What Keeps Us Awake: the Neuropharmacology of Stimulants and Wakefulness-Promoting Medications

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Abstract: Numerous studies dissecting the basic mechanisms that control sleep regulation have led to considerable improvement in our knowledge of sleep disorders. It is now well accepted that transitions between sleep and wakefulness are regulated by complex neurobiologic mechanisms, which, ultimately, can be delineated as oscillations between two opponent processes, one promoting sleep and the other promoting wakefulness. The role of several neurotransmitter or neuromodulator systems, including noradrenergic, serotonergic, cholinergic, adenosinergic, and histaminergic systems and, more recently, the hypocretin/orexin and dopamine systems, has been clearly established. Amphetamine-like stimulants are known to increase wakefulness by blocking dopamine reuptake, by stimulating dopamine release, or by both mechanisms. Modafinil may increase wakefulness through activation of noradrenergic and dopaminergic systems, possibly through interaction with the hypocretin/orexin system. Caffeine inhibits adenosinergic receptors, which in turn can produce activation via interaction with GABAergic and dopaminergic neurotransmission. Nicotine enhances acetylcholine neurotransmission in the basal forebrain and dopamine release. Understanding the exact role of the hypocretin/orexin and dopamine systems in the physiology and pharmacology of sleep-wake regulation may reveal new insights into current and future wakefulness-promoting drugs.

Key Words: stimulant, wake-promoting medication, sleepiness, cocaine, amphetamine, methylphenidate, modafinil, caffeine, nicotine

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INTRODUCTION

DISCOVERING TREATMENTS TO FIGHT EFFICIENTLY AGAINST EXCESSIVE DAYTIME SLEEPINESS IS A CHALLENGE FOR BOTH SLEEP MEDICINE AND BASIC SCIENCE. Indeed, sleep disorders are increasingly prevalent, and their association with significant morbidity has become a public health concern.[1] Numerous disorders and diseases lead to excessive somnolence, but 80% of individuals who present with these symptoms have sleep apnea, narcolepsy, or idiopathic hypersomnia.[2] Many people with these disorders find controlling excessive sleepiness to be crucial to maintaining the ability to interact in their social, professional, and family lives. Primary treatments for sleepiness associated with these disorders are based on psychomotor stimulants, which are known for exerting an efficient wake-promoting effect. However, their high potential for abuse and side effects represent a limitation for their prescription and use. For the last decade, modafinil has become an increasingly popular wake-promoting medication used for the treatment of narcolepsy because little or no addiction potential has been shown with the consumption of this compound.

Interestingly, problems of excessive daytime sleepiness are not exclusively linked to sleep disorders or diseases. In industrial societies, work efficiency and productivity have become a primary goal that has contributed to mass consumption of psychostimulants, the wake-promoting properties of which allay fatigue and enhance attention, sometimes to counterbalance excessive nighttime wakefulness. Amphetamine and cocaine consumption are marginal compared to caffeine and nicotine, considered as the most widely consumed psychostimulants in the world. The impact of the intake of these psychoactive substances on public health is a growing concern that should not be underestimated.

The aim of this review is to summarize the neuropharmacology of the most commonly used stimulants and wake-promoting medications by examining their effects on sleep, molecular and cellular mechanisms of action, and undesirable side effects. To comprehend the molecular and cellular aspects of this review, a succinct presentation of basic sleep-waking mechanisms is necessary. Briefly, sleep-waking regulation involves reciprocal interactions between two opponent processes, one promoting arousal and inhibiting sleep, and the other promoting sleep and inhibiting wakefulness. Wake-promoting agents act through different mechanisms, but ultimately they all stimulate the waking system, slow down the sleep-promoting system, or both. Neuropharmacologic mechanisms for the wake-promoting effects of stimulants then will be discussed with a focus on interactions with wake- and sleep-promoting systems. Finally, the role of dopamine in promoting arousal associated with the use of psychostimulant drugs will be explored, and particular attention will be given to other mechanisms of action that could lead to new wake-promoting treatments in the near future.

PHYSIOLOGIC BASIS OF SLEEP-WAKE REGULATION

The Monoaminergic and Cholinergic Control of Sleep

An early report of a wake-promoting system appeared with the description of a brainstem-ascending reticular-activating system that regulates the level of forebrain wakefulness.[3] Wakefulness currently is described as the expression of a complex neuronal network[4,5] characterized by electroencephalogram desynchronization. The waking executive network is composed of two pathways, both originating from the midbrain reticular formation and mainly composed of glutamatergic neurons, the electrophysiologic activity of which depends on cholinergic and monoamin-

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ergic tone. One of these pathways innervates the thalamus, and the other extends to the hypothalamus and basal forebrain (Figure 1). The primary origin of the thalamic projection from the brainstem has been identified as the cholinergic pedunculopontine and laterodorsal tegmental nuclei. Three structures can be considered as key relays between the midbrain reticular formation and the cortex: the posterior hypothalamus, thalamus, and basal forebrain.[6] In this model, cholinergic projections to the thalamus are crucial to electroencephalogram activation, complementing cholinergic projections from the basal forebrain to the cortex that are involved in the maintenance of arousal.[7] The synchronization of thalamocortical circuits results in the expression of sleep spindles or slow-wave activity during so-called slow-wave sleep. These sleep spindles are considered to be essential to blocking sensory input during sleep.[4,5] Sleep oscillates between rapid eye movement (REM) sleep, and light and deep slow-wave sleep, also referred to as non-REM sleep. The regulation between these two sleep-states has been attributed to reciprocal monoaminergic-cholinergic interactions in the brainstem.[8-10] In this model, serotonergic (in the dorsal raphe nuclei), noradrenergic (in the locus coeruleus), and histaminergic (in the tuberomammillary nucleus) neurons fire fastest during wakefulness, slow down during non-REM sleep, and nearly stop firing entirely during REM sleep. In contrast, brainstem cholinergic activity (in the laterodorsal/pedunculopontine tegmental nuclei) is high during wakefulness and REM sleep (Figures 1 and 2).

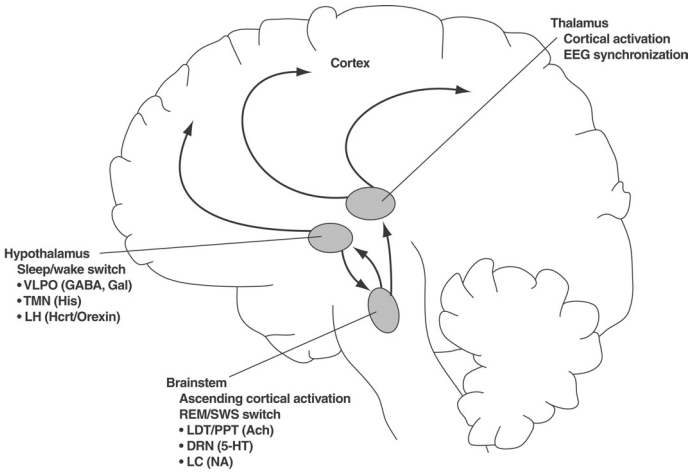

Figure 1—Vigilance is orchestrated by the ascending arousal system, which projects from the brainstem to the thalamus and the hypothalamus, two key structures dispatching the cortical activation. The hypothalamus is considered to be the sleep/wake switch where reciprocal interactions between opponent processes (one promoting waking, the other promoting sleep) regulate the oscillation between sleep and wakefulness. The thalamus relays sensory input from the brainstem to the cortex during wakefulness. When inhibitory influences dissipate, sleep spindles appear and block sensory input during sleep. Neurons of the laterodorsal tegmental nucleus and pedunculopontine tegmental nucleus (LDT/PPT), those of the dorsal raphe nucleus (DRN) and those of the locus coeruleus (LC) send cholinergic (Ach), serotonergic (5-HT) and noradrenergic (NA) fibers, respectively. Neurons of the tuberomammillary nucleus (TMN) and those of the lateral hypothalamus (LH) send histaminergic and hypocretinergic fibers, respectively, to maintain arousal. Sleep-waking neurons of the ventrolateral preoptic nucleus (VLPO) contain GABA and galanin. EEG refers to electroencephalogram.

The Hypothalamus: A Key Structure Regulating the Switch Between Sleep and Wakefulness

The importance of the preoptic hypothalamus in the generation of slow-wave sleep has long been recognized. Electrophysiologic recordings have identified slow-wave sleep-active neurons in this area where lesions produce insomnia in animals and humans. More recently, it has been shown that a subgroup containing γ-aminobutyric acid (GABA)-ergic and galaninergic cells in the ventrolateral preoptic area (an anterior hypothalamic cell group) projects to all monoaminergic systems,[11] and especially to the tuberomammillary nucleus, a posterior hypothalamic cell group.[12] The relationship between the ventrolateral preoptic area and the major monoamine groups appears to be reciprocal. The ventrolateral preoptic area is innervated by histaminergic axons from the tuberomammillary nucleus and receives inhibitory inputs from noradrenergic, serotonergic, and cholinergic waking systems.[13] When neurons in the ventrolateral preoptic area fire rapidly during sleep, they inhibit monoaminergic cell groups, thus disinhibiting and reinforcing their own firing. Conversely, when monoamine neurons fire at a high rate during wakefulness, they inhibit the ventrolateral preoptic area, thereby disinhibiting their own firing (Figure 2). To summarize, sleep-waking regulations are orchestrated by reciprocal interactions between wake- and sleep-promoting neurons that inhibit each other.[6]

The Hypocretins/Orexins: A System That Orchestrates Arousal

Since their discovery[14,15] hypocretin/orexin peptides have been implicated in sleep-wake regulation, energy homeostasis, and

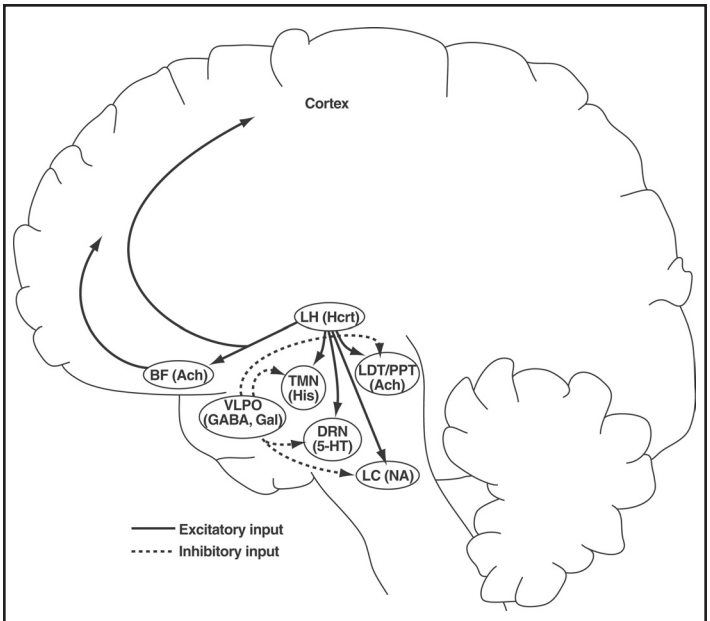

Figure 2—Hypocretin neurons in the lateral hypothalamus project to the main components of the ascending arousal system and participate in wakefulness consolidation. Neurons from the ventrolateral preoptic nucleus innervate also the same structures. Switching off the arousal system is a critical step before sleep can be induced. Abbreviations: BF, basal forebrain; Ach, acetylcholine; LH, lateral hypothalamus; Hcrt, hypocretin; VLPO, ventrolateral preoptic nucleus; GABA, γ-aminobutyric acid; Gal, galanin; TMN, tuberomammillary nucleus; His, histamine; LDT/PPT, laterodorsal tegmental and pedunculopontine tegmental nuclei; DRN, dorsal raphe nucleus; 5-HT, serotonin; LC, locus coeruleus; NA, noradrenaline.

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neurocrine and cardiovascular function.[16] Their wide projection in the brain[17] and their interaction with autonomic, neuroendocrine, and neuroregulatory systems[18-25] strongly suggest they act as neuromodulators in a wide array of neural circuitry. They also have been implicated in the modulation of noradrenergic,[20,26-28] cholinergic,[29] serotonergic,[30,31] histaminergic,[32] and dopaminergic systems,[33,34] as well as in the regulation of the hypothalamic-pituitary-adrenal axis.[35-37] A key contribution in the etiology of narcolepsy was provided by several studies linking the hypocretin/orexin system to this disease. First, two different animal models with an impaired hypocretin/orexin system—genetic narcoleptic dogs with a mutation in the Hcrt receptor 2 gene,[38] and mice with a null mutation of the prepro-hypocretin gene that produces Hcrt-1 and Hcrt-2 peptides[39]—showed symptoms of narcolepsy, suggesting that impairment of the hypocretin/orexin system may underlie the syndrome of human narcolepsy. It then was confirmed that human narcoleptic patients exhibit a drastic reduction (85%-95%) in hypocretin-1 in the cerebrospinal fluid[40] and in the number of hypocretin neurons,[41,42] leading to the hypothesis that narcolepsy could be related to ongoing loss of hypocretin neurons.[43] In the current models, the hypocretin/orexin system stabilizes the firing of brainstem neurons that control wakefulness and REM sleep (cholinergic in the laterodorsal/pedunculopontine tegmental nuclei, noradrenergic in the locus coeruleus, serotonergic in the dorsal raphe nucleus, and histaminergic in the tuberomammillary nucleus; Figure 2). Interestingly, hypocretins also have a strong and direct excitatory effect on the cholinergic neurons in the basal forebrain that contribute to cortical arousal, but they have no effect on GABA sleep-promoting neurons within the ventrolateral preoptic area.[44] Furthermore, the arousal effect of the hypocretin-1 neuropeptide seems to depend on activation of the histaminergic system.[45] In conclusion, the hypocretin/orexin system may be considered as a key regulator that integrates sensory inputs and orchestrates the arousal threshold.[16] Absence of hypocretin/orexin peptides or specific components of their signaling system may cause destabilization of the boundaries between sleep states that are found in narcolepsy.

Adenosine: Mediator of Sleepiness After Prolonged Wakefulness

The sedative properties of adenosine were first studied during the 1950s in the cat and were confirmed in the dog 20 years later,[46] without eliciting any appreciable scientific interest. Attention returned to adenosine when it was established during the early 1980s that caffeine was able to bind to adenosine receptors and therefore block its endogenous action.[47] Currently, it is a well-accepted hypothesis that adenosine acts as a mediator of non-REM sleep.[48,49] Indeed, adenosine is derived from the breakdown of adenosine triphosphate,[50] the main cellular energetic reserve in nervous tissue. During prolonged arousal, cerebral activity leads to the consumption of adenosine triphosphate and a concomitant adenosine accumulation.[51-53] Extracellular concentration of adenosine doubles in the basal forebrain after sleep deprivation and returns to baseline upon sleep recovery.[54] Adenosine A_1 receptor density also doubles with prolonged arousal.[55] Adenosine binds to A_1 receptors on cholinergic neurons in the basal forebrain, decreasing the firing of these neurons,[56] thereby contributing to a reduction of cortical arousal. Adenosine also may decrease GABAergic neuronal activity within the same area, disinhibiting neurons in the preoptic/anterior hypothalamus that promote sleep.[48,57] Thus, the transition from wakefulness to slow-wave sleep could be promoted by the accumulation of adenosine within the forebrain, leading to (1) the inhibition of cholinergic neurons that activate cortical arousal and (2) the inhibition of GABAergic neurons projecting to the preoptic/anterior hypothalamus and inhibiting sleep-promoting neurons there.

Dopamine: A Potential Role in Arousal?

Multiple neurotransmitters—noradrenaline, serotonin, acetylcholine, histamine, adenosine, and hypocretin/orexin—have been studied closely for their relationship to the behavioral arousal state (see above). In contrast, the role assigned to dopamine in sleep-wake regulation has been relatively limited, mainly because the dopamine neuron firing rate varies little between sleep and wake states.[58,59] However, lesions of dopamine cell groups in the ventral tegmentum that project to the forebrain have been shown to induce a drastic reduction in behavioral arousal in rats,[60] and patients with Parkinson disease, who exhibit consistent dopamine lesions, experience severe sleep disorders.[61,62] More recently, dopamine D_1 and D_2 receptors have been clearly implicated in the induction of hyperarousal,[63] and the existence of sleep-state-dependent dopaminergic neurons have been reported in the ventral periaqueductal gray.[64] Interestingly, it has been shown that dopamine neurons in the primate fire in response to salient events in the environment, particularly those that predict reward.[65-67] Finally, it has been suggested that presynaptic activation of dopamine transmission is a key pharmacologic property mediating the wake-promoting effects of stimulants.[68,69] Therefore, despite a complex pattern, there is growing evidence that emphasizes dopamine's role in arousal.

The accurate role of dopamine release in the neuropharmacology of wake-promoting agents remains unclear; however, the aim of this review is to point out that, despite partially different mechanisms of action, the most powerful stimulant agents (ie, amphetamine-like stimulants) as well as those that are thought to possess a nondopaminergic mechanism of action (eg, modafinil, caffeine, nicotine), all have in common the property of inducing dopamine release.

AMPHETAMINE-LIKE STIMULANTS

Introduction

Psychomotor stimulants are drugs that produce behavioral activation, usually accompanied by increases in arousal, motor activity, and alertness. One of the most commonly known psychostimulants, cocaine, is derived from the coca plant (*Erythroxylon coca*) and has a long history as a stimulant. It has been used for centuries in tonics and other preparations to allay fatigue.[70,71] One class of stimulants, amphetamines, was synthesized originally as possible alternative drugs for the treatment of asthma and was the principal component of the original benzedrine asthma inhaler. They were used (and are still used) by the United States military as antifatigue medications, and they currently are legally available for medical use as adjuncts for short-term weight control, in attention-deficit/hyperactivity disorder, and in narcolepsy. Oral and intravenous doses of amphetamines increase systolic and diastolic blood pressure and stimulate heart rate, although high doses may induce a reflex slowing of the heart rate.

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Amphetamines produce bronchial and pupillary dilation as well as decreases in glandular secretion, all effects observed after activation of the sympathetic nervous system. Beneficial effects reported include increased alertness, improved coordination, increased strength and endurance, and increased mental and physical activation, with mood changes of boldness, elation, and friendliness.[72] The nature of the stimulant effects of cocaine and amphetamines depends on the route of administration. Intravenous (8-16 mg of cocaine, 10 mg of D-amphetamine) or inhaled freebase preparations (30 to 50 mg) produce marked, intense, pleasurable sensations characterized as a "rush" that has been likened to sexual orgasm and is thought to be a powerful motivation for the abuse of these drugs. Intranasal doses of 20 to 30 mg of cocaine also produce euphoria, increased confidence and talkativeness, a sense of well-being, and fatigue reduction for approximately 30 minutes. Cocaine has less powerful effects administered orally, presumably due to a markedly slower absorption. Intranasal or oral administration of D-amphetamine in the dose range of 2.5 to 15 mg produces stimulant effects similar to those of cocaine. Intranasal absorption is faster with more intense effects than oral administration, and the stimulant effects of amphetamines last considerably longer than those of cocaine (up to 4 to 6 hours).

Amphetamine has a relatively long half-life, in the range of 8 to 16 hours.[73] Cocaine is rapidly metabolized; its half-life ranges from 48 to 75 minutes.[74] Methylphenidate, an indirect sympathomimetic commonly used for the treatment of narcolepsy,[2] decreases fatigue but not appetite as much as D-amphetamine, and has a half-life of 2 to 4 hours.[75]

Effects on Sleep

Amphetamine-like stimulants are known and consumed especially for their activity-sustaining effects (increased alertness, strength, and endurance). Their wake-promoting properties are obvious, but objective studies have clearly established their effects on sleep. In rats, cocaine (6 mg/kg, orally and intraperitoneally administered) has been shown to induce a significant increase in sleep latency and a reduction in total sleep time, including a decrease in both slow-wave sleep and REM sleep.[76] In humans, cocaine, amphetamines, and methylphenidate also produce decreases in sleepiness, an increased latency to sleep, and a drastic decrease in REM sleep associated with an increased latency to the onset of this particular vigilance state.[77-80]

Molecular and Cellular Action of Amphetamine-like Stimulants in the Brain

Amphetamine, methylphenidate, and cocaine are known to act neuropharmacologically by enhancing the amount of monoamines available within the synaptic cleft of monoamine synapses in the central nervous system. They block the reuptake and also enhance the release of norepinephrine, dopamine, and serotonin.[81-85] There is considerable evidence suggesting that the primary neuropharmacologic action responsible for their psychostimulant effects is on the dopamine system in the central nervous system.[86,87]

The brain dopamine system can be divided into two major pathways that originate in the midbrain and project to the forebrain and appear to be responsible for different aspects of psychomotor stimulant actions. The mesocorticolimbic dopamine system originates in the ventral tegmental area and projects to the ventral forebrain, including the nucleus accumbens, olfactory tubercle, septum, and frontal cortex. The nigrostriatal dopamine system arises primarily in the substantia nigra and projects to the corpus striatum and represents 80% of brain dopamine. Whereas the mesocorticolimbic dopamine system has been hypothesized to be involved in incentive motivational processes and in the reinforcing properties of psychostimulants,[88-90] the nigrostriatal dopamine system has been primarily involved in the elaboration and control of movements. Degeneration of the latter dopamine system is at the origin of the severe motor disturbances of Parkinson disease, including tremor, dystonic involuntary movements, and akinesia.[91]

At the molecular level, several different dopamine receptors have been identified both by pharmacologic and molecular biologic techniques.[92] Five dopamine receptors have been cloned[93-96] and to date, D_1,[97] D_2,[98,99] D_3,[100] D_4,[101] D_5[102,103] and dopamine transporter (DAT)[104-107] knockout mice exist and have been subjected to challenges with psychomotor stimulants. D_1, D_2, and DAT-mutant mice, but not D_3 and D_4 knockout mice, show a blunted response to psychostimulants, the latter ones exhibiting supersensitivity to psychostimulants. All the mutant mice are hyperactive, but D_2 knockouts also exhibit severe motor deficits. Low doses of D_1 and D_2 dopamine-receptor antagonists[108] and intravenous cocaine self-administration[109] potently block amphetamine-induced locomotion. It has been shown that while D_2 dopamine-receptor activation is not necessary for the induction of locomotor sensitization to amphetamine, D_1 dopamine receptors located in the ventral tegmental area play a critical role in the development of behavioral sensitization.[110,111] In line with this observation, it has been reported that the overall locomotor responses to cocaine and amphetamine administration of D_1-receptor mutant mice were significantly reduced compared to those of wild-type mice.[112]

The exact mechanisms by which amphetamine-like stimulants induce their wake-promoting effects remain to be elucidated. The participation of noradrenergic mechanisms has been suggested to explain such effects on sleep[113,114]; nevertheless, the wake-promoting effect of amphetamine is maintained after severe reduction of brain norepinephrine.[115] It has been demonstrated recently that amphetamine-like compounds require the DAT for their wake-promoting effects, given that DAT knockout mice were totally insensitive to the wake-promoting properties of classical stimulants.[116] Thus, amphetamine-like drugs may promote wakefulness primarily by increasing dopaminergic tone. Accordingly, it has been found that intracerebroventricular infusion of D_1 and D_2 dopamine-receptor agonists in sleeping rats induces a dose-dependent increase in waking time measured by electroencephalographic and electromyographic indexes of arousal.[63] A recent study has shown that amphetamine infusions directly within basal forebrain sites initiate and maintain alert waking by involving most likely a participation of norepinephrine, dopamine, and serotonin neurons in a region of the medial basal forebrain encompassing the medial septum/nucleus accumbens shell and the preoptic area of the hypothalamus.[117] Interestingly, this site appeared to be distinct from sites previously associated with amphetamine-induced locomotion. Finally, considerable evidence has shown that acute psychostimulant administration

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produces a stress-like activation of the hypothalamic-pituitary-adrenocortical axis,[118] leading to increased plasma corticosterone in rats and plasma cortisol in humans, both known to promote wakefulness.[119,120]

Undesirable Side Effects

Amphetamines and cocaine have high abuse potential and are now well documented to produce substance dependence (addiction) by most modern definitions.[121] However, most users (85%) do not become addicted to the drug.[122,123] Indeed, estimates of stimulant abuse in patients being treated for sleep disorders are low. Clinical observations indicate that controlled use often shifts to more compulsive use, either when there is increased access to the drug or when a more rapid route of administration is employed. Compulsive use results in an exaggeration of the binge stage, with chronic intake of the drug every 10 minutes, usually lasting for an average of 12 hours, and sometimes for up to 7 days. Following a binge, the abstinence syndrome has been characterized by an exaggeration of the dysphoria stage and consists of major decreases in mood and motivation, including limited interest in the environment and a limited ability to experience pleasure.[121,124]

High doses of amphetamines and cocaine also can lead to significant behavioral pathologic behaviors. Amphetamine abusers show stereotyped behaviors in which they persist in repetitive thoughts or acts for hours (repetitively cleaning the home or items such as a car, bathing in a tub all day, endlessly dismantling or putting back together small objects such as clocks or radios, and so on). Amphetamines also are well documented to produce paranoid psychotic episodes in chronically abusing individuals, or even by taking large doses acutely.[70] In a study of otherwise healthy volunteers, repetitive oral administration of 5 to 10 mg of D-amphetamine produced paranoid delusions, often with blunted affect in all subjects when a cumulative dose range of 55 to 75 mg was reached.[125] This paranoid psychosis induced by stimulants in its severest form can produce actual physical toxicity in which subjects believe that bugs under their skin need to be gouged out ("crank bugs"). This stereotyped behavior and psychosis associated with high-dose stimulants may also contribute to the cycle of abuse associated with these drugs.

Nevertheless, psychosis and hallucinations are rare in narcoleptics treated with stimulants, and the reported frequency of side effects of stimulants in clinical practice and in clinical trials, although extremely variable, has shown limited perturbations, including notably headaches, irritability, nervousness or tremors, anorexia, insomnia, gastrointestinal complaints, dyskinesias, and palpitations.[2]

Summary

Amphetamine-like stimulants promote wakefulness by enhancing the amount of dopamine available within the synaptic cleft of dopamine synapses in the central nervous system. An extended region of the medial basal forebrain, demarcated anteriorly by the anterior portion of the medial septal area and posteriorly by the posterior fraction of the preoptic area of the hypothalamus has been hypothesized to be a possible candidate to explain the action of amphetamines to initiate and maintain alertness. Whether or not other systems (eg, norepinephrine, serotonin, or the hypothalamus-pituitary-adrenal axis) could participate in these wake-promoting effects is still a matter of debate, but clearly amphetamine-like compounds require the DAT for their wake-promoting effects.

MODAFINIL

Introduction

Management strategies for daytime sleepiness traditionally have included lifestyle changes and the use of psychostimulants (amphetamine, methylphenidate, pemoline) which have been shown to efficiently enhance arousal.[2] Despite this efficacy, some patients or physicians may not be satisfied with psychostimulant therapies, usually because of tolerance or, more often, adverse events. For the last decade, modafinil has become a first-line wake-promoting medication and a useful therapeutic alternative to psychostimulant medications for the treatment of excessive daytime sleepiness.[126-129] Modafinil-mediated wake promotion initially was reported to be the result of central α_1-adrenoceptor stimulation,[130] but recent studies have linked this stimulant effect to the selective activation of hypothalamocortical pathways (see below) involved in the physiologic regulation of sleep and wakefulness.[131] Modafinil is not a direct or indirect dopamine-receptor agonist[132-134] and has a low potential for abuse.[135-138]

Effects on Sleep

It has been shown that modafinil prolongs wakefulness in several species, apparently without associated behavioral excitation, and its waking effect is not followed by any obvious sleep rebound in the cat.[130,133,139,140] In humans, modafinil is efficient and well tolerated,[141] with no evidence of tolerance developing during 40 weeks of treatment.[142] Nevertheless, a study based on maintaining alertness and performance during sleep deprivation has shown equivalent performance- and alertness-enhancing effects after a single dose of either modafinil or caffeine, leading to the conclusion that modafinil does not appear to offer advantages over caffeine (which is more readily available and less expensive) for improving performance and alertness during sleep loss in otherwise normal, healthy adults.[143]

Molecular and Cellular Action of Modafinil in the Brain

The wake-promoting mechanism of action of modafinil remains uncertain, despite numerous reports of its neuropharmacologic action in the brain. Early studies highlighted the absence of an interaction between modafinil and the dopamine system.[132,134,144] It also was established that the dopamine D_1/D_2 antagonist haloperidol did not block the arousal effect of modafinil, whereas it consistently decreased the amphetamine-induced increase in wakefulness.[133] Finally, modafinil showed a low affinity for dopamine reuptake sites.[145] It has been suggested, therefore, that the arousal effects of modafinil could be related to noradrenergic neurotransmission, given that the arousal produced by modafinil was blocked by α_1 and ß adrenergic receptor antagonists,[133] and that modafinil affected the firing of locus coeruleus noradrenergic neurons.[132] Using c-Fos immunocytochemistry in cats, it has been shown that amphetamine and methylphenidate do not share with modafinil the same pattern of c-Fos activation in the brain.[146] Indeed, whereas the use of

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amphetamine and methylphenidate induced labeled neurons mainly in the cortex and the striatum, modafinil-induced wakefulness was associated mainly with activated neurons in the anterior hypothalamus, emphasizing therefore that modafinil induces wakefulness by mechanisms distinct from those of amphetamine and methylphenidate. Despite a confirmation of c-Fos immunoreactivity in the anterior hypothalamus in modafinil-treated rats,[147] a recent study involving c-Fos labeling in modafinil-treated rats highlighted Fos activation mainly in the tuberomammillary nucleus and in hypocretin/orexin neurons of the perifornical area (and to a lesser extent, in the central nucleus of the amygdala, the striatum, and the cingulate cortex).[131] Thus, these authors concluded that modafinil may exert its stimulant effects via an activation of these two regions implicated in the promotion of normal wakefulness.

However, modafinil is efficient in promoting wakefulness even in narcoleptic patients, whereas it has been demonstrated that narcoleptic patients exhibit a drastic reduction in hypocretin-1 in the cerebrospinal fluid[40] and in the number of hypocretin neurons.[41,42] Such a discrepancy might be explained by the fact that modafinil may also generate waking by increasing both dopaminergic and serotonergic neurotransmission in the cortex, and by increasing noradrenergic release in the hypothalamus.[148] An early study had also suggested that modafinil could induce dopamine release in the rat nucleus accumbens, but this study did not demonstrate a role for dopamine release per se in the waking effect of modafinil.[149] Finally, using DAT-knockout mice, it has been reported recently that both amphetamine-like compounds and modafinil require the DAT for their wake-promoting effects,[116] leading one to question the hypothesis that modafinil does not exert its waking effects via the dopaminergic system and that modafinil induces wakefulness by mechanisms distinct from those of amphetamine. Interestingly, it has been shown that both hypocretin/orexin and amphetamine act within the basal forebrain to promote waking and suppress sleep.[117,150] It therefore can be hypothesized that both the hypocretin/orexin and dopaminergic systems act in concert in the basal forebrain to promote wakefulness, but further studies are needed to clarify this hypothesis.

Undesirable Side Effects

No obvious side effects have been observed in the usual range of use and prescription of modafinil (200 mg/day), leading several authors to suggest switching patients to modafinil from psychostimulants such as methylphenidate.[151] Though it has been shown that modafinil was able to affect mood in humans,[152-154] modafinil does not appear to possess any addiction potential in drug-naive individuals. It has been suggested from studies with animal models that modafinil possibly could have reinforcing effects in cocaine-experienced individuals. Nevertheless, the reinforcing and discriminative stimulus effects of modafinil required very high doses (up to 256 mg/kg intraperitoneally in rats), and modafinil was more than 200 times less potent than D-amphetamine.[155,156]

Summary

Modafinil is an increasingly popular wake-promoting medication used for the treatment of narcolepsy due to its safety profile and given that no obvious side effects have been reported. The main advantage of modafinil over amphetamine-like stimulants is that this compound does not possess any addiction potential, although growing evidence shows that its mechanism of action in the brain may involve more interaction with some component of the dopaminergic system than has been thought for the last decade.

CAFFEINE

Introduction

Caffeine is the most widely consumed psychoactive substance in the world.[50,157] As a component of tea, coffee, and soft drinks, caffeine is the most commonly ingested methylxanthine. Caffeine consumption per capita in the United Kingdom, Sweden, and Finland is estimated to be between 100 and 400 mg per person per day, with peak consumption, where caffeine intake comes predominantly from tea and coffee, respectively. Peak plasma caffeine is reached between 15 and 120 minutes after oral ingestion in humans at doses of 5 to 8 mg/kg. The caffeine half-life for these corresponding doses ranges from 0.7 to 1.2 hours in rodents, 3 to 5 hours in monkeys, and 2.5 to 4.5 hours in humans.

Effects on Sleep

There is consensus that caffeine produces an enhanced vigilance performance on psychomotor tasks[158] and concomitant negative side effects on sleep, particularly when taken at bedtime. Generally, more than 100 to 150 mg of caffeine is needed to significantly affect sleep.[159] The most prominent effects are prolonged sleep latency, shortened total sleep time with increases in the light sleep stages at the expense of the later deep ones and REM sleep, numerous shifts between sleep stages, and even agitation with higher doses.[160-162] Electroencephalographic studies have shown that sleep is of a lesser quality in the 3 to 4 hours following ingestion of caffeinated coffee, which corresponds to the time required for the liver to metabolize caffeine. It has been suggested that subjects who are sensitive to the side effects of coffee might metabolize caffeine more slowly than others.[163] However, some people seem to have no sleep troubles despite drinking regular evening coffee, which could be attributed to tolerance to its psychoactive effects. In rats, caffeine (12.5-25 mg/kg) decreases the overall duration of sleep and lengthens sleep latency,[164,165] whereas when chronically administered to cats (20 mg/kg), caffeine initially shortens the total sleep duration, but then sleep amounts returned to baseline with repeated exposure.[166]

Molecular and Cellular Action of Caffeine in the Brain

Although caffeine is known to mobilize intracellular calcium, to inhibit phosphodiesterase activity,[167] and to increase *in vitro* serotonin and norepinephrine concentrations in the brainstem,[168,169] it is now widely accepted that the vigilance mechanism of action of caffeine (in the dose range produced by voluntary caffeine intake) is via the antagonism of adenosine receptors. The caffeine-induced increase of cortical acetylcholine release is dose dependent, and the increased cortical cholinergic activity, resulting from the blockade of A_1 receptors, may provide a basis for the psychostimulant effects of caffeine.[170] Caffeine's wake-promoting effects also could be due to the blocking of adenosine receptors on GABA neurons, which reinforces the inhibition of

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neurons in the preoptic/anterior hypothalamus that are specifically active during sleep.[48] Thus, by blocking the firing-rate cessation normally induced by adenosine, caffeine reinforces arousal by two different and complementary mechanisms: (1) stimulation of cholinergic neurons in the basal forebrain and (2) reinforcement of the inhibition exerted on sleep-promoting neurons.

Despite the ability of caffeine to increase vigilance, which is an important reason why people consume caffeine, it has been suggested that the dopaminergic system also could contribute to the widespread consumption of caffeine-containing beverages.[167] However, while it has been clearly shown that caffeine induces dopamine and glutamate release in the shell of the nucleus accumbens,[171] these actions are not thought to contribute to its psychoactive effects.[172-174] Furthermore, whereas DAT-knockout mice are unresponsive to the normally robust wake-promoting action of methamphetamine, these mice are hypersensitive to the wake-promoting effects of caffeine.[116]

Actually, the adenosine A_1 and A_{2a} receptors seem to be primarily involved in the effects of caffeine on vigilance states, whereas A_{2b} and A_3 receptors seem to play only a minor role given that the inhibition of the actions of adenosine at this receptor level is incompatible with caffeine activity under physiologic conditions.[50] Adenosine A_1 receptors are present in almost all brain areas, with the highest levels in the hippocampus, cerebral and cerebellar cortices, and certain thalamic nuclei.[175,176] Only moderate levels have been observed in the caudate putamen and nucleus accumbens.[177] Adenosine A_{2A} receptors are found to be concentrated in dopamine-rich regions of the brain and are colocalized with D_2 receptors in rat striatum.[178,179] Whereas caffeine affects transmitter release and neuronal firing rates via actions on adenosine A_1 receptors, the effects of caffeine on dopaminergic transmission are exerted mainly via actions on adenosine A_{2A} receptors.[50] This indirect interaction of caffeine with the dopamine system is through the opposite actions of adenosine A_{2a} receptors with dopamine D_2 receptors.[180,181] Indeed, it has been shown that stimulation of adenosine A_{2a} receptors opposes the effect of dopamine at striatal output cells.[182] Notably, dopamine administered in the striatum has been shown to block release of GABA in the globus pallidus[183] and this effect is reduced by endogenous adenosine. In line with this observation, it has been observed that adenosine A_{2a} receptor stimulation blocks the inhibitory effect of a dopamine D_2-receptor agonist on acetylcholine release from striatal slices.[184] Finally, it has been suggested that a therapeutic potential exists for the use of A_{2a} antagonists in the treatment of Parkinson disease.[181]This observation is in line with the potential wake-promoting effect of A_{2a} antagonists that could counterbalance the sleepiness usually observed in Parkinson disease patients.

Undesirable Side Effects

Tolerance develops to some, but not all, effects of caffeine in humans and experimental animals.[50] For example, tolerance to the psychostimulant and cardiovascular effects of caffeine usually develops within a couple of days. High-dose caffeine intake has been reported to elicit symptoms of nervousness, agitation, anxiety and insomnia, a syndrome called *caffeinism*. The majority of patients suffering from caffeinism develop a variety of nervous, gastrointestinal, or cardiac symptoms after consumption of differing quantities of caffeine, usually more than 250 mg.[185] Acute states of confusion also have been associated with very high levels of caffeine intake, more than 1000 mg per day.[186] Anxiety and somatic abnormalities have been observed in regular coffee drinkers even after absorption of small quantities of caffeine (< 250 mg), but these people most likely were very sensitive to caffeine effects.[187] Caffeinism also has been associated with delirium, psychoses, and anorexia nervosa.[188,189] Finally, several cases of death have been reported following intravenous and oral absorption of an excessive amount of caffeine (5-10 g). Symptoms observed in caffeine poisoning are agitation, anxiety, convulsions, tachycardia, and coma, with death by pulmonary edema, ventricular fibrillation, and cardiopulmonary arrest.[190-194]

Summary

Caffeine, the most widely consumed psychoactive substance in the world, increases wakefulness by stimulating neurons (notably cholinergic) involved in the maintenance of arousal, by inhibiting neurons (notably GABAergic) involved in the promotion of sleep, and possibly by an indirect modulation of dopamine postsynaptic receptors. The postsynaptic interactions of adenosine receptors and dopamine receptors may be involved in caffeine's stimulant activity and could play a role in the arousal and decreased sleep induced by the motivation for drinking caffeine-containing beverages.

NICOTINE

Introduction

There are over 4000 chemicals in cigarette smoke, but it is well accepted that nicotine is a major component in tobacco smoke responsible for addiction.[195,196] Daily smokers smoke cigarettes to maintain nicotine levels in the brain (cigarettes usually contain between 0.5 and 1.5 mg of nicotine) and presumably a certain level of arousal; hence, nicotine acts as a stimulant similar to amphetamine and caffeine. Withdrawal from nicotine is associated with both somatic and affective symptoms, and avoiding the aversive effects of withdrawal is a further motivating factor for smoking in dependent animals.[196]

Effects on Sleep

Like caffeine, nicotine is thought to have some potential for enhancing attention and arousal.[197,198] Cigarette smoking also has been associated with sleep disturbance, both during regular intake and after withdrawal.[199-201] Qualitative analysis indicates that smoking induces a characteristic psychostimulant profile involving increases in alpha power and peak alpha frequency at the expense of delta and theta power spectra.[202] Sleep fragmentation has been reported in patients who wake up during their regular sleep time in order to smoke a cigarette before going back to sleep. This symptom has been explained by decreasing levels of nicotine in the brain during sleep, which result in nicotine craving.[203] This aspect is not linked to the wake-promoting effect of nicotine but, rather, to a profound dependence on this compound.

In humans, a transdermal nicotine delivery system (nicotine patch) induces a significant reduction in total sleep time and sleep efficiency, prolonged sleep latency, and decreased REM sleep.[204] In rats, a sleep-suppressant effect has been reported after

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an acute administration of nicotine (0.5 and 1.0 mg/kg, subcutaneously), an effect reversed by repeated administration of nicotine (0.1 mg/kg), suggesting that compensatory mechanisms are triggered by chronic treatment.[205]

Molecular and Cellular Action of Nicotine in the Brain

In rats, it has been shown that the effects of nicotine on sleep can be prevented by pretreatment with the nicotinic-receptor antagonist mecamylamine (0.5 mg/kg, intraperitoneally) suggesting that the effects of nicotine on sleep are modulated by nicotinic receptors.[205] Although systemic administration of nicotine stimulates all neuronal systems involved in the maintenance of arousal,[206] one can legitimately surmise that nicotine promotes wakefulness by stimulating cholinergic neurotransmission in the basal forebrain. Nicotine also has been shown to stimulate the hypothalamic-pituitary-adrenal axis in rodents, leading to elevated plasma levels of adrenocorticotropic hormone and corticosterone,[207,208] known to exert a wake-promoting effect.[119] However, studies with humans have shown that only intense smoking is able to activate the hypothalamic-pituitary-adrenal axis.[209,210] It also is well known that repeated injections of nicotine produce progressively larger increases in locomotor activity, an effect referred to as behavioral sensitization. This effect has been clearly associated with an increase in dopamine release, and the striatum and the nucleus accumbens may play a major role in nicotine-induced behavioral sensitization.[211-213] This effect appears to be mediated in part by nicotinic receptors located in the ventral tegmental area in the mesolimbic dopamine system,[214] most likely via the α_4 nicotinic acetylcholine receptors located on dopaminergic neurons,[215] and also requires the activation of both D_1 and D_2 dopamine receptors.[216]

Undesirable Side Effects

Though smoking cigarettes does not appear to induce an acute intoxication state, considerable evidence has established the high abuse potential of nicotine. Therefore, cigarette smoking is the most preventable cause of cardiovascular morbidity and mortality. Smoking cigarettes leads to a dependent state, and smoking cessation usually induces a withdrawal syndrome comprising somatic and affective symptoms.[196] Briefly, the most common somatic symptoms include bradycardia, gastrointestinal discomfort, and increased appetite. Affective symptoms primarily include craving, fatigue, depressed mood, dysphoria, anxiety, irritability, and attention deficit.

Summary

Nicotine enhances attention and vigilance likely by directly stimulating cholinergic neurotransmission in the basal forebrain responsible for cortical arousal. Interestingly, this observation provides a biochemical explanation for the wake-promoting association for coffee and cigarettes. Nicotine stimulates cholinergic neurotransmission and concomitantly enhances arousal, and caffeine limits the effects of sleepiness induced by increasing levels of adenosine. Again, it can be hypothesized that the dopamine system could play an indirect role in the wake-promoting properties of nicotine by mediating the enhanced motivational components of arousal.

OTHER TREATMENTS FOR SLEEP DISORDERS

The effects of gammahydroxybutyrate (GHB) on sleep have been investigated for more than 25 years.[217,218] GHB has some effectiveness on narcolepsy,[219-222] but it is not a psychostimulant. In laboratory animals, as well as in humans, GHB is rapidly absorbed, freely crosses the blood-brain barrier, and induces a short-lasting central nervous system depression.[223,224] At low doses, GHB is anxiolytic and myorelaxant, and at intermediate doses, it increases REM sleep and slow-wave sleep. At higher doses, GHB is still used as an anesthetic adjuvant. The mechanisms of GHB action are still unclear.[225] However, the current hypotheses suggest that GHB prevents sleepiness during the daytime in narcoleptic patients by increasing their sleep continuity at night. However, despite an absence of misuse or tolerance in narcoleptic patients,[226] GHB users may be at risk for addiction, characterized by repeated consumption, tolerance, craving, compulsive drug-seeking, and withdrawal.[223,224] Interestingly, GHB has been shown to have an effect on dopamine systems in the brain, notably by inhibiting dopamine release[224]; no evidence to date supports the hypothesis that decreased dopaminergic transmission could mediate the hypnotic properties of GHB.

The histaminergic system has a key role in waking, and the effectiveness of histamine H_3-receptor antagonists to promote wakefulness has been clearly established in rats.[227-229] More recently, H_3-receptor blockade has been shown to enhance cognition in rats,[230] and their action on cortical desynchronization has been clearly established.[231] However, no clinical trial has yet been published showing that H_3 antagonists to promote wakefulness in humans.

Finally, recent data have demonstrated a key involvement of the hypocretin/orexin system in the etiology of narcolepsy (see above). Thus, a hypocretin agonist should be able to compensate for hypocretin deficiency and, therefore, should be efficient in promoting wakefulness.[232] However, no available clinical data so far support the effectiveness of this approach in treating sleep disorders.

CONCLUSIONS

Excessive sleepiness is thought to result from the lack of maintenance of the arousal threshold, which, ultimately, alleviates the inhibition exerted on the sleep-promoting system during wakefulness. Wake-promoting agents reinforce wakefulness by stimulating the release of neurotransmitters involved in the maintenance of the arousal threshold and, therefore, counterbalance the inhibitory inputs from the sleep-promoting system to the wake-promoting one. Nicotine stimulates the cholinergic neurons in the basal forebrain that lead to cortical activation. Caffeine participates to the cortical activation by blocking adenosine receptors located on cholinergic neurons in the basal forebrain. Caffeine also blocks adenosine receptors located on GABAergic neurons, thus reinforcing the inhibition exerted on neurons in the preoptic/anterior hypothalamus that are involved in sleep induction and may indirectly increase dopamine neurotransmission. Modafinil may promote waking via activation of the tuberomammillary nucleus and hypocretin neurons, which leads to an activation of the ascending arousal system. The fact that either amphetamine-like stimulants or modafinil have failed to exert any waking effect on DAT knockout mice suggests that the dopamine system

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may play a role in the wake-promoting properties of these compounds. Understanding how wake-promoting drugs interact with different components of the dopamine system to induce arousal remains a challenge for future research to establish new stimulant treatments.

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