



Commentary

Good night and good luck: Norepinephrine in sleep pharmacology

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ABSTRACT

Sleep is a crucial biological process that is regulated through complex interactions between multiple brain regions and neuromodulators. As sleep disorders can have deleterious impacts on health and quality of life, a wide variety of pharmacotherapies have been developed to treat conditions of excessive wakefulness and excessive sleepiness. The neurotransmitter norepinephrine (NE), through its involvement in the ascending arousal system, impacts the efficacy of many wake- and sleep-promoting medications. Wake-promoting drugs such as amphetamine and modafinil increase extracellular levels of NE, enhancing transmission along the wake-promoting pathway. GABAergic sleep-promoting medications like benzodiazepines and benzodiazepine-like drugs that act more specifically on benzodiazepine receptors increase the activity of GABA, which inhibits NE transmission and the wake-promoting pathway. Melatonin and related compounds increase sleep by suppressing the activity of the neurons in the brain's circadian clock, and NE influences the synthesis of melatonin. Antihistamines block the wake-promoting effects of histamine, which shares reciprocal signaling with NE. Many antidepressants that affect the signaling of NE are also used for treatment of insomnia. Finally, adrenergic receptor antagonists that are used to treat cardiovascular disorders have considerable sedative effects. Therefore, NE, long known for its role in maintaining general arousal, is also a crucial player in sleep pharmacology. The purpose of this review is to consider the role of NE in the actions of wake- and sleep-promoting drugs within the framework of the brain arousal systems.

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1. Introduction

1.1. Sleep

Sleep is one of the most universal biological processes in existence. It is highly conserved, and creatures from *Drosophila melanogaster* and *Caenorhabditis elegans* to humans experience at

least some form of it [1]. Depriving an organism of sleep altogether can be extremely detrimental, and may even lead to death [2]. Sleep is therefore considered necessary for life, but why this is so remains unclear. Sleep is subdivided into rapid eye movement (REM) sleep, which is characterized by high-frequency electroencephalogram (EEG) recordings and muscle atonia [3], and non-REM (slow-wave) sleep, characterized by low frequency EEG recordings and body rest [4].

1.2. Sleep disorders

Although sleep is a tightly controlled process orchestrated by multiple regulatory systems, sleep disorders do occur, some as a result of disruptions in sleep circuitry, some secondary to other conditions, and others as a result of modern lifestyles. Sleep complaints are in fact the second-leading cause for seeking medical attention, after pain [5]. Sleep disorders can be categorized broadly into conditions of excessive wakefulness (e.g., insomnia) and excessive sleepiness (e.g., narcolepsy, shift-work disorder, jet lag). Insomnia is defined as difficulty falling asleep and maintaining adequate sleep, and is the most commonly reported sleep problem in the United States. In addition to the associated lack of nighttime sleep, there are a host of daytime consequences, as well,

Abbreviations: 5-HT, serotonin; AMP, adenosine monophosphate; AR, adrenergic receptor; BDNF, brain-derived neurotrophic factor; DA, dopamine; DAT, dopamine transporter; Dbh, dopamine beta hydroxylase; DMH, dorsal medial hypothalamus; DRN, dorsal raphe nucleus; EEG, electroencephalogram; GABA, gamma-aminobutyric acid; GPCR, G protein-coupled receptor; H, histamine (receptor); KO, knockout; LC, locus coeruleus; MAOI, monoamine oxidase inhibitor; MPOA, medial preoptic area; MSA, medial septal area; MT, melatonin (receptor); NE, norepinephrine; NET, norepinephrine transporter; PFC, prefrontal cortex; PKA, protein kinase A; REM, rapid eye movement; SCN, suprachiasmatic nucleus; SERT, serotonin transporter; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; TMN, tuberomammillary nucleus; TrkB, tyrosine kinase receptor B; VLPO, ventrolateral preoptic area; VPAG, ventral periaqueductal grey; z-drug, drug that acts specifically on the $\alpha 1$ subunit of the benzodiazepine receptor.

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such as tiredness, stress, and attentional deficits [5]. Conversely, narcolepsy and hypersomnias involve excessive daytime sleepiness and sleep attacks or unintended napping. This can have a profound impact on an individual's ability to function and limits even basic tasks like driving a car [5]. In addition to the effects these conditions have on sleep itself, problems such as cardiovascular disease and diabetes are often worsened by insufficient sleep [6]. Furthermore, patients with conditions from depression to Parkinson's and Alzheimer's diseases often experience comorbid sleep disturbances [7–9]. Thus, medications to treat sleep disorders are a necessity in our society, and understanding the pathways and neurotransmitter systems that regulate sleep is crucial.

1.3. Regulation of arousal states

Sleep is a global process, controlled by regions throughout the brain and by multiple neurotransmitters and neuropeptides (Fig. 1). The first studies that attempted to localize regions of the brain responsible for sleep maintenance were conducted in the early twentieth century by von Economo, who noticed correlations between sleeping sickness and lesions in certain brain areas

[10]. He reported that patients who had encephalitis lethargica and slept for 20 h a day had lesions at the base of the midbrain, and he hypothesized that this site might be the origin for an ascending arousal pathway. Subsequent studies revealed an arousal system with two main branches (reviewed in [11]). The first branch begins in the cholinergic neurons of the pedunculopontine and laterodorsal tegmental nuclei and projects up, relaying through the thalamus, and into the cortex; the second begins in monoaminergic neurons, the noradrenergic locus coeruleus (LC), dopaminergic neurons in the ventral periaqueductal grey (vPAG), the serotonergic dorsal raphe nucleus (DRN), and also the histaminergic tuberomammillary nucleus (TMN), and progresses to the cerebral cortex. These neurons also receive inputs from orexin neurons in the perifornical area of the lateral hypothalamus [12]. The orexins are especially important for controlling transitions between sleep and wake and between stages of sleep, and as a result, disruptions in this system cause narcolepsy [13]. These two branches also interact with the circadian pacemaker of the brain, the suprachiasmatic nucleus (SCN), mainly via relay through the dorsal medial hypothalamus [14,15]. This provides the intersection of the homeostatic regulation of sleep, based on accumulated sleep drive or tiredness, and circadian regulation of sleep, based on a 24-h cycle set by the SCN via integration of light inputs from the retina.

While the cholinergic and monoaminergic systems act to promote wakefulness in conjunction with the orexins, there are other neuronal groups that act to promote sleep. The primary population of sleep-promoting neurons is located in the preoptic area, specifically the ventrolateral preoptic area of the hypothalamus (VLPO). These neurons express c-Fos protein and have elevated discharge rates specifically during sleep, and lesions to this area prevent sleep [16–18]. In addition, these VLPO neurons project to, and share mutual inhibition with, the neuronal groups involved in the ascending arousal pathways [19,20]. The majority of these cells are GABAergic, though some contain enkephalin and galanin [20,21]. The interaction of the VLPO neurons with the ascending arousal systems provides what is described by Saper et al. as a “flip-flop switch” that regulates and controls transitions between sleep and wake [11].

1.4. NE and sleep regulation

As described above, norepinephrine (NE) is one of the main neurotransmitters involved in arousal. LC neurons fire in a wake-dependent manner; they are highly active during wake, slow-firing during non-REM sleep, and almost completely quiescent during REM sleep [22]. The A1 and A2 brainstem noradrenergic nuclei also provide input to regions of the hypothalamus known to be involved in sleep regulation [23]. Pharmacological suppression of LC activity leads to sedation and drives forebrain EEG recordings into sleep-like patterns. We know that dopamine β -hydroxylase knockout (*Dbh* $-/-$) mice, which lack norepinephrine, have altered sleep and arousal patterns. They show decreased latency to sleep after stress, require stronger stimuli to wake them after sleep deprivation, and have increased overall sleep, albeit with less REM, in a 24-h period [24–26]. Pharmacological studies have revealed robust wake-promoting effects of α 1- and β -adrenergic receptor (AR) agonists when administered to the medial septal area (MSA) and the medial preoptic area (MPOA), both wake-promoting regions, reviewed in detail by Berridge [23,27]. Conversely, blockade of ARs results in sedation. These effects appear to be mediated mostly by antagonism of α 1ARs, though there are synergistic effects when combined with β AR antagonists. While one group has found that microinjection of the α 1AR antagonist prazosin into the MPOA induces sleep rather than wake, the magnitude of

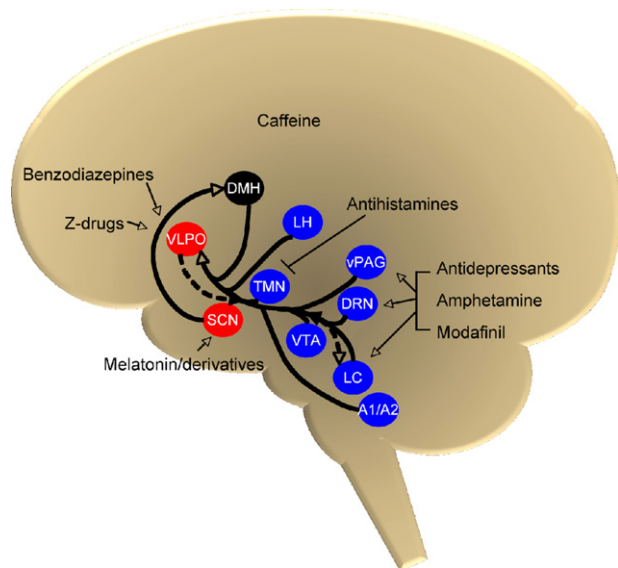


Fig. 1. Arousal pathways and sites of actions of wake- and sleep-promoting pharmacotherapies. The ascending arousal pathway is pictured here with putative sites of actions of the aforementioned medications. Wake-promoting regions are shown in blue, sleep-promoting regions are shown in red, and relays are shown in black.

The noradrenergic LC and A1/A2, along with the dopaminergic VTA and vPAG, the serotonergic DRN, and the histaminergic TMN share reciprocal inhibition with the sleep-promoting neurons of the GABAergic VLPO. The orexinergic neurons of the LH further increase wake by enhancing the actions of these aminergic neurons. The circadian clock influences these pathways via relays through the DMH. Benzodiazepines and z-drugs promote sleep by increasing activity along the sleep-promoting pathway, originating in the VLPO, while melatonin and melatonin receptor agonists decrease the firing of SCN neurons, thereby removing inhibition from VLPO neurons. Antidepressants increase extracellular monoamines through a variety of mechanisms, which then influence both the arousal and inhibitory pathways. Antihistamines suppress wake by preventing the actions of histamine on the arousal pathway. Amphetamine provokes monoamine release and blocks reuptake to increase activity along the wake-promoting pathways. While the exact mechanism of modafinil remains unclear, it appears to block catecholamine reuptake and promote wake via monoaminergic transmission. Caffeine acts on multiple brain systems by globally suppressing the inhibitory effects of adenosine. Abbreviations: LC, locus coeruleus; VTA, ventral tegmental area; vPAG, ventral periaqueductal grey; DRN, dorsal raphe nucleus; TMN, tuberomammillary nucleus; VLPO, ventrolateral preoptic area; LH, lateral hypothalamus; DMH, dorsomedial hypothalamus; SCN, suprachiasmatic nucleus. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of the article.)

changes in wake time were relatively small and depended on ambient temperature [28,29]. Thus, it seems likely that NE primarily acts through α 1ARs in the MPOA to increase wake, although stimulation of α 1ARs in this brain region may be sedative under some conditions.

While NE is important for maintaining normal sleep states, it also plays a role in cataplexy. Cataplexy is a component of narcolepsy in which patients experience abrupt transitions from waking into a state akin to REM sleep, with complete muscle atonia. These cataplexy attacks can be spontaneous or triggered by extreme emotion. α 1AR antagonism exacerbates cataplexy, as measured both by the number of attacks and duration of the attacks, whereas activation of these receptors decreases the number of attacks [30]. This indicates that dysregulated NE signaling, most likely working in conjunction with acetylcholine, is responsible for cataplexy attacks.

In addition to its role in the regulation of normal and pathological sleep, NE is also critical to the efficacy of sleep pharmacotherapies, both wake- and sleep-promoting, which will be the focus of the rest of this review.

2. Wake-promoting medications

Wake-promoting drugs are among the most commonly used pharmacotherapies in our society. Patients suffering from conditions of excessive daytime sleepiness, such as narcolepsy and shift-work sleep disorder, are often prescribed modafinil or amphetamine, which are used off-label and recreationally, as well. Caffeine, in coffee, soda, and energy drinks, is the most popular psychoactive substance in the world. And while all these work through diverse mechanisms, NE appears to contribute, with the exception of caffeine, either directly or indirectly to their wake-promoting activities.

2.1. Amphetamines

Amphetamines were developed in 1927 and first used to treat narcolepsy in 1935 [31]. The amphetamines include several compounds, each with its own wake-promoting efficacies and abuse liability. Those typically used to treat excessive sleepiness are dexamphetamine (Dexedrine) and methylphenidate (Ritalin). Although amphetamines are highly successful at promoting wakefulness, they have a number of unpleasant side effects that limit their usefulness. Amphetamines induce sympathomimetic effects, such as increased heart rate and blood pressure, and are also known for their addictive properties. Despite this, for many years they remained the frontline of treatment for conditions of excessive sleepiness, such as narcolepsy and phase-shift disorder.

Amphetamine has been shown to increase wakefulness in rats when administered both acutely and chronically [32]. When given acutely, amphetamine increased sleep latency, and decreased the amount of sleep and sleep efficiency compared with saline, as measured by EEG. Furthermore, it eliminated REM sleep for the duration of the 3-h test session. When administered chronically (every day for seven days), amphetamine decreased sleep efficiency on the first day, but efficiency improved gradually over subsequent days. Similarly, whereas amphetamine drastically reduced slow-wave sleep on the first day of testing, this decrease was attenuated over subsequent days, indicating the development of a tolerance to its wake-promoting effects. Sleep latency was increased by amphetamine on each day of the test. In humans, both dexamphetamine and methylphenidate increase sleep latency and improve self-reported sleepiness [31]. Dexamphetamine reduces total sleep, both REM and slow-wave, as measured by EEG, and decreases sleep efficiency. It is effective at sustaining wake in military pilots, in addition to its more traditional use as a

narcolepsy treatment. However, administration of amphetamines typically results in rebound hypersomnolence when the individual is allowed to sleep, and because of the associated drop off in sleep efficiency, individuals usually feel residual sleepiness. Furthermore, users can develop a tolerance to both methylphenidate and low-dose dexamphetamine [33,34].

Amphetamines act on the monoamine system to facilitate release and block reuptake of serotonin (5-HT), dopamine (DA), and NE. As described, all three monoamines are known to play a role in the regulation of arousal state. The DRN, the LC, and DA neurons in the vPAG are primary components of the ascending arousal system. Elevated extracellular levels of these neurotransmitters promote wakefulness through excitatory actions on the ascending arousal pathway, while simultaneously preventing sleep by inhibiting the sleep-promoting neurons of the VLPO.

NE is a particularly important component because, aside from wake-promoting effects of its own, it also acts to promote the firing of DA neurons, thereby increasing their wake-promoting effects [35]. Furthermore, the LC has reciprocal connections with 5-HT neurons in the DRN [36]. The importance of NE is underscored by several findings. For example, the wake-promoting effects of low-dose amphetamine observed in wild-type mice is abolished in *Dbh*^{−/−} mice that specifically lack NE [25]. Direct infusion of low-dose amphetamine into sleep-related adrenergic projection fields containing both α 1 and β ARs increases wakefulness and arousal, as measured by EEG (reviewed by Berridge [23]). Microdialysis studies have shown a correlation between NE release in the prefrontal cortex (PFC), which receives direct innervation from the LC, and the time spent awake after administration of low-dose amphetamine. Central infusion of β AR antagonists in anesthetized animals can completely block the effects of low-dose amphetamine on wake, although no effect is seen in unanesthetized rats. This potential discrepancy could be evaluated further in normally sleeping animals, and the addition of α 1AR antagonists may yield more insight. Combined, these results indicate that facilitation of NE release is critical for the wake-promoting actions of amphetamine.

2.2. Modafinil

Modafinil (Provigil) was first developed in the early 1990s and was approved for use in the United States in 1998. Since then, it has become the most prescribed medication in the United States for treatment of excessive daytime sleepiness; it is also used off-label for conditions as diverse as attention deficit disorder and cocaine dependence. One reason for the success of modafinil is its lack of negative side effects that are common to other medications used to treat excessive sleepiness. For example, unlike amphetamines, modafinil does not induce sympathomimetic effects, does not cause sleep rebound, and has low abuse liability [37–39].

Initial animal studies revealed that modafinil increased wake in a dose-dependent manner, with no signs of sleep rebound, as measured by EEG recordings [39,40]. Amphetamine, in comparison, also dose-dependently increased wake, but with a subsequent sleep rebound period and considerable side effects like hyperactivity [40]. When compared with methamphetamine in rats, modafinil increased wake to a similar extent, but with longer bouts of sustained wakefulness and less marked locomotor effects [39]. In humans, modafinil is approved to treat excessive daytime sleepiness associated with narcolepsy, shift-work sleep disorder, and obstructive sleep apnea (reviewed by [38]). In several trials for narcolepsy, modafinil decreased daytime sleepiness without affecting nighttime sleepiness, and when tested for shift-work sleep disorder, it increased sleep latency during nighttime shifts. Modafinil is also well tolerated by patients who experience sleepiness secondary to other conditions or illnesses. When compared with amphetamine,

volunteers given modafinil showed less need for recovery sleep after sleep deprivation and fewer sleep disturbances with no REM sleep deficit [41]. Further, modafinil has been shown to boost performance and alertness to a similar level as caffeine [42].

Despite the high prevalence of its use, however, the exact molecular mechanism underlying modafinil's efficacy has yet to be elucidated. An early screen of possible targets revealed only low-affinity binding to the dopamine transporter (DAT). Subsequent studies confirmed this, and also found potential binding to the norepinephrine transporter (NET) [43–45]. Moreover, DAT knockout, α 1AR antagonists, and DA receptor antagonists blunt the wake-promoting effects of modafinil, highlighting the importance of catecholamine signaling [46].

As described above, both NE and DA are important components of the ascending arousal pathway, and both are important for modafinil efficacy. Modafinil activates the LC in animal models and in humans [47–49]. NE neurons in both the locus coeruleus and in the A1/A2 groups form reciprocal connections with the sleep-promoting neurons of the VLPO and decrease VLPO neuron firing via presynaptic α 2ARs [19,50]. Wake-active DA neurons in the vPAG also project to the VLPO [51,52]. Importantly, these vPAG neurons express and are activated by α 1ARs [52,53]. These data have led us to propose a model in which modafinil blocks both DAT and NET, thereby increasing extracellular DA and NE, which then act downstream. We believe that the NE could promote wake in several different ways in parallel: (1) by providing excitatory input on wake-promoting DA neurons via α 1ARs, (2) by activating wake-promoting neurons in the hypothalamus via α 1ARs and β ARs, and (3) by providing inhibitory input onto sleep-promoting neurons in the hypothalamus (potentially via α 2ARs). The higher levels of NE may also be stimulating histamine neurons, as modafinil administration increases histamine release [54]. However, this is most likely a downstream effect, because modafinil does not appear to bind histamine receptors directly [55]. Many aspects of this model remain to be tested.

2.3. Caffeine

Caffeine is the most popular psychoactive substance in the world; 80% of the population reports regular use of caffeine. It is present in coffee, tea, chocolate, and sodas, as well as many over-the-counter remedies.

Animal studies have shown that caffeine dose-dependently increases wakefulness at the expense of slow-wave sleep, REM sleep, and total sleep time [56]. Much of caffeine's effects on sleep and arousal in humans have been self-reported, but there have also been some laboratory-controlled studies (reviewed in [57]). At doses equivalent to a single cup of coffee, caffeine has been found to increase latency to sleep and decrease total sleep time without affecting REM sleep. In a model of chronic caffeine administration, total sleep time was decreased over the course of the study, but some tolerance developed over time. In EEG studies, caffeine decreased slow-wave activity, consistent with “shallower” sleep. When compared with methylphenidate, caffeine had a greater effect on increasing sleep latency and reducing total sleep.

Caffeine is an antagonist for adenosine receptors, blocking the actions of adenosine, a purine that is synthesized throughout the brain. Levels of adenosine accumulate during wakefulness and decrease during sleep, especially in specific brain regions, such as the basal forebrain [58]. Adenosine's effects on sleep regulation are diffuse, and involve multiple neurotransmitter systems. It acts to inhibit wakefulness by decreasing the frequency of action potentials of orexin neurons, and also inhibits histamine release via excitation of GABA neurons in the TMN [59,60]. In parallel, it increases sleep by exciting a subset of neurons in the VLPO [61]. The effects of adenosine are mediated by four distinct G protein-

coupled receptors (GPCRs) (A1, A2A, A2B, and A3). Those receptors with the most convincing evidence for sleep involvement are the A1 and A2A receptors [58]. Caffeine is a selective antagonist of the A2A receptors, as studies in knockout (KO) mice have revealed that caffeine effectively increases wakefulness in A1 receptor KO mice, but has no effect on A2A receptor KO mice [62]. By preventing the binding of adenosine, caffeine blocks its sleep-promoting effects in the VLPO, and prevents its inhibition of wake-promoting effects on the histamine and orexin systems.

Caffeine is one of the rare stimulant-type drugs that does not appear to act through the noradrenergic system, and there is scant evidence of even an indirect role for NE. Indeed, *Dbh* $-/-$ mice lacking NE respond normally to caffeine [25]. Rather, caffeine prevents the actions of adenosine on other elements of the sleep regulatory system, such as histamine, orexin, and the GABAergic neurons of the VLPO.

3. Sleep-promoting medications

Just as there is an abundance of medications and treatments for conditions of excessive sleepiness, there are also many pharmacotherapies for insomnia. Insomnia is described as difficulty falling asleep, or maintaining good quality sleep. In the United States, between 10 and 30% of the general population reports experiencing insomnia, with serious daytime consequences for about half of them [63]. Insomnia can be either primary, or secondary to another disorder, such as stress, depression, or chronic pain. Furthermore, insomnia raises the risk for depression as much as 5-fold, and treating the insomnia itself can ameliorate depression and other psychiatric conditions [64]. Because insomnia can have such a profound impact on daily life, medications that treat it are a real boon for sufferers. These medications fall into several categories: benzodiazepines, benzodiazepine-related compounds, melatonin and melatonin receptor agonists, and medications intended for other uses that also affect sleep.

3.1. Benzodiazepines

Benzodiazepines were first developed as sedatives in the 1960s and quickly gained prominence with drugs such as chlordiazepoxide (Librium) and diazepam (Valium) [63]. These drugs were more effective as sedatives than the previously used class of compounds, the barbiturates, and had fewer side effects. Yet despite the more favorable side-effect profile, benzodiazepines do have the potential for tolerance and dependence, with side effects that include memory impairment and lingering drowsiness.

A rat EEG study compared the benzodiazepines etizolam (Sedekopan) and triazolam (Halcion) with the 5-HT receptor agonist tandospirone (Sediel), both acutely and chronically [65]. Acute administration of all three drugs was found to decrease sleep latency compared to vehicle control. Both etizolam and triazolam increased sleep and decreased wake, whereas tandospirone did not. When given chronically (daily injections for seven days), the benzodiazepines decreased sleep latency on each day. Following one day of drug withdrawal, the etizolam and triazolam groups had a significant increase in sleep latency over the baseline control, while the tandospirone group did not. Decreased sleep time and efficiency, resulting in feelings of withdrawal sleepiness, have also been reported in human benzodiazepine studies [66,67].

Benzodiazepines act as allosteric modulators of GABA-A receptors [68]. GABA-A receptors exist as heteropentamers, made up of two α subunits, two β subunits, and one γ subunit. The type and arrangement of subunits determine the function and binding properties of the receptor. Benzodiazepines bind to a site between α and γ subunits on receptors that possess γ 2 and either the α 1,

$\alpha 2$, $\alpha 3$, or $\alpha 5$ subunits. Because GABA-A receptors are located throughout the brain and benzodiazepines can act on multiple subtypes of GABA-A receptors, the specific location of benzodiazepine-induced sleep is difficult to determine. Benzodiazepines could be acting on receptors directly within the VLPO to promote sleep, or they could be acting more globally to facilitate inhibitory GABA transmission.

Increasing GABA transmission would be expected to have an inhibitory effect on NE transmission through wake-promoting pathways, thereby increasing sedation; indeed, administering midazolam to rats markedly decreases NE release in the prefrontal cortex (PFC) as measured by microdialysis [69]. When used as an anesthetic in humans, midazolam suppresses glucose utilization in the LC [70]. Radiolabeled flunitrazepam binds to benzodiazepine receptors in the LC of human brains, and LC neurons are inhibited by activation of GABA-A receptors [71,72]. The benzodiazepines chlordiazepoxide and diazepam decrease stress-induced release of NE [73,74]. However, chronic administration of diazepam increases firing of LC NE neurons, which could contribute to benzodiazepine withdrawal symptoms, similar to the role of noradrenergic neurons in opiate withdrawal [75]. In addition, administration of GABA-A antagonists into the LC significantly reduces REM sleep [76].

3.2. Benzodiazepine-related compounds

As mentioned above, benzodiazepines have several adverse effects, including memory impairment, lingering drowsiness, and potential for abuse. For these reasons, nonselective benzodiazepines have fallen out of favor in recent years, with the advent of more specific medications that have efficacy at targeting a particular type of benzodiazepine receptor.

Studies have revealed that the $\alpha 1$ subunit of the GABA-A receptor is especially important for benzodiazepine-induced sedation. For example, mice with mutations in the $\alpha 1$ subunit are insensitive to the sedative effects of the traditional benzodiazepine diazepam, but maintain sensitivity to its anxiolytic, myorelaxant, and motor-impairing functions, indicating that the sleep-promoting effects of benzodiazepines are primarily mediated by actions on the $\alpha 1$ subunit [77]. This led to a focus on finding selective drugs for this receptor subtype, and a new class of medications has been developed with selectivity for receptors containing the $\alpha 1$ subunit [77]. These are often referred to as the “z-drugs,” because they include zolpidem (Ambien), zaleplon (Sonata), zopiclone (Imovane), and eszopiclone (Lunesta). Zaleplon and zolpidem have much higher efficacy at benzodiazepine receptors containing the $\alpha 1$ subunit compared with other types of α subunits, whereas the traditional benzodiazepine triazolam lacks this specificity [78,79]. The principle differences between the z-drugs are their duration of action, and therefore their clinical indications [79]. Drugs with a longer duration of action, such as zopiclone, are used to induce and maintain sleep, while zaleplon, which has an extremely short duration of action, is used only to induce sleep. $\alpha 1$ subunits are the most widely distributed in the brain of all the α subunits, which makes localizing the brain regions responsible for the hypnotic properties of these drugs difficult [80]. As with the traditional benzodiazepines, z-drug effects on these receptors could involve the direct promotion of sleep via disinhibition of the VLPO, and receptor activation in the VLPO might be promoting sleep directly, or they could be acting more globally to increase inhibitory transmission throughout the brain.

The sleep-promoting effects of the z-drugs have been explored in both rodents and humans. Zaleplon and zopiclone produced a drowsy EEG pattern in rabbits, reminiscent of one produced by a canonical benzodiazepine [81]. Intravenously administered zale-

plon produced EEG spectra consistent with physiological sleep. Oral administration of zolpidem to rats reduced sleep fragmentation, causing fewer entries from slow-wave sleep into wakefulness, the same pattern seen with diazepam [82]. In a clinical trial with eszopiclone and zolpidem, patients reported comparable reduced latency to sleep and increased sleep efficiency [83]. Zolpidem not only increased slow-wave sleep at the expense of wakefulness, but also decreased REM sleep. During a withdrawal day after seven days of zolpidem, rats displayed increased shallow sleep, but reduced slow-wave sleep duration as measured by EEG. REM and active wake were unaffected during this withdrawal period. When zolpidem was readministered after a one-week washout period, its sleep-promoting activity was enhanced compared with the first week with zolpidem. When given to insomnia patients, zolpidem increased self-reported sleep efficacy and decreased time to sleep onset and number of wakings. It also improved sleep quality, and feelings of freshness after sleep [84]. Nonetheless, despite its efficacy at promoting sleep, there have been frequent reports of complex behaviors, such as sleep-eating, sleep-driving, and sleep-conversations, which occur without the patient's knowledge or remembrance after taking zolpidem [85].

While it is likely that benzodiazepines exert their anxiolytic and sedative effects via inhibition of wake-promoting brain regions, the exact role of their effects on the LC and NE transmission remain to be explored. $\alpha 1$ subunit-containing GABA-A receptors are expressed in the LC, and in fact are expressed to a greater degree in the LC in a rodent model of anxiety resilience [86]. Future experiments addressing the functional significance of these receptors in the LC could include examination of LC activity and NE release following administration of z-drugs, or assessment of the sleep-promoting effects of z-drugs in animals with LC lesions or NE depletion.

3.3. Melatonin and melatonin receptor agonists

Melatonin is an endogenous neuromodulator synthesized by the pineal gland, and its secretion is regulated by the SCN, the circadian pacemaker of the brain [87]. Secretion of melatonin is low during the day and high at night, and the onset of melatonin secretion coincides with the onset of nightly sleepiness. Exogenous melatonin crosses the blood–brain barrier, and various over-the-counter melatonin preparations are used to treat insomnia, jet lag, shift-work-related sleepiness, and delayed phase syndrome, with various degrees of effectiveness [88]. One reason melatonin is less effective than other regulated sleep treatments is its relatively short duration of action. However, there are now other medications, such as ramelteon (Rozerem) and agomelatine (Valdoxan), which target melatonin receptors with a higher affinity and longer half-life.

A number of animal studies have explored the effects of melatonin and melatonin receptor agonists on sleep. Because melatonin has different effects in nocturnal species compared with diurnal species, these studies are usually not performed in rodents. Melatonin is found to decrease locomotor activity and sleep latency in pigtail macaques, and also induces sleep during the day with an increase in slow-wave EEG activity in pigeons [89,90]. In a rat study, melatonin increased slow-wave sleep, the number of sleep cycles, and total REM sleep [91]. In humans, studies on melatonin efficacy are somewhat contradictory and depend on the outcomes measured (i.e., sleep quality, number of awakenings, sleep efficiency) and methodology (EEG recordings versus self-reports) (reviewed in [87]). In healthy volunteers, melatonin improved sleep efficiency versus placebo during the light period, as measured by EEG [92]. A range of doses of ramelteon decreased latency to sleep and increased total sleep time, without any effects the subsequent day [93]. In addition to its efficacy as an

antidepressant, agomelatine also subjectively improves sleep in depressed patients and decreases sleep latency, waking after sleep onset, and sleep stability, as measured by EEG [94].

Melatonin, ramelteon, and agomelatine are all agonists for melatonin 1 (MT1) and melatonin 2 (MT2) receptors [87]. Ramelteon has an affinity for both receptors that is 3–16 times greater than melatonin, and it has a longer half-life. Agomelatine also has a high affinity for melatonin receptors, in addition to acting as an antagonist at serotonin 5-HT_{2C} receptors to decrease anxiety as well as promote sleep. Both MT1 and MT2 play a role in sleep induction; MT1 activation suppresses firing of SCN neurons, and MT2 receptors are involved in entraining circadian rhythms. Melatonin and the SCN impact sleep and wake in several ways. The SCN receives light signals from the retina, which are transmitted to the dorsal medial hypothalamus (DMH). The DMH acts as a relay center for signals to regions involved in sleep and wake maintenance, including inhibitory inputs to the VLPO and excitatory inputs to the LC [14,95]. Melatonin acts through MT1 receptors to suppress firing of SCN neurons, thereby disinhibiting the sleep-promoting neurons in the VLPO, suppressing excitatory signals to wake-promoting regions, and increasing sleepiness [87].

NE has a reciprocal role in arousal states related to melatonin; it is one of the effector systems impacted by activation of melatonin receptors, and its activity controls the synthesis of melatonin [87]. There is dense innervation of the DMH by the SCN, and this nucleus acts as a positive relay between the SCN and the LC to increase wake [19]. Activation of MT1 receptors in the SCN by melatonin and melatonin receptor agonists decreases firing in these neurons, which suppresses wake drive. Additionally, NE is crucial for the synthesis of melatonin [87]. The SCN projects to the paraventricular nucleus, which then connects to the forebrain bundle and the reticular formation. Neurons from these areas synapse onto preganglionic sympathetic fibers of superior cervical ganglia. These fibers then release NE, which activates β -adrenergic receptors (β ARs) in the pineal gland to stimulate the production of cyclic AMP, which in turn promotes the synthesis of melatonin via PKA-mediated transcription. Melatonin secretion can be suppressed by β AR antagonists, thus increasing wake [96].

3.4. Antihistamines

The final classes of pharmacotherapies to be discussed includes those medications developed for other purposes that are also used to treat disorders of sleep and wake because of their actions on arousal systems. Although first-generation antihistamines were developed as anti-allergy medications and for motion sickness, due to their actions on histamine receptors they have considerable sedative effects. While newer generations of allergy treatments do not cross the blood–brain barrier and lack hypnotic effects, the first-generation antihistamines are still used over-the-counter for insomnia.

Antihistaminergics exert their sedative effects by antagonizing the H1 receptors in the brain. The H1 antagonist cyproheptadine (Periactin) is effective at increasing slow-wave sleep and REM sleep in rats [97], whereas the H1 antagonists diphenhydramine (Benadryl) and chlorpheniramine (Chlor-Trimeton) decrease sleep latency, but have no effect on amount of sleep. In humans, diphenhydramine initially increases subjective sleepiness and reduces latency to sleep compared with placebo, but after four days of administration, this effect is abolished, indicating tolerance to its effects [98]. Furthermore, on the first day after administration, performance on a battery of psychomotor tests was impaired when compared with placebo; this effect, too, was lost by the fourth day of diphenhydramine administration.

Because histamine from the TMN is part of the ascending arousal system, blocking its transmission would decrease wake,

and also prevent the inhibitory effects of these neurotransmitters on the sleep-promoting neurons of the VLPO. Since NE and histamine have reciprocal feedback and enhance each other's release, NE may be important for the sedative effects of antihistamines [99]. Interestingly, blockade of either α 1-adrenergic or histaminergic signaling attenuates the wake-promoting and anticonvulsant effects of modafinil, further indicating a potential interaction between these two neuromodulators [100,101].

3.5. Antidepressants

Although their first-line use is for the treatment of depression, antidepressants are also used off-label to treat insomnia. Depressed patients often suffer from sleep disturbances, and antidepressant therapy can ameliorate these disturbances; however, it is unclear whether this is a direct effect of the antidepressant on sleep, or whether the insomnia fades as mood improves [102]. On the other hand, antidepressants often have unwanted side effects on sleep and wakefulness, ranging from drowsiness to insomnia. Antidepressants are categorized by mechanism, and include tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), and others, which typically act through combinations of transporter and receptor blockade. These variations in mechanism lead to a range of effects on sleep (as reviewed extensively by [103]).

The effects of antidepressants on sleep are diverse, even within a class of medications. Sedation and drowsiness are common side effects of the TCAs (e.g., desipramine (Norpramine), imipramine (Tofranil), amitriptyline (Elavil)). Amitriptyline increases drowsiness and shortens sleep latency compared with placebo, whereas imipramine actually increases sleep latency and decreases total sleep time. MAOIs and SSRIs (e.g., fluoxetine (Prozac), sertraline (Zoloft), citalopram (Celexa)) can cause insomnia and decreased sleep efficiency. Compared with other antidepressants, fluoxetine is associated with significantly more fractured and less efficient sleep. Notably, all these classes of antidepressants suppress REM sleep to some degree.

Trazodone (Desyrel) is an antidepressant that is also commonly prescribed for insomnia [104]. In a study examining its effects on primary insomnia, trazodone improved self-reports of sleep latency, sleep duration, and decreased number of wakings. In another study, trazodone improved self-reports of sleep, but when measured by EEG, had no impact on sleep duration or sleep latency, with only a modest reduction in number of wakings. However, even trazodone has been shown to suppress REM sleep. Besides being observed in the clinic, animal models also show suppression of REM sleep following antidepressant administration [9].

Most antidepressants act through monoamine systems, though their specific mechanisms are variable, which may account for the diverse effects on sleep. Some TCAs are specific for NET blockade (e.g., desipramine), while others block both NET and SERT (e.g., imipramine). TCAs also have interactions with histamine, serotonin, and adrenergic receptors. SSRIs are specific for the SERT [103], whereas MAOIs interfere with monoamine metabolism. Trazodone, the most commonly prescribed antidepressant for insomnia, is a weak inhibitor of serotonin synaptosome reuptake and is also an antagonist at 5-HT_{1A}, 5-HT_{1C}, 5-HT₂, and α -adrenergic receptors [104]. The contribution of NE to these effects on sleep is not clear. Among the tricyclics, the NET-selective desipramine is the least effective at promoting sleep [103]. However, the dual NET–SERT inhibitor imipramine, which is also less effective at promoting sleep than other TCAs, decreases c-Fos in the LC [105]. In rats, antidepressants that act by inhibiting the NET, either alone or in combination with SERT, showed the highest amount of sleep disruption [9]. These seemingly paradoxical effects could be because

treatments that increase extracellular NE, such as NET blockers, increase availability not only at excitatory $\alpha 1$ ARs and β ARs, which would be expected to increase sleep, but also at $\alpha 2$ ARs, which act as inhibitory autoreceptors to decrease LC activity and NE release.

Interestingly, short-term sleep deprivation has antidepressant effects. While the mechanism of this is not yet clear, research indicates that it may be linked to NE from the LC (reviewed in [106]). Sleep deprivation increases the expression of a variety of genes, including brain-derived neurotrophic factor (BDNF) and its receptor TrkB, both of which are hypothesized to play a role in the antidepressant effects of sleep deprivation. However, if the LC is lesioned, the upregulation of these genes following sleep deprivation does not occur. Moreover, sleep deprivation increases LC firing and levels of extracellular NE. Behavioral studies should be conducted in the future to explore the impact of LC lesions on sleep deprivation as an antidepressant therapy.

3.6. Sedative effects of adrenergic drugs

While not typically prescribed for insomnia or other sleep disorders, many medications that suppress the adrenergic system have sedative side effects, lending further support for an essential role of NE in sleep pharmacology. Adrenergic receptor antagonists are most often used to decrease hypertension or treat congestive heart failure, but when these drugs cross the blood–brain barrier, neuropsychiatric effects can be seen [107]. Sedation and fatigue are among the most common side effects in patients taking β AR antagonists, $\alpha 1$ AR antagonists, and clonidine, an agonist for $\alpha 2$ AR inhibitory autoreceptors that attenuates NE release. Interestingly, prazosin is used to alleviate nightmares in post-traumatic stress disorder patients [108], potentially by acting as a dual anxiolytic and sedative.

4. Summary

Sleep disorders of both insomnia and excessive sleepiness present major public health problems, making medications that can successfully treat these disorders without side effects most valuable. Sleep is regulated by multiple neurotransmitter systems, and pharmacotherapies act on many aspects of its regulation to treat various disorders. Wake-promoting medications frequently act by increasing transmission along an ascending arousal pathway, whereas sleep-promoting medications typically inhibit this pathway through neurons in the VLPO, the main sleep-promoting nucleus in the brain. New sleep-promoting treatments are targeting the circadian pathway instead of the homeostatic pathway, and acting as agonists for melatonin receptors.

A common thread in the mechanism of action of many sleep pharmacotherapies is NE. A pictorial representation integrating and summarizing the anatomical connections between noradrenergic neurons and the wake- and sleep-promoting systems, as well as potential sites of action of wake- and sleep-promoting drugs, is depicted in Fig. 1. For example, amphetamine directly induces release and blocks reuptake of NE, increasing its extracellular concentration and activating the ascending arousal pathway. And though the mechanism of modafinil has not been determined conclusively yet, its actions are blocked by $\alpha 1$ AR antagonists, and there is some evidence that it may act as a NET inhibitor. In contrast, caffeine is one wake-promoting agent that does not appear to have a significant adrenergic component. On the other end of the sleep/wake spectrum, both benzodiazepines and z-drugs act to increase GABA transmission, resulting in inhibition of excitatory signals along arousal pathways, including those from the LC. NE is also involved in the synthesis of melatonin, and thus may help to regulate the circadian as well as the homeostatic sleep processes. Finally, most antidepressants,

including those used as insomnia treatments, affect the adrenergic system.

The diversity of the mechanisms of these drugs demonstrates the breadth of transmitter systems involved in sleep regulation. One obstacle to developing effective treatments for sleep disorders is that all these neurotransmitters are crucial for numerous biological processes in addition to sleep, and enhancing or inhibiting their activity often leads to a number of unpleasant or even dangerous side effects. However, as we learn more about how to differentiate the effects on arousal from other systemic effects, we may be able to develop increasingly specific medications that target the arousal system more directly, just as the z-drugs were developed when the specific $\alpha 1$ subunit of the benzodiazepine receptor was revealed as the primary mediator of benzodiazepine-induced sedation. And while the z-drugs have a much-improved safety profile over the benzodiazepines, there still is considerable room for further drug development. This type of specific targeting of receptor subtype or more specific anatomical localization may provide the key to developing safer and more effective medications to treat disorders of the arousal system.

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