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Review Article

Novel Pharmacological Strategies for the Management of Insomnia

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Abstract

Insomnia is a common sleep disorder depicted as a difficulty in initiating or maintaining sleep, or non-restorative sleep with impairment of daytime functioning, such as irritability or fatigue during wakefulness. The etiology and pathophysiology of insomnia is complex, it involves genetic, environmental, behavioral, and physiological factors that culminate in hyperarousal, a state of increased psychological and physiological stress. This condition results in a disarray of the sleep-wake cycle, and the development of subsequent collateral symptoms such as fatigue, attention deficit, and mood wavering, among many others. Current pharmacological treatment for insomnia is in the form of benzodiazepine (BZD) receptor agonist drugs (GABA-A receptor). Nonetheless, the administration of these molecules is not idyllic, due to their safety profile and inadequate efficacy.

The recent progress in elucidating the processes that orchestrate sleep/wake regulation will improve the way that insomnia is approached. Current studies have emphasized new targets for drug discovery.

In this Review, we will summarize the research on sleep–wake cycle modulators that may be of relevance for treating insomnia.

Keywords: Insomnia; Hyperarousal; Benzodiazepines; Orexin; Histamine; Sleep-Wake Regulation

Introduction

Insomnia is the most common sleep disorder, affecting 15% of the population worldwide. It is defined, according to fifth edition of the diagnostic and statistical manual of mental disorders (DSM V), as the subjective perception of difficulty with sleep initiation, duration, consolidation, or quality, that occurs despite an adequate opportunity for sleep; with daytime consequences, such as fatigue, attention deficit and mood instability, with symptoms lasting for 4 weeks or more [1].

This disorder is one of the most widespread health concerns; however, it represents an everyday struggle to clinicians given its many potential causes, unawareness with behavioral treatments, and concerns about pharmacologic treatment.

Insomnia has a dramatic impact on quality of life; sleep loss and the subsequent drowsiness affect attention span and daytime performance. Moreover, mood variability and irritability may severely impact social life, leading to poor social integration. In addition, weight gain (a commonly observed feature) may degrade self-esteem and reduce physical performance.

The pathophysiology of insomnia can actually be rather complex (or at least multi-factorial), given the many inputs that modulate the sleep-wake system, the additional specific behaviors and cognitions that an individual layers on top of the physiologic substrates. Consequently, an early diagnosis with appropriate pharmacological treatment is fundamental to allow patients to reach a normal everyday performance and to reduce social impairment [2-4].

In this review we will focus on compounds that modulate both aspects of the sleep-wake cycle, arousal and sleep.

Sleep-wake regulation

The essential theory of sleep–wake regulation has been formulated as a two-process model. Two separate biological mechanisms in the body that interact together and balance each other. First, the circadian process located in the suprachiasmatic a nucleus. It is synchronized with the light-dark cycle over a 24-hour period, and regulates the body's sleep patterns, feeding patterns, core body temperature, brain wave activity, cell regeneration, hor-

mone production, and other biological activities. And second, the homoeostatic process, an internal biochemical system that operates as a counter, generating a homeostatic sleep drive or pressure to sleep and regulating sleep intensity [5].

Wakefulness depends on modulation of the intrinsic cortical activity that is attained through ascending activating systems through a ventral route (ascending reticular activating system), and a dorsal route whose main representative is the hypothalamus. Both pathways send direct projections to the cortex and indirect ones through the thalamus. Arousal and rapid-ey movement (REM) sleep are behavioral states that need activation by subcortical structures (each through different pathways) [6].

Brainstem and basal forebrain cholinergic neurons discharge during both wakefulness and REM (rapid-eye movement) sleep, this ends in direct activation of cortical neurons, and facilitation of thalamocortical transmission by inhibition of the sleep-onset generator. These neurons are excited by glutamatergic, noradrenergic, and histaminergic neurons. Monoaminergic ascending projections (catecholamines and serotonin-producing neurons) are involved in sleep-waking regulation and the pathophysiology of major psychiatric disorders like schizophrenia, and depression, all of which include sleep-waking disturbances. Inhibition of catecholamine synthesis decreases waking, and psychostimulants, such as amphetamine, increase waking through accumulation of catecholamines [6-8].

Neurobiology of Insomnia

Insomnia is a result of an excessive activation of the arousal systems of the CNS. Hyperarousal is believed to thwart the regulatory processes that promote sleep, from naturally occurring in patients with insomnia. In addition, sleep-wake traits such as sleep duration and timing, are hereditary and regulated by numerous genes, and have a great influence on the development of insomnia. The most significant polymorphisms correlated with insomnia are those involved in neuroplasticity (ROR1, PLCB1, EPHA4, and CACNA1A), stress reactivity (STK39, USP25, and MARP10), neuronal excitability (GABRB1 and DLG2), and mental health (NPAS3) [9].

Moreover, epigenetic mechanisms might also be involved in the development and maintenance of insomnia. Stressful-life events could modify the activity of stress-regulatory systems (hypothalamic-pituitary-adrenal axis) and induce long-term changes in brain structures that result in hyperarousal, and thus, the development of insomnia.

Pharmacological Targets for the Treatment of Insomnia

Throughout the history of insomnia, the pharmaceutical companies have invested a great deal of effort in promoting the use of CNS molecules that enhance signaling of γ-aminobutyric acid (GABA), an inhibitory neurotransmitter [10].

These undertakings have succeeded in establishing the GABA compounds as the leading sleep aids; nevertheless, there are numerous concerns that still raise many questions as to their use, specifically, the fact that all of these compounds are classified as controlled substances.

Recently, novel targets that modulate the sleep-wake cycle have gained significant popularity due to their highly conserved nature and its ability to regulate either arousal or sleep. The two more promising ones are the orexin/hypocretin system and the histaminergic system.

The posterior hypothalamus is the main waking center; this area contains two major neuronal populations, the orexin (or hypocretin) and histaminergic neurons, which have distinct and complementary roles in the sleep-wake cycle. Orexin orchestrates motor and other behavioral aspects of the waking state, whereas histamine is involved in the maintenance of arousal. Both of these major waking systems are inhibited by GABAergic inputs from the sleep-active ventrolateralpreoptic area.

Orexinergic system

Orexins were first described in 1999 [11-13] and shortly thereafter; their deficiency was associated to the development of the sleep disorder narcolepsy [14-16]. Since then, orexins have been intensely studied for their role in the sleep-wake cycle primarily as wake-promoting neurotransmitters [17]. Orexin-producing neurons are found in the lateral hypotalamus (LH) (Figure 1A), where they synthesize two excitatory neuropeptides named orexin A and B (hypocretin 1 and 2, respectively), cleaved from a common protein precursor called prepro-orexin (prepro-hypocretin). Orexinergic neurons extensively innervate the CNS, specifically, areas known for their role in promoting arousal like the locus coeruleus (LC), the tuberomamillary nucleus (TMN), the basal forebrain (BF), the dorsal raphe (DR) and the cerebral cortex. Orexins exert their actions by interacting with two G protein-coupled receptors called OX1R and OX2R (hcrtR1 and hcrtR2, respectively) [11-13]. These receptors have different affinities for the orexin peptides, while orexin A binds both receptors, orexin B exclusively binds to OX2R.

Orexin-exited neurons become more excitable through an inhibition of potassium channels, including G protein–regulated inward rectifier (GIRK) channels; in addition, activation of orexin receptors can induce a fast and sustained rise in intracellular calcium, either through transient receptor potential channels or from intracellular stores. In addition to these postsynaptic effects, orexins can also act presynaptically on nerve terminals to induce re-

lease of GABA or glutamate, thus generating more complicated effects on downstream neurons. Through these many mechanisms, orexins are thought to excite neurons that promote many aspects of arousal [18, 19].

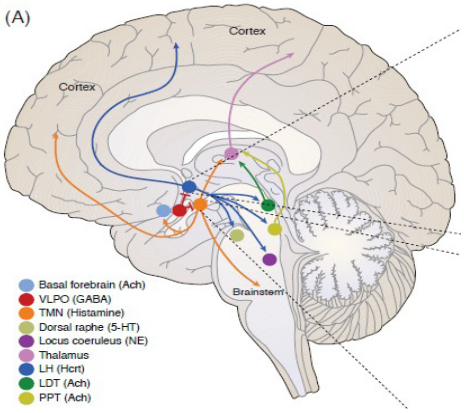

Figure 1A.

Histaminergic system

Histaminergic neurons send inputs to numerous areas of the brain, particularly those involved in the sleep-wake cycle, such as the thalamus, preoptic/anterior hypothalamus, brainstem, forebrain cholinergic and monoaminergic nuclei, and the cerebral cortex [20-22].

Histaminergic neurons exert their excitatory effect through postsynaptic H1 and H2 receptors, both of which contribute to neuronal activation. This has been extensively observed with drugs that impair histamine-mediated neurotransmission, which enhance slow cortical activity and favor sleep. First-generation antihistaminic compounds (H1 receptor antagonists) cause sedation and drowsiness when used as anti-allergic. The H1 receptor is the fundamental player in the maintenance of arousal. H1 receptors are found throughout the whole body (blood cells, and vessels) and the CNS (neurons, glia). They are present in several brain regions concerned with neuroendocrine, behavioral, and metabolic control, such as the hypothalamus, aminergic and cholinergic brainstem nuclei, thalamus, and cerebral cortex [20-22].

H3 receptors provide feedback on histaminergic neurons, acting as autoreceptors; any interference with them will indirectly affect actions mediated by H1 and H2 receptors. H3 receptors are a particularly complex, given that they display constitutive activity. They inhibit cell firing, as well as histamine synthesis and release from varicosities [23]. As presynaptic heteroreceptors, H3 receptors control the release of a variety of other neurotransmitters involved in sleep–waking regulation, including biogenic amines, acetylcholine, glutamate, GABA, and neuropeptides. It has a widespread distribution in the CNS; particularly, high densities are found in the hypothalamus, hippocampus, amygdala, nucleus accumbens, striatum, olfactory tubercles, cerebellum, substantianigra, brainstem, and the cerebral cortex. This widespread distribution is consistent with the extensive range of functions it has in the CNS [23-25]. Loss of the H3 receptor results in several behavioral irregularities; H3 receptor knockout mice display reduced locomotion, metabolic syndrome with hyperphagia, late-onset obesity phenotypes, and an increased onset of neuroinflammatory diseases [26].

Novel Drugs for the Management of Insomnia

Dual orexin receptor antagonists

These compounds are the most widely studied orexin receptor antagonists. It had been hypothesized that antagonizing both orexin receptors would elicit the most powerful sleep-promoting effects by inhibition of arousal [27, 28] (Figure 1B); therefore, most of the studies around orexin antagonists have concentrated on these compounds. To this day, DORAs are the only orexin antagonists currently undergoing clinical trials for the treatment of insomnia.

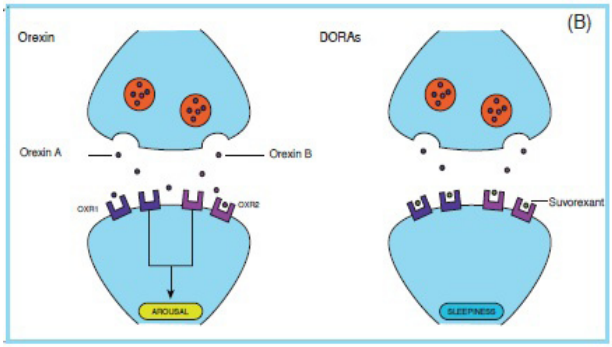

Figure 1B.

Almorexant

Almorexant is a DORA that was well tolerated in clinical trials. Doses beyond 200 mg diminished alertness, and increased fatigue, drowsiness, and sleepiness. Interestingly, sleep efficiency, measured as an increase in slow-wave sleep (SWS) and REM sleep was also increased. In patients with primary insomnia, it proved to be effective for boosting sleep, increasing total sleep time, and reducing both REM sleep latency and the frequency of awakenings. This effect was dose-dependent, with the most notorious effect on sleep architecture achieved at doses of 400 mg; doses of 100 and 200 mg had modest effects on sleep, with fewer adverse effects (e.g.: headache, dizziness, blurred vision) [29, 30].

Suvorexant

Another of the promising DORAs aimed at treating insomnia is suvorexant. This molecule is in phase III clinical trials

(NCT01097616) and is presently under evaluation for approval by the FDA. In healthy humans, the lowest dose (10 mg) reduced the number of awakenings after sleep onset; and at higher doses (50 mg) it reduced sleep latency, while increasing sleep efficiency and total sleep time. Higher doses (100 mg) prompted undesirable side effects, such as an increase in reaction time, difficulty in waking up and reduced alertness following awakening; in addition, it lead to mild complaints like headaches and somnolence [31].

When administered to patients with primary insomnia (40mg), suvorexant reduced sleep latency and increased the time patients spent asleep after a single administration. The increase in total sleep time was mostly due to an increase in REM sleep. Common adverse effects were somnolence, headaches, dizziness and atypical dreams, all of which occurred in a dose dependent manner. Residual effects like rebound insomnia, complex sleep-related behaviors or withdrawal effects were not observed after a 4-week administration. During this study, there were a few reports of sleep paralysis (1, n = 59, at 40 mg), excessive daytime sleepiness (1, n = 61, at 80 mg), and hypnagogic hallucinations (1, n = 61, at 80 mg) [32, 33]. These are the main symptoms of narcolepsy, and should be carefully monitored due to the close association between narcolepsy and the orexinergic system.

Given that suvorexant is a well-tolerated compound at effective dosages of 30 and 40 mg, the pharmaceutical company manufacturing suvorexant submitted a dose range of 15–40 mg for FDA approval. To date, suvorexant has not been approved, and the FDA has requested a lower starting dose of 10 mg for the general population and a 5 mg dose for those taking concomitant CYP3A4 inhibitors.

H3 receptor inverse agonist

Sleep disorders arise from alterations of the sleep-wake cycle. These alterations usually result in the development of comorbid sleep-related disorders. This is the case for insomnia, which often leads to fatigue as a result of abnormal sleep architecture. The notion that a compound that promotes an adequate vigilance state during the day in order to restore a normal sleep architecture should be considered.

Pitolisant

Pitolisant is an inverse agonist that enables the release of histamine in the hypothalamus and cerebral cortex by directly blocking the docking of histamine to H3 receptors; in addition, it also enhances histamine release over the basal level [34].

The safety of this compound was proven in a series of preclinical regulatory tests. Remarkably, 6-month rat and 9-month monkey toxicity studies did not reveal any significant histopathological or biochemical alterations, and the only adverse effects were convulsive episodes found at very high doses (several orders of magnitude higher than those necessary to saturate cerebral H3 receptors) [35].

In healthy human volunteers, doses of 120 mg (6X the therapeutic dose) were well tolerated without any adverse effects; however, at 120 mg, there were some minor manifestations of irritability. The pharmacokinetic parameters were found consistent with a once-a-day administration in the morning, with plasma levels reduced at the end of the day, ensuring a lack of waking effect during night. Pitolisant breakdown involves two distinct CYP 450 isoforms; this tends to avoid any major metabolic drug–drug interaction with compounds interacting with CYP 2D6. This was demonstrated when pitolisant (40 mg) was co-administered with olanzapine (10 mg) to a group of healthy volunteers. Plasma levels were not modified as compared with their individual administration.

Different phase II studies have been undertaken in which patients received placebo on the first week, and a single dose of the drug (40 mg/day) on the second week. These studies demonstrated that pitolisant reduced somnolence (5.9 points less on the Epworth Sleepiness Scale) as compared to baseline. Furthermore, somnolence and sleepiness episodes (recorded in sleep diaries) gradually decreased and were nearly absent at the end of the week, suggesting that pitolisant required several days to achieve optimal efficacy. In addition, pitolisant reduced sleepiness in narcoleptic patients with excessive daytime sleepiness (EDS) refractory to all existing previous stimulants (including amphetamines and amphetamine-like drugs) [36].

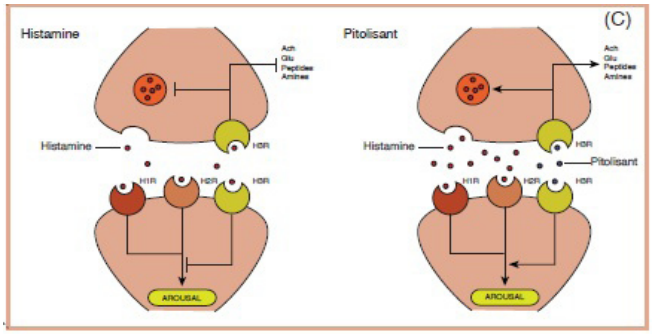

Figure 1C.

More recently, a study determined that pitolisant at doses up to 40 mg was effective on EDS compared with placebo, and well tolerated compared with modafinil (NCT01067222). Over the 8-week treatment period, it was concluded that pitolisant was superior to placebo, but not "non-inferior" to modafinil. They recorded 22 adverse events with pitolisant, 26 with modafinil, and 10 with placebo. Six severe adverse events were treatment-related: one with pitolisant (abdominal discomfort) and five with modafinil (abdominal pain, abnormal behaviour, amphetamine-like withdrawal symptoms, lymphoadenopathy, and inner ear disorders)

[37, 38].

Overall, pitolisant is a drug that effectively promotes wakefulness during the day. This compound could be effective for treating fatigue secondary to insomnia, and thus, may aid in the instauration of a more cohesive sleep-wake cycle in patients suffering from insomnia (Figure 1C).

Discussion

Current sleep research is leading to a better understanding of insomnia and its symptoms; it is through this emergent knowledge that drug development for this disorder will evolve. It is a challenging endeavor to foresee which drug targets will be most beneficial to patients, taking into consideration that the pathophysiology of insomnia involves many different aspects.

One advantage of the previously mentioned drugs over classic insomnia treatments, such as benzodiazepines, is the possibility of inducing normal sleep architecture. For example, while DORAs enhance REM sleep, benzodiazepines have proven to suppress this sleep stage. In addition, orexin antagonists appear to have a better side effect profile, with mild complaints of headaches and dizziness being the most common.

Also, because orexin antagonists and histamine inverse agonists have a novel mechanism of action, they have the potential to improve insomnia in patients who have found other agents ineffective. Clinical studies now under way should better define the benefits and limitations of these compounds.

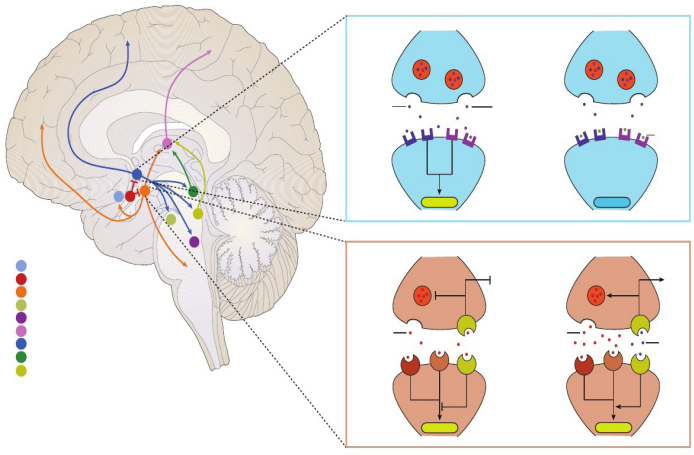

Figure 1

H3 receptors have gained widespread attention for promoting arousal. It is clear that pitolisant is a drug with a robust pharmacology, and thus, it is the first candidate in a new generation of wake-promoting drugs that could restore the delicate balance of the sleep-wake cycle. These new drugs might have an improved efficacy, tolerability, and sensitivity for treating insomnia and represent a promising alternative for the treatment of insomnia. H3 receptor inverse agonists may have enduring wake-promoting effectiveness, and thus, contribute to the instauration of a normal sleep-wake cycle (Figure 1C).

Though benzodiazepines are effective for treating insomnia and still are the first choice for pharmacological treatment, their adverse effect profiles and limitations on long-term use may prompt patients and clinicians to seek other options. The recent study of orexin and histamine receptors has led to the development of new therapy targets. Evidence suggests that some of these medications may offer a sustained benefit for patients with symptoms of chronic insomnia.

Patients with insomnia may contemplate at the future with optimism and growing assurance that in the near future we will have an ideal pharmacological option for the management of insomnia.

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