Review Article

Beyond Benzodiazepines: The Orexin System as A Transformative Target for Sleep Pharmacotherapy

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ABSTRACT

Traditional sedative-hypnotics include benzodiazepines and Z drugs. However, these drugs are accompanied by side effects such as dependence, tolerance, and next-day drowsiness. Orexin receptor antagonists represent a new class of drugs that focus on the orexin system. Orexin-A and -B, also known as hypocretin-1 and hypocretin-2, are neuropeptides produced in the lateral hypothalamus. They bind OX1 and OX2 receptors and play a crucial role in maintaining wakefulness. When orexin-producing neurons are lost, it results in narcolepsy in humans as well as in rodents. This finding has sparked interest in developing small-molecule orexin receptor antagonists as a novel therapy for insomnia. Several compounds are currently in Phase III trials. There are already marketed orexin receptor antagonists like suvorexant, lemborexant, daridorexant, vornorexant, and filorexant. While these drugs provide benefits, they also have side effects such as drowsiness, sleep paralysis, and symptoms similar to narcolepsy. Consequently, ongoing research mainly aims at creating the next generation of orexin antagonists. The primary aim is to enhance safety while reducing side effects and maintaining effectiveness for treating insomnia.

Keywords: Insomnia, Orexin, Suvorexant, Daridorexant, Lemborexant, Filorexant, Vornorexant.

INTRODUCTION

Sleep

Sleep is a fundamental human need, directly linked to health and overall quality of life. Sleep is crucial for a person to perform their bio-psycho-social and cultural functions.[1] Sleep plays an important role in our life, as it affects neuro-behavioral, cognitive, and safety-related performance, memory consolidation, nociception, and mood regulation. It also aids in the elimination of brain metabolites. Sleep is also crucial for maintaining systemic physiology, which includes metabolism, appetite regulation, immune and hormone function.[2] A good sleep also plays an important role in reducing the threat of accidents and injuries caused by sleepiness and fatigue. A healthy sleep should meet the requirements of having adequate sleep duration with applicable timing and regularity, absence of sleep problems, and good quality.[3] Lack of quality sleep over time increases the risk of serious health problems, including cardiovascular and cerebrovascular diseases, obesity, diabetes, depression, and cancer.

Stages of Sleep

Adults generally require about 7–9 hours of sleep each night to maintain normal physiological functioning. Human sleep progresses through repeating cycles and consists of two phases: Rapid eye movement (REM) and Non-rapid eye movement (NREM). A typical sleep cycle begins with NREM sleep, with REM sleep occurring shortly after a brief period of NREM sleep. Sleep occurs in five stages: wake, N1, N2, N3, and REM. Stage N1 indicates relaxed wakefulness, Stage N2 represents light sleep, and Stage N3 indicates deep or slow-wave sleep.[4.] Stages N1, N2, and N3 are considered to be NREM. Each stage or phase of sleep is associated with distinct changes in muscle tone, brain wave activity, and eye movements. NREM sleep is characterized by non-rapid eye movement. Stage N1 is the changeover from wakefulness to sleep, or it is a period of light sleep that lasts from 1 to 7 minutes. The N2 stage reflects a deeper sleep, during which heart rate and body temperature drop. Stage N3, also known as slow wave sleep (SWS), is the period of deep sleep. REM sleep occurs in the last phase of sleep and is highly marked by high brain activity, and there is an increased level of acetylcholine.[5]

Insomnia

The word "insomnia" originates from the Latin terms "in" (meaning not) and "somnus" (meaning sleep). Known as sleeplessness, insomnia is a widespread sleep disorder that hinders individuals from falling asleep, staying asleep, or achieving restorative sleep, thereby impacting overall health and well-being. It can also lead to daytime difficulties or emotional distress. This condition arises from a mix of physiological, psychological, and environmental influences. Insomnia may manifest as a state of hyperarousal experienced throughout the day. Research indicates that insomnia impacts a significant portion of the adult population, potentially affecting up to 30%, with higher prevalence in women, older individuals, and those from lower socioeconomic backgrounds. Furthermore, insomnia is linked to a greater likelihood of cardiovascular issues, cognitive decline, mood disorders, substance misuse, and various other negative health outcomes.[6]

Pathophysiology of insomnia

The regulation of sleep and wakefulness is governed by a complex interplay of distinct neurological systems acting in a reciprocal feedback loop. This mechanism is frequently characterized as a "flip-flop switch," a model which posits that wakefulness and sleep are mutually exclusive states; the activation of one system inherently inhibits the other to prevent an intermediate state. This transition is modulated by two primary forces: the circadian rhythm (the biological clock) and homeostatic drive (the accumulation of sleep pressure).

Mechanisms of Wakefulness: Wakefulness is primarily maintained by the Ascending Reticular Activating System (ARAS), which originates in the brainstem and projects widely into the cerebral cortex. A critical component of this system involves the lateral hypothalamus, where neurons release hypocretin (orexin). Orexinergic signaling (involving Orexin A and B) reinforces arousal by projecting to brainstem nuclei and maintaining continuous depolarization. Essentially, the orexin system acts as a stabilizer for the "wake" state, preventing sudden transitions into sleep.

Mechanisms of Sleep: Sleep is initiated when the Ventrolateral Preoptic Region (VLPR) in the anterior hypothalamus becomes active. The VLPR exerts inhibitory control over the arousal centres of the ARAS. This inhibition is mediated primarily by two neurotransmitters: γ-aminobutyric acid (GABA) and galanin. When the homeostatic sleep drive sufficiently inhibits the wake-promoting orexin neurons, the "switch" flips, allowing the VLPR to suppress arousal systems and consolidate sleep. The sleep-wake balance is governed by distinct neurotransmitters: norepinephrine, dopamine, and orexin drive and sustain wakefulness, while GABA acts as the primary inhibitory neurotransmitter to facilitate sleep.[7]

Hypnotics

Hypnotics are commonly used to manage insomnia. Hypnotic medications are a category of substances that depress the central nervous system in a dose-dependent way, leading to progressive drowsiness or sedation. A hypnotic induces sleep that mimics natural sleep. Sedative-hypnotics play a crucial role in managing insomnia and are advised for short-term use. These drugs can be employed for addressing various issues such as insomnia, fear, anxiety, panic disorders, sedation, and alcohol withdrawal.[8]

Pharmacotherapy for insomnia

Medications for insomnia mainly include four pharmacodynamic categories that mostly work on receptors for GABA, melatonin, histamine, and orexin (hypocretin).

Table 1: Drugs approved by the FDA for the treatment of insomnia [9]

CATEGORY	DRUG
Benzodiazepine receptor agonist	**Benzodiazepine Immediate Release**
	Estazolam
	Flurazepam
	Quazepam
	Temazepam
	Triazolam
	Non-Benzodiazepine Immediate Release
	Eszopiclone
	Zaleplon
	Zolpidem
Selective Melatonin Receptor	Ramelteon
Selective Histamine Receptor Antagonist	Doxepin
Dual Orexin Receptor Antagonist	Suvorexant

Barbiturates

Barbiturates are derivatives of barbituric acid (malonyl urea) and act by increasing chloride ion flux and causing post-synaptic hyperpolarization, resulting in CNS depression. However, they possess certain side effects, such as having a low therapeutic index, which can result in fatal overdose. They are also addictive and produce cross-tolerance to other GABAergic sedatives. Unlike benzodiazepines, a barbiturate overdose cannot be reversed, and therefore, due to severe safety risks and insufficient clinical data, barbiturates are no longer recommended for insomnia treatment.[10]

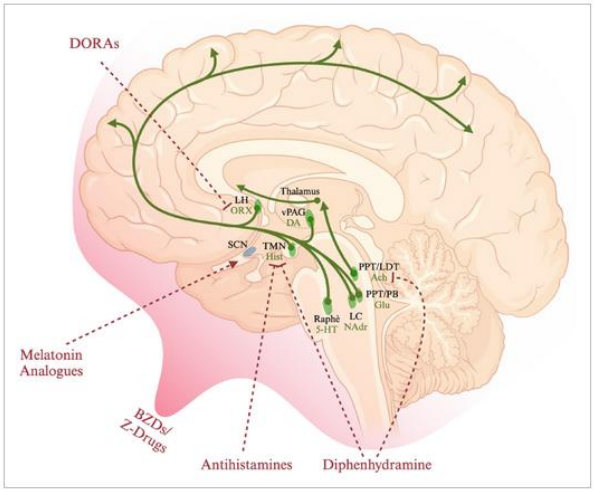
Benzodiazepines

Benzodiazepines (BZDs) are a class of psychoactive agents that quickly diffuse through the brain barrier and exert their sedative action by acting on the GABA-A receptor subunit. Classic hypnotic agents such as flurazepam, temazepam, and triazolam function as Positive Allosteric Modulators (PAM) of the GABA-A receptor. They act by causing an increased influx of chloride ions, and thus a subsequent reduction in neuronal firing occurs. The chronic use of BZDs may lead to a decline in cognitive function and memory and an increased risk of dementia. Other side effects of BZDs are their addictive potential. BZDs show increased risk of dependence and tolerance, and the dependence on these medications often leads to withdrawal symptoms.[11]

Receptors involved in sedative-hypnotic action
Receptors involved in the effects of sedative-hypnotic drugs include GABAergic receptors, melatonin receptors, orexin receptors, serotonin receptors, and histamine receptors. The sedative-hypnotic effects of different drugs come from their interactions with key receptors in the central nervous

system. The ascending reticular activating system (ARAS) keeps us awake through the excitatory actions of neurotransmitters like orexin, dopamine, norepinephrine, serotonin, histamine, and acetylcholine. In contrast, the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) promotes sleep. Activation of GABA receptors causes an influx of chloride ions, causing hyperpolarization, leading to an inhibitory effect.[12,13] Traditional hypnotics, such as benzodiazepines (BZDs) and Z-drugs, enhance this inhibitory effect by acting as positive allosteric modulators of GABA receptors. This broadly suppresses neuronal activity. Newer sleep aids work differently by blocking specific pathways that promote wakefulness. Dual orexin receptor antagonists (DORAs) encourage sleep by blocking orexin receptors, which halts their excitatory signal. Antihistamines like diphenhydramine make people drowsy by blocking both histamine (H1) receptors and, to a lesser extent, muscarinic cholinergic receptors. Melatonin receptor agonists, such as ramelteon, promote sleep by acting on melatonin (MT1 and MT2) receptors in the suprachiasmatic nucleus, which regulates the circadian rhythm.[14] 5-HT receptors also influence sedative hypnotic action. This variety of receptor targets explains the different mechanisms and side effects of various hypnotic drugs.[15]

Figure 1: showing a summary of neuronal circuits in the sleep-wake cycle and the drugs acting on it.[16]



OREXIN RECEPTOR

Discovery of the orexin system

The discovery of the orexin signaling pathway in 1998 marked a pivotal moment in sleep research. Two independent research groups identified these neuropeptides almost simultaneously: Yanagisawa's team termed them "orexins" due to their perceived role in appetite regulation. In contrast, Sutcliffe's group named them "hypocretins" based on their hypothalamic origin and structural similarity to secretin. Establishing orexin as a key regulator of wakefulness led to the "hyperarousal model" of insomnia, suggesting that chronic sleeplessness stems from an overactive wake drive. This sparked a race among major pharmaceutical companies (including GlaxoSmithKline, Merck, and Actelion) to develop Orexin Receptor Antagonists (ORAs). While Almorexant provided the first clinical proof-of-concept in 2007, it was eventually discontinued. However, its success paved the way for suvorexant, which became the first Dual Orexin Receptor Antagonist (DORA) to receive FDA approval in 2014.[17]

Orexin peptides

Orexin-A and orexin-B are the peptides derived from the precursor peptide known as prepro-orexin. Orexin A is made of 33 amino acids with two disulfide bridges, while orexin B is a linear peptide of 28 amino acids that presumably forms two alpha helices. At the C terminus, each peptide gets amidated, and a pyroglutamyl residue is cyclized at the N terminus of the orexin A peptide. These orexin peptides are produced by a network of neurons in the hypothalamus that surrounds the fornix and also extends up to the lateral hypothalamus. Orexin neurons also innervate various arousal and motivational areas of the brain, such as the noradrenergic neurons of the locus coeruleus, the histaminergic neurons of the tuberomammillary nucleus (TMN), the serotonergic neurons of the raphe nuclei, and the dopaminergic neurons of the ventral tegmental area (VTA), and thus result in various aspects of arousal.[18]

Orexin receptors

The orexin peptides specifically bind to the OX1 and OX2 receptors, referred to as HCRTR1 and HCRTR2. These receptors are G protein-coupled and have seven transmembrane domains, showing resemblance to other neuropeptide receptors. These receptors are highly conserved throughout evolution, with human and rat sequences exhibiting around 94% similarity. In terms of structure, the two types of human receptors have 64% amino acid similarity. Although they are structurally similar, they have differing pharmacological characteristics in relation to ligand binding. OX1R displays marked selectivity, binding Orexin-A (OA) with high affinity (IC_{50} of 20 nM) while binding Orexin-B (OB) with considerably lower affinity (IC_{50} of 420 nM). Conversely, OX2R acts as a non-selective receptor that interacts with both OA and OB with high affinity (IC_{50} values of 38 nM and 36 nM, respectively). Importantly, neither receptor shows notable affinity for related peptides such as secretin or neuropeptide Y.[19]

Role of orexin receptor

The orexin system functions as a critical physiological integrator, primarily orchestrating the stability of sleep and arousal states within the central nervous system (CNS) by modulating monoaminergic and cholinergic neurons. Acting through G-protein-coupled receptors (OX1R and OX2R), orexins operate across the entire neuroaxis to induce neuronal depolarization, while simultaneously modulating synaptic plasticity and adjusting the responsiveness of both presynaptic and postsynaptic neurons. This dynamic regulation ensures the maintenance of wakefulness, and its dysfunction is directly linked to disorders such as narcolepsy and sleep-wake instability.[20] They are also involved in the regulation of appetite, along with

maintaining energy metabolism. Apart from these functions, they also get engaged in activating the brain reward systems. The orexin neurons produce two chemicals from the same vesicle simultaneously, namely orexin and dynorphin, which can induce dysphoria. The orexin prevents this depressive state by antagonizing dynorphin. They aid in treating conditions like phobias and post-traumatic stress disorders. The orexin receptor regulates emotions, and its higher amount induces pain and anxiety-like behaviours.[21,22]

Insomnia and Orexin Signaling

Current neurobiological models define insomnia not merely as a sleep deficit but as a disorder of "hyperarousal." Functional neuroimaging indicates that wake-promoting brain regions fail to deactivate sufficiently during sleep, potentially driven by a hyperactive stress system. While the exact etiology remains complex, the orexin system is a primary suspect due to its role in modulating vigilance and stress responses. Interestingly, animal studies suggest an age-related paradox in this system: while the total number of orexin neurons decreases with age, the surviving neurons become hyperexcitable. This neural hyperexcitability lowers the arousal threshold, contributing to the sleep fragmentation commonly seen in the elderly.[17,21]

Orexin Receptor Antagonists

Orexin neuropeptides, orexin-A and orexin-B, are excitatory molecules made in the lateral hypothalamus. They play a key role in controlling wakefulness, appetite, and energy use.[20] These neuropeptides bind to two G-protein-coupled receptors, OX1R and OX2R, which are found throughout the brain and other tissues. Activation of OX2R is especially important for staying awake, while OX1R is more involved in regulating reward, stress, and emotional reactions. Orexin antagonists block these receptors, which stop the excitatory signalling that keeps us alert and awake. This blockage reduces activity in brain areas that promote arousal, like the locus coeruleus and tuberomammillary nucleus, making it easier to start and stay asleep. Unlike regular sedatives that increase GABA inhibition, orexin antagonists maintain normal sleep structure. They ensure that REM and deep sleep stages occur without causing significant drowsiness the next day or leading to dependence.[23,24,25]

Selective orexin receptor antagonists (SORA)

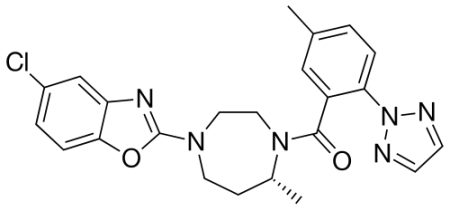
The first small molecules identified by high-throughput screening, such as SB-334867 and JNJ-10397049, were found to inhibit only single orexin receptors. SORAs at a dosage of 20 and 50 mg show an increase in REM sleep duration and improve sleep efficiency by reducing sleep latency. They were found to be effective for improving depressive symptoms with increased perceived sleep quality.[24]

Dual orexin receptor antagonists (DORA)

DORAs act by targeting the orexin system by antagonizing both orexin receptors and producing sleep with a more localized effect. DORAs promote REM sleep without reducing REM sleep.[23,25,26]

SUVOREXANT

Suvorexant is the first orexin receptor antagonist approved for the treatment of insomnia, mainly in the US by the FDA in August 2014 and in Japan in November 2014.



Chemistry

Suvorexant is chemically [(7R) -4-(5-chloro-1,3-benzoxazole-2-yl) -7-methyl-1,4 -diazepan -1-yl] [5-methyl-2-(2H-1,2,3 -triazol -2-yl) phenyl] methanone. Earlier, Almorexant, the first DORA, entered clinical trials. It shows improved activity and reduces sleep onset time and wakefulness during the studies; however, its development was halted due to concerns regarding elevated liver enzyme levels. Then, later, Merck Research Laboratories directed its interest towards identifying DORA molecules as an orexin antagonist. They conducted high-throughput screening and identified one hit molecule, i.e., a seven-membered diazepane ring compound having good binding affinity towards orexin receptors. Then, for preparing large compound libraries, parallel synthesis was performed, and radioligand binding assays were developed for both OX1R and OX2R. This led to the identification of another molecule as having good brain penetration and permeability. The quinazoline ring in the second molecule is a site for bioactivation, but it is highly prone to oxidation, which can generate reactive electrophilic species that may cause idiosyncratic toxicity. Replacing this ring with chlorobenzoxazole produces MK4305 (suvorexant), which has improved stability and has good target potency, reduces production of reactive metabolites, and increases NREM and REM sleep.[27,28]

Mechanism of action

Suvorexant, when it binds to the orexin receptor, adopts a U-shaped bioactive conformation. When it is bound to the transmembrane helices of the orexin receptor, this U-shaped conformation helps to maximize hydrogen bonds and van der Waals forces with residues in the ligand binding site. This prevents neuropeptide binding and promotes sleep.[29]

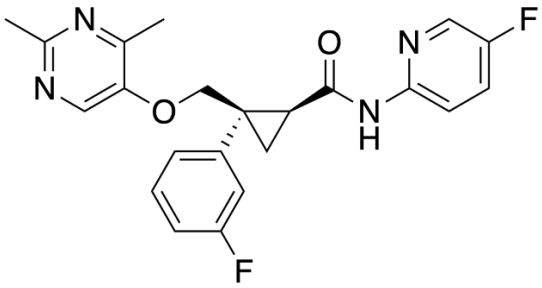
Adverse effects

Suvorexant is likely contraindicated in Prader–Willi syndrome because the condition involves hypothalamic dysfunction and narcoleptic traits. Somnolence is the common side effect observed with suvorexant. It may also result in other adverse effects such as motor impairment, sleepwalking, hypnagogic hallucinations, and abnormal

dream patterns and cause cataplexy-like effects when the dose exceeds the recommended one.[28,29,30]

LEMBOREXANT

Lemborexant can be considered a DORA, as it is a unique drug, as it has inhibitory activity only at scheduled times.



Chemistry

Lemborexant, chemically known as (1R,2S) -2-{[(2,4-dimethylpyrimidin-5-yl) oxy] methyl}-2-(3-fluorophenyl)-N-(5-fluoropyridin-2-yl) cyclopropanecarboxamide. Lemborexant has more binding affinity to orexin 1 receptors than orexin 2 receptors. Also, they bind to and dissociate from orexin 2 receptors more rapidly. Its N-aryl ring modification with a fluorine atom may increase penetration and show good activity. Also, lemborexant reduces daytime sleepiness and reduces sleep latency. Lemborexant on orexin 2 receptors form a hydrogen bond between its carboxamide nitrogen and the oxygen atom of Gln134. A second hydrogen bond forms between the Gln134 amide group and a fluorine atom on the lemborexant molecule. The pyrimidine and pyridine rings of lemborexant are stabilised by a π-π interaction and are held in place by His350 and Pro131. This specific structure is enabled by the tight bend of the lemborexant molecule's cyclopropane ring.[31,32]

Mechanism of action

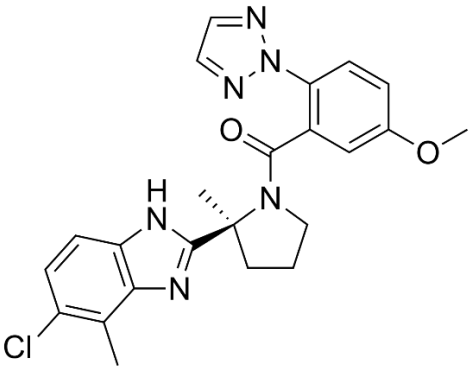
Lemborexant has a unique mechanism of binding that underlies its action. Lemborexant is a DORA that binds to both OX1 and OX2 receptors. However, they show more affinity towards OX2 receptors (2.6 nm) than for OX1 receptors (6.1 nm). This selectivity is mainly due to a single residue difference in their binding pocket: Thr135 in the OX2 and Ala127 in the OX1 receptor. In OX2R, the threonine residue creates steric hindrance, which forces the lemborexant into a single specific conformation where the amide proton forms a hydrogen bond with Gln134. Thus, this conformation increases affinity. In OX1R, the alanine residue with a small side chain creates less hindrance, which allows the lemborexant to fluctuate between different configurations, resulting in less affinity.[33]

Adverse effects

The most common adverse effect of lemborexant is carrying over the sleepiness into the next morning. It may also be associated with nightmares, as lemborexant works by blocking orexin receptors, whose job is to suppress REM sleep. Also, approximately 17-19% of patients reported worsening symptoms of insomnia on treatment discontinuation. Some patients have a headache when taking lemborexant. It may also result in decreased night postural stability, attention, and memory. It is contraindicated in patients with narcolepsy.[33,34,35]

DARIDOREXANT

Daridorexant (Nemorexant) is a benzimidazole derivative, and it is chemically (S)-(2-(5-chloro-4-methyl-1H-benzo[d]imidazol-2-yl)-2-methylpyrrolidin-1-yl) (5-methoxy-2-(2H-1,2,3-triazol-2-yl) phenyl) methanone. Through intracellular Ca2+ release assays, it is demonstrated that Daridorexant acts as a competitive orthosteric antagonist with an apparent partition coefficient.[36,37]



Mechanism of action

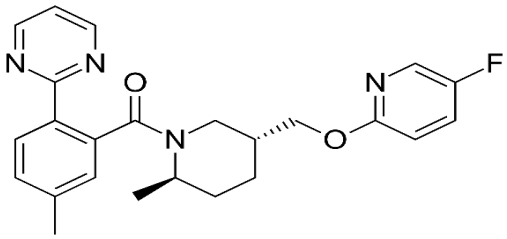
Daridorexant acts as a DORA by acting on both OX1 and OX2 receptors. In the brain, there are many wake-promoting regions like cholinergic neurons of the basal forebrain, the pedunculopontine, and laterodorsal tegmental nuclei, histaminergic neurons of the Tuber mammillary nucleus, noradrenergic neurons of the locus coeruleus, serotonergic neurons of the dorsal raphe and dopaminergic neurons of the ventral tegmental area, which are part of the ascending reticular activating system and function as a feedback loop. Daridorexant acts by blocking the binding of neuropeptides to orexin receptors and inhibiting downstream neuronal pathways that cause wakefulness.[38,39]

Adverse effects

Daridorexant does not affect memory and attention; however, it is associated with certain side effects. In less than 2% of the population treated with Dariodrexant, patients experience nasopharyngitis, headache, fatigue, and dizziness. Other side effects are sleep paralysis and hypnagogic and hypnopompic hallucinations.[40,41]

FILOREXANT

Filorexant (MK-6096) is a DORA that completed the phase II clinical trials in the year 2014. It acts on both OX1 and OX2 receptors to elicit its action.[42]



Chemistry

Filorexant consists of an ether-linked fluoropyridine instead of the benzoxazole found in suvorexant. This fluoropyridine will form a π-stacking arrangement with the benzamide part of the molecule, which will help to maintain the drug in that specific conformation. The drug's orientation is primarily determined by the presence of the central piperidine ring. The drug also consists of an axial methyl group that forces the substituents on the ring into a specific "trans-diaxial" orientation. Thus, this orientation results in a horseshoe shape. The drug sits in a hydrophobic pocket defined by Ala102, Ser103, Val106, Ile122, Pro123, Gln126, and Tyr348. The ligand's polar binding is anchored by the amide carbonyl, which establishes a direct hydrogen bond with Asn318 and interacts with a specific water molecule (Wat 1.1) stabilized by a network involving Asn318 and His344. Additionally, the pyrimidine substituent contributes to stability through edge-face π-stacking interactions with Phe219 and Tyr311, while potentially forming a weak hydrogen bond with Gln126.[43]

Mechanism of action

The structure of filorexant takes a horseshoe shape when it combines with the receptor. As a dual orexin receptor antagonist, filorexant prevents the binding of Orexin A and Orexin B, the arousal neuropeptides, to their respective receptors, specifically the OX1 and the OX2 receptor subtypes present in the brain. By inhibiting the orexin receptor subtypes, filorexant indirectly inhibits the activity of the orexin system, which plays a vital role in maintaining arousal. This condition causes a resultant effect that facilitates the natural transition into a sleep state and, in the process, enhances both the onset and maintenance of sleep in patients with insomnia.[43]

Adverse effects

The most common side effect of Filorexant is somnolence. Other adverse effects reported in patients are headache, fatigue, periorbital cellulitis, and atrial fibrillation. They may also be associated with incidences of upper respiratory tract infection. Sleep paralysis is another side effect caused by filorexant.[43,44]

LIMITATIONS OF CURRENTLY AVAILABLE OREXIN ANTAGONISTS

1. Limited Efficacy Across Populations

Drugs like suvorexant, lemborexant, and daridorexant are promising, although with differential efficacy between patients. Some patients barely get better in terms of sleep onset and maintenance.[45]

2. Safety Concerns and Side Effects

Although dual orexin receptor antagonists (DORAs) avoid some of the risks of benzodiazepines, we remain apprehensive about next-day somnolence, cognitive impairment, and abuse potential in vulnerable populations.[46]

3. Lack of Practical Data

The majority of clinical research is short and controlled. There is a requirement for long-term, real-world safety data in order to determine how such drugs perform in less-than-ideal situations.[47]

4. Narrow Therapeutic Scope

Present antagonists are primarily credited for insomnia. But orexin signalling is also linked with other conditions, including depression, anxiety, and neurodegenerative diseases. New antagonists might get targets in broader usages.[48]

5. Selectivity and Precision Required

Bilateral antagonists act upon both orexin receptors (OX1R and OX2R) and might not be perfect for every patient. Selective antagonists—such as seltorexant, acting upon OX2R—are also being studied with the intention of lessening side effects and augmenting outcomes in conditions such as major depressive disorder.[49]

CONCLUSION

The introduction of orexin receptor antagonists (ORAs) has changed the way we treat insomnia. Unlike traditional hypnotics that affect the widespread GABA system to induce sleep, ORAs such as suvorexant, lemborexant, daridorexant, filorexant, and vornorexant encourage sleep by blocking the wakefulness-promoting effects of the orexin neuropeptide system. The orexin system represents a transformative target in sleep pharmacotherapy, offering a mechanism-based alternative to traditional hypnotics and modulating arousal pathways more selectively, preserving sleep architecture, and reducing risks of tolerance and dependence. However, these medications have some drawbacks. Common side effects include daytime sleepiness, and their high cost can limit access. Therefore, the major focus is on developing new compounds with better selectivity and a good safety profile to overcome these side effects.

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