arousal systems of the brain, the inhibition produced by this activity deactivates the cortex.

## HISTAMINE

The histaminergic cells, which are located in the posterior hypothalamus, play a major role in the maintenance

of wakefulness.<sup>6,7</sup> It has long been known that lesions in the posterior hypothalamus produce a comatose-like continuous sleepiness,<sup>7</sup> just as it has also been shown that lesions of the basal forebrain and anterior hypothalamus—the sleep-active cell group—produce a persistent insomnia (for review, see Szymusiak<sup>8</sup>). One could say that humans have a sleep center in the anterior hypothalamus and basal forebrain and a wake center in the posterior hypothalamus. Further, histaminergic cells in the posterior hypothalamus are strongly and directly inhibited by the GABAergic neurons.<sup>6,7,9</sup> Therefore, the GABAergic neurons not only turn off the cholinergic cells, but they also turn off the histaminergic cells. Activity in the histaminergic cells appears to be tightly linked to wakefulness,<sup>6</sup> and their inactivity, caused by GABAergic cells, appears to be tightly linked to sleepiness,<sup>7</sup> as evidenced by the general observation that antihistamine medications that cross the blood-brain barrier make people drowsy.<sup>6</sup>

## NOREPINEPHRINE

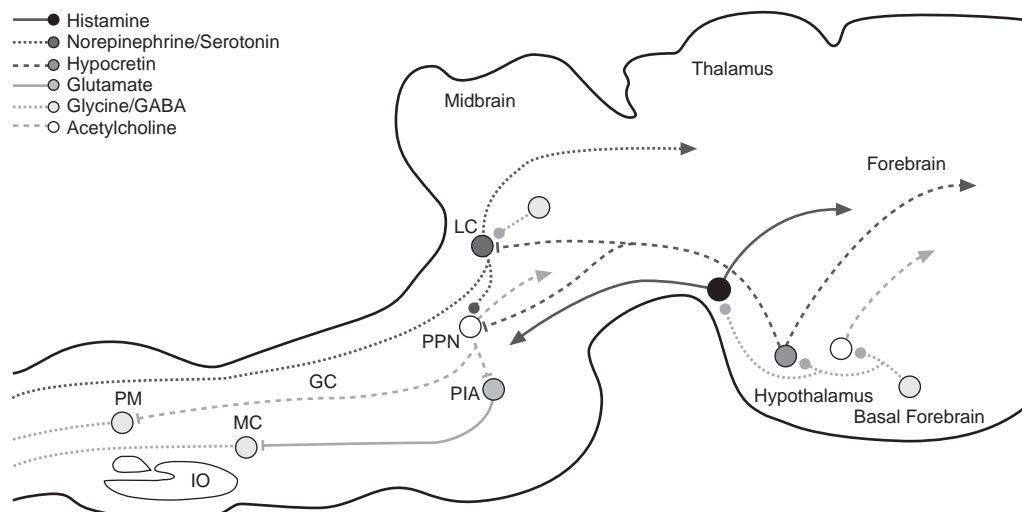
Norepinephrine cells are mostly localized to the locus ceruleus of the pons. Like histaminergic cells, the norepinephrine cells are inactive during REM sleep. However, there is one important difference between the activity of norepinephrine and histamine cells: only the norepinephrine cells become inactive during cataplexy, which is an episodic loss of muscle tone while awake and occurs in patients with narcolepsy. Neuronal recording studies<sup>6</sup> suggest that the normal cessation of activity of norepinephrine cells during sleep may be related to the loss of muscle tone during sleep, while the normal cessation of activity of histamine cells during sleep may be directly related to the loss of consciousness during sleep. Several studies support the concept that activity in histaminic cell groups is

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Figure 1. Synaptic Relationships Underlying the Loss of Consciousness and Correlated Loss of Muscle Tone in Normal Sleep<sup>a</sup>

<sup>a</sup>This simplified drawing of a sagittal section of a cat's brain shows some of the major connections that play an important role in sleep control. It also illustrates the complexity of the synaptic relationships underlying the loss of consciousness and correlated loss of muscle tone that characterize normal sleep. Systemic drug application can affect sleep through actions on any one of these synapses as well as on many other synapses not illustrated. Lines ending in solid dots indicate inhibitory output. Lines ending in arrows indicate excitatory output.

Abbreviations: GABA =  $\gamma$ -aminobutyric acid, GC = nucleus gigantocellularis, IO = inferior olive, LC = locus coeruleus, MC = nucleus magnocellularis, PIA = pontine inhibitory area, PM = nucleus paramedianus, PPN = pedunculopontine nucleus.

strongly linked to forebrain arousal,<sup>6,10,11</sup> whereas norepinephrine and serotonin cell groups are associated with the regulation of muscle tone and perhaps motor activity.<sup>6,12-15</sup>

### SEROTONIN

The next cell group in this caudal progression contains serotonin and is located in the raphe nuclei (a midline system extending from the midbrain to the medulla). These serotonin cells, like the histamine and norepinephrine cells, are inactive in sleep (most completely in REM sleep), and they may have a role in maintaining arousal and regulating muscle tone and in regulating some of the phasic events of REM sleep.<sup>6,12,16</sup> If these cells are destroyed, these phasic events are released from inhibition. The tonic activity of these serotonin cells during waking would tend to suppress phasic events, and their inactivity during REM sleep allows high voltage electrical activity (called ponto-geniculo-occipital [PGO] spikes) to propagate from the pons to the thalamus and cortex, releasing associated eye movements and twitches.<sup>1</sup>

Serotonin, histamine, and norepinephrine cells normally turn off during REM sleep (i.e., they are normally silent during REM sleep and active in waking) because they are inhibited by GABAergic neurons. GABA is the most common inhibitory transmitter in the brain. The fact that under some conditions, such as in cataplexy, these 3 cell groups do not cease activity together shows that they can be controlled individually by various GABAergic cell popula-

tions.<sup>6,9</sup> GABA applied to the serotonin and norepinephrine cell groups triggers REM sleep,<sup>9,17,18</sup> demonstrating that the cessation of activity in these brain stem cell groups is important in the control of REM sleep.

### HYPOCRETIN

The most recently discovered transmitter related to sleep control is located in a cell group in the hypothalamus, situated between the rostral region, where there are sleep-active neurons, and the caudal regions, where there are histamine wake neurons. These neurons contain a peptide called hypocretin, also called orexin. They were first connected with sleep when it was found that the loss of these neurons is linked to human narcolepsy.<sup>19-23</sup> Most narcoleptics with cataplexy exhibit about a 90% decrease in the number of hypocretin cells.<sup>21</sup> In contrast, other degenerative diseases of the central nervous system cause no appreciable loss of these cells. For example, hypocretin cells were present in almost normal numbers in the one postmortem Alzheimer's patient examined<sup>21</sup>; whereas in postmortem brains of people with narcolepsy, even in young postmortem narcoleptic brains, this cell population was depleted, and hypocretin levels in the cerebrospinal fluid were low.<sup>21,24</sup> Although the cause of cell loss in narcolepsy is not well established, it may be a consequence of autoimmune attack. Mechanical damage to the hypothalamus that affects the hypocretin system also causes symptoms of narcolepsy.<sup>25</sup> The hypocretin system appears to

drive many of the other arousal systems—there are strong hypocretin projections to the histamine, norepinephrine, and serotonin neurons.

### GLUTAMATE

An unusual relationship appears to exist between hypocretin neurons and amino acids. Hypocretin can cause the release of the amino acid glutamate.<sup>25–28</sup> Applying hypocretin to trigeminal motor neurons causes excitation, but only in the presence of glutamate. If glutamate receptors are blocked, hypocretin does not activate the motoneurons.<sup>29</sup>

Similarly, in other systems and sometimes in the same system, hypocretin releases GABA. For example, in the locus ceruleus, hypocretin releases both glutamate and GABA, which results in a simultaneous excitation and inhibition that may tend to stabilize the electrical polarization of the membranes.<sup>25</sup> In the absence of hypocretin, physiologic and behavioral instability occurs. Narcolepsy, for instance, appears to be the result of an unstable arousal system that causes individuals to be sleepy during the day yet sleep poorly at night. This instability is associated with cataplexy in waking. Conversely, the normal suppression of muscle tone during REM sleep tends to be disrupted in narcoleptics by periods without muscle tone suppression. This overt motor activity during REM sleep is called REM sleep behavior disorder and frequently accompanies narcolepsy.<sup>30</sup> The instability of the arousal and motor control systems in narcolepsy appears to be a function of the loss of the dual action of hypocretin on excitatory and inhibitory neurotransmitters.

### CONCLUSION

Until recently, sleep experts assumed that the transmitters histamine, norepinephrine, and serotonin worked together to regulate arousal and became inactive during REM sleep to keep the body from acting out dreams. In fact, each of these neurotransmitters plays a distinct role in the sleep-wake cycle. Histamine has a major role in the control of arousal and a limited direct role in muscle tone control, whereas norepinephrine and serotonin affect both muscle tone and arousal but are not as tightly linked to the maintenance of the waking state as is histamine.

Suppression of muscle tone at the motor neuronal level in REM and NREM sleep has been the focus of recent investigation. Obstructive sleep apnea, for example, is a sleep disorder that is triggered by the suppression of tone in muscles that normally hold the airway open. Conversely, in REM sleep behavior disorder, there is not enough suppression of muscle tone and people act out their dreams.<sup>31</sup> Other parasomnias, such as nocturnal bruxism, result from a hypofunction of motor inhibition systems during sleep.

Motor neurons are inhibited in REM sleep by glycine.<sup>32</sup> Recent studies<sup>6,9,13,33</sup> have shown that there is a concurrent GABA inhibition and withdrawal of serotonin and norepinephrine facilitatory input onto motoneurons in REM sleep.

The discovery of hypocretin and the subsequent inquiry into its clinical and biological significance has substantially advanced our understanding of narcolepsy. Loss of hypocretin in the hypothalamus is linked to narcolepsy and cataplexy. The precise role of hypocretin in motor activity and arousal, however, has not yet been elucidated, and further inquiry into its function may lead to its use in treating narcolepsy<sup>34</sup> as well as other motivated behaviors.

*Disclosure of off-label usage:* The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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