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Orexin Receptors: Pharmacology and Therapeutic Opportunities

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Abstract

Orexin-A and -B (also known as hypocretin-1 and -2) are neuropeptides produced in the lateral hypothalamus that promote many aspects of arousal through the OX1 and OX2 receptors. In fact, they are necessary for normal wakefulness, as loss of the orexin-producing neurons causes narcolepsy in humans and rodents. This has generated considerable interest in developing small-molecule orexin receptor antagonists as a novel therapy for the treatment of insomnia. Orexin antagonists, especially those that block OX2 or both OX1 and OX2 receptors, clearly promote sleep in animals, and clinical results are encouraging: Several compounds are in Phase III trials. As the orexin system mainly promotes arousal, these new compounds will likely improve insomnia without incurring many of the side effects encountered with current medications.

Keywords

hypocretin; insomnia; hypnotic; sedative; narcolepsy; substance abuse

INTRODUCTION

In 1998, two groups searching for new signaling molecules independently discovered the orexin neuropeptides and their receptors. Sakurai, Yanagisawa, and colleagues (1) named these peptides orexin-A and -B because they were originally thought to promote feeding (the term orexin comes from *orexis*, the Greek word for appetite). The team led by de Lecea and Sutcliffe (2) named the peptides hypocretin-1 and -2 because they are produced in the hypothalamus and have some similarities to the incretin family of peptides. Over the past decade, it has become clear that although the orexin peptides have only a modest influence on feeding and appetite, their effects on arousal and sleep are profound. In fact, narcolepsy, one of the most common causes of sleepiness, is caused by a loss of the orexin-producing neurons, and this has fueled a strong interest in developing orexin antagonists as a novel approach for promoting sleep and treating insomnia.

Almost all hypnotics used in the clinic enhance γ-aminobutyric acid (GABA) signaling or alter monoamine signaling, but these neurotransmitters affect numerous brain functions, which can result in side effects such as unsteady gait and confusion. In contrast, orexin antagonists are expected to promote sleep with fewer side effects, and recent, large clinical studies look promising. In this article, we review the neurobiology of orexin signaling,

DISCLOSURE STATEMENT

T.E.S. has consulted on the subject of orexin antagonists for Merck & Co., GlaxoSmithKline (GSK), Hoffmann–La Roche, and Actelion. C.J.W. is an employee of Merck Sharp & Dohme Corp. and owns stock and holds stock options in the company.

recent preclinical and clinical studies with orexin antagonists, and potential applications of these compounds for the treatment of insomnia and other disorders.

OVERVIEW OF OREXIN SIGNALING

Orexin Peptides

Orexin-A and -B are derived from the cleavage of prepro-orexin (1,2). Orexin-A consists of 33 amino acids with two disulfide bridges, and orexin-B is a linear peptide of 28 amino acids that probably forms two alpha helices (3). Each peptide is amidated at the C terminus, and the N terminus of orexin-A is also cyclized with a pyroglutamyl residue. The peptides are packaged in dense core vesicles and most likely synaptically released (2). Little is known about the kinetics of the orexins, but orexin-A seems to induce longer-lasting behavioral effects, perhaps because of the post-translational modifications (1,4). The orexin peptides are highly conserved between humans and mice, with identical orexin-A sequences and just two amino acid substitutions in orexin-B (1). Many other vertebrates including zebrafish also produce orexins, but invertebrates seem to lack orexin-like peptides.

The orexin peptides are produced by a cluster of neurons in the hypothalamus that encircles the fornix and extends across the lateral hypothalamus. The human brain contains 50,000–80,000 orexin-producing neurons (5,6), and these cells have extensive projections to many brain regions (7). Some of the heaviest projections are to nuclei that regulate arousal and motivation, including 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) (Figure 1). The orexin neurons also innervate cholinergic and noncholinergic neurons in the basal forebrain and project directly to the cortex. Through these projections, the orexin system is well positioned to coordinate the activation of many neural systems involved in various aspects of arousal.

The orexin neurons are also well situated to respond to a variety of neural signals (8,9). They receive strong inputs from brain regions that mediate responses to stress and autonomic tone such as the amygdala and insular cortex, as well as from nuclei that regulate reward and motivation such as the nucleus accumbens and VTA. Information related to circadian rhythms and the timing of wakefulness may influence the orexin neurons via the dorsomedial nucleus of the hypothalamus (DMH) (10). By integrating information from these diverse inputs, the orexin neurons can appropriately promote arousal across a variety of conditions. Although not yet demonstrated, inappropriate activation of the orexin neurons at night may contribute to insomnia because people with insomnia frequently exhibit signs of hyperarousal such as increased metabolic rate and sympathetic tone (11,12).

Orexin Receptors

The orexin peptides bind selectively to the OX1 and OX2 receptors (OX1R and OX2R, also known as HCRTR1 and HCRTR2) (1). These are G protein–coupled receptors that have 7-transmembrane domains and some similarity to other neuropeptide receptors. OX1R and OX2R are strongly conserved across mammals, with 94% identity in the amino acid sequences between humans and rats (1).

OX1R binds orexin-A with high affinity (IC_{50} 20 nM in a competitive binding assay), but it has considerably less affinity for orexin-B (IC_{50} 420 nM) (Figure 2). This selectivity for orexin-A is even more apparent in the measurement of calcium transients in CHO cells transfected with OX1R (EC_{50} 30 nM for orexin-A versus 2,500 nM for orexin-B) (1). OX2R shares 64% amino acid homology with OX1R, but it is less selective, binding both orexin-A and -B with high affinity (IC_{50} 38 nM and 36 nM, respectively) (1). Although they have

some structural similarities to other neuropeptide receptors, neither OX1R nor OX2R has any significant affinity for neuropeptide Y, secretin, or similar peptides (1,13).

OX1R and OX2R mRNA is widely expressed in the brain in a pattern similar to that of orexin nerve terminals (14). Some nuclei such as the locus coeruleus express only OX1R mRNA, and others such as the TMN express only OX2R mRNA. Many regions such as the raphe nuclei, VTA, amygdala, and cortex produce both receptors, but whether OX1R and OX2R are expressed by the same neurons remains unknown. The most reliable studies mapping orexin receptors have examined the distribution of mRNA; studies using immunostaining to detect orexin receptor proteins should be viewed cautiously because many of the current antisera can produce nonspecific staining.

Most research has focused on the brain, but small amounts of orexins and their receptors may be produced elsewhere. The testes contain moderate amounts of prepro-orexin mRNA, but receptor expression seems low (1,15). Orexin and OX2R mRNA have been detected in adrenal cortex (15,16). Orexin-producing neurons have also been described in the submucosal and myenteric plexuses of the stomach and small intestine (17), but this claim is controversial because it may represent an orexin-like peptide that cross-reacts with orexin antisera (18). As orexin peptide expression outside the brain seems to be low, orexin antagonists are unlikely to produce substantial peripheral effects.

Orexin Receptor Signaling Mechanisms

Numerous studies have shown that orexins depolarize neurons and increase excitability and firing rate for many minutes (19–22). In general, OX1R is thought to couple to G_q, and OX2R can signal through G_q or G_i/G_o, but coupling mechanisms seem to differ by cell type and have not been thoroughly examined in neurons (16,23).

The acute effects of orexins are mediated by several ionic mechanisms. Some neurons may become more excitable through an inhibition of potassium channels, including GIRK (G protein–regulated inward rectifier) channels (24). In addition, signaling through the orexin receptors can induce a rapid and sustained rise in intracellular calcium through voltage-gated calcium channels, through transient receptor potential channels, or from intracellular stores (1,25–27). Finally, activation of the sodium/calcium exchanger can contribute to excitation of target neurons (28,29). In addition to these postsynaptic effects, orexins can act presynaptically on nerve terminals to induce release of GABA or glutamate, thus generating more complicated effects on downstream neurons (21,25). Orexin signaling can also produce long-lasting increases in neuronal excitability: In the VTA, orexins increase the number of *N*-methyl-*D*-aspartate (NMDA) receptors in the cell membrane, making the neurons more responsive to the excitatory effects of glutamate for several hours (30,31). Through these mechanisms, the orexins are thought to generally excite neurons that promote many aspects of arousal.

The orexin-producing neurons also produce glutamate, dynorphin, and probably other neuropeptides derived from prepro-dynorphin (32,33). Much less is known about the roles of these co-neurotransmitters or the conditions under which they are released, but they may be physiologically significant. For example, orexins excite TMN neurons, and coadministration of dynorphin also reduces inhibitory postsynaptic potentials, synergistically enhancing the excitation of TMN neurons (34). In addition, compared with mice lacking just the orexin peptides, mice lacking the orexin neurons have stronger tendencies toward obesity and dysregulation of rapid eye movement (REM) sleep (35,36). Thus orexin antagonists may block the effects of orexins, but coreleased neurotransmitters may still have physiologic effects.

FUNCTIONS OF THE OREXIN SYSTEM

Orexins and the Control of Sleep and Wakefulness

Orexins exert some of their most potent behavioral effects on arousal and sleep (Figure 1). Injection of orexin-A or -B into the brains of rodents markedly increases wakefulness for several hours, probably through direct excitation of neurons in the locus coeruleus, TMN, raphe nuclei, basal forebrain, and cortex (4,20,37–40). The orexin neurons are physiologically active during wakefulness—especially wakefulness with motor activity—and then fall silent during non-REM and REM sleep (41–43). Consequently, extracellular levels of orexin-A are high during the active, waking period in rats and fall to approximately half their peak levels during sleep (44). A similar pattern is seen in squirrel monkeys; the highest levels occur at the end of the day and remain high if the monkey is kept awake at night (45). Thus orexins likely promote arousal during the normal active period in both rodents and primates. In humans, the diurnal variation in cerebrospinal fluid (CSF) orexin levels seems much smaller (46,47), but this is probably because CSF is generally collected from the lumbar region, far from the major sites of release.

The necessity of orexins in the regulation of normal wakefulness is apparent in people and mice lacking orexin signaling. Individuals with narcolepsy have chronic, often severe sleepiness, and those with the full narcolepsy phenotype have a roughly 90% loss of the orexin-producing neurons in addition to a marked reduction in CSF levels of orexin-A (5,33,48,49). Orexin peptide knockout mice also seem to have severe sleepiness, with an inability to maintain long bouts of wakefulness during their active period (50,51). Interestingly, these mice have nearly normal total amounts of wakefulness, but their wake bouts are much shorter than normal, and they transition quickly from wakefulness into sleep (52). Rats and dogs with disrupted orexin signaling also have similar behavior, with short bouts of wakefulness interrupted by brief periods of sleep (53,54). These observations provide compelling evidence that the orexin peptides are necessary for the normal maintenance and stabilization of wakefulness.

In addition to chronic daytime sleepiness, narcolepsy produces symptoms that probably reflect dysregulation of REM sleep. Normally, REM sleep occurs only during the usual sleep period, but in people and animals with narcolepsy, REM sleep can occur at any time of day (Figure 3) (36,55,56). In addition, narcoleptic individuals often have vivid hypnagogic hallucinations or sleep paralysis for a minute or two when dozing off or upon awakening, although these symptoms can also occur in normal individuals who have been deprived of sleep. Most strikingly, people with narcolepsy often have brief episodes of paralysis known as cataplexy that are triggered by strong, positive emotions such as those associated with laughing or hearing a joke. Mild episodes may manifest as subtle weakness of the face or neck lasting just a few seconds, but in severe episodes, an individual may crumble to the ground and remain immobile though fully conscious for up to one or two minutes (57). Mice and dogs with genetically disrupted orexin signaling also have abrupt episodes of cataplexy in the midst of wakefulness (50,51,54). Approximately half of all people with narcolepsy lack cataplexy, and they often have less severe hypnagogic hallucinations and sleep paralysis. Most of these less affected individuals have normal CSF levels of orexin, suggesting that they may have less extensive injury to the orexin-producing neurons (49,58). More clinical research is needed to determine whether orexin antagonists can cause hallucinations, paralysis, or other signs of REM sleep dysregulation because acute blockade of orexin signaling may have different effects from those that arise from chronic loss of the orexin peptides.

Less is known about the specific roles of OX1R and OX2R in controlling arousal and sleep. Genetic deletion of OX1R in mice has no obvious impact on wakefulness and sleep (59), but

disruption of OX2R produces moderate sleepiness without cataplexy (60). Mice lacking both receptors have severe sleepiness similar to that seen in orexin peptide knockout mice, and they also exhibit some cataplexy (61). Considered together, these observations suggest that drugs that block OX2R should be moderately effective in promoting sleep, and drugs that block both OX1R and OX2R should be very effective.

Orexins and the Control of Appetite, Reward, and Other Behaviors

As their name implies, the orexin peptides are also thought to play some role in the control of appetite. When administered during the light period, orexins increase food intake in rats, although the response is much smaller than that seen with classical appetite-stimulating peptides such as neuropeptide Y (1,62). However, when orexin-A is given in the dark period when rats normally eat, it does not increase food intake, suggesting that the increase in feeding during the light period may arise from an increase in arousal (63). Still, the orexin neurons clearly respond to appetite signals: Several studies have shown that 1–2 days of fasting activates the orexin neurons and roughly doubles prepro-orexin mRNA (1,64). In part, these appetite signals may be mediated by neural inputs from the arcuate and ventromedial nuclei of the hypothalamus (8,9). In addition, the orexin neurons respond directly to metabolic signals: They are excited by ghrelin or low glucose levels (indicative of hunger) and inhibited by leptin (an indicator of ample energy stores) (65–67). When deprived of food for more than 12 h, mice have much more wakefulness and locomotor activity, which may be a response to hunger that spurs foraging. However, mice lacking the orexin neurons show much smaller responses when food deprived, suggesting that signals related to hunger act through the orexin neurons to drive arousal, foraging, and other adaptive behaviors (66).

Arousing in response to hunger may be part of a much broader role of the orexin system in responding to salient and potentially rewarding stimuli. Dopaminergic neurons of the VTA strongly innervate neurons of the nucleus accumbens, and this mesolimbic pathway plays a central role in addiction to most drugs of abuse. This pathway may also contribute to the hedonic and motivating aspects of everyday stimuli such as food and sexual behavior. The orexin neurons are activated by rewards such as food or morphine (64,68), and orexins directly excite neurons of the VTA and nucleus accumbens via OX1R and OX2R (69,70). Orexins also make VTA neurons more excitable by increasing the expression of NMDA receptors on the cell surface for many hours (30,31). This form of long-term potentiation may underlie the locomotor sensitization seen in rats treated repeatedly with cocaine, as both responses can be blocked by pretreatment with an OX1R antagonist (30,71). Thus orexins may acutely and chronically enhance activity in pathways that motivate animals to seek drugs, food, or other rewards.

The orexin neurons may also contribute to the behavioral and autonomic responses to some forms of stress (72). Stressful stimuli such as foot shock activate the orexin neurons, most likely via corticotropin-releasing factor (73). When confronted with the stress of an intruder mouse in their cage, orexin peptide knockout mice have smaller increases in blood pressure and locomotion than wild-type (WT) mice (74). In addition, the OX1R/OX2R antagonist almorexant reduces autonomic responses to various stressors, especially those that require a high level of vigilance (75). Still, there is little evidence that orexin antagonists reduce anxiety, and it remains an open question whether orexins regulate responses to stress independently of their effects on arousal.

The orexin peptides also influence autonomic control and metabolism. Orexins directly excite neurons that regulate autonomic tone (76,77), and orexins increase blood pressure, heart rate, sympathetic tone, and plasma norepinephrine (78). Under normal conditions, orexins probably have a small influence on basal autonomic tone and metabolic rate because

orexin peptide knockout mice have slightly lower blood pressure, and mice lacking the orexin neurons have lower energy expenditure during the rest period and are mildly obese (35,79,80). In fact, many people with narcolepsy are mildly overweight despite eating less than normal (81,82). This could result from a lower metabolic rate or perhaps less physical activity, as orexin peptide knockout mice have much less locomotor activity than normal (51,83).

Considered together, these behavioral and physiological effects suggest that the orexin neuropeptides coordinate many aspects of arousal. Orexins promote and stabilize wakefulness, inhibit and regulate REM sleep, and increase locomotion and sympathetic tone. Most likely, the orexin system is engaged throughout the waking period, and it may be especially active when driven by internal signals such as stress or external signals such as the prospect of a reward. These observations coupled with the limitations of current therapies provide the main rationale for developing orexin antagonists as a novel and selective approach for reducing arousal and improving insomnia.

INSOMNIA

Overview of Insomnia

Insomnia is a common clinical problem that has numerous impacts on individuals and society. People with insomnia often have difficulty initiating or maintaining sleep, and daytime consequences include fatigue, inattention, and difficulty with school or work. Most everyone has experienced transient insomnia related to stress, illness, or changes in schedule, but 10–20% of people have chronic insomnia—i.e., persistent trouble sleeping more than 3 nights each week (84,85). Individuals with insomnia often experience daytime fatigue, poor mood, and impaired quality of life to an extent comparable with individuals who have congestive heart failure or depression (86). People with insomnia also have reduced productivity, higher rates of missing work, and an increased risk of developing depression or substance abuse (87,88). In 1995, the direct costs attributable to insomnia in the United States were estimated at $14 billion per year, with $2 billion spent on medications (89), and costs now are certainly much higher.

Insomnia is a disorder in which an individual is prone to sleep disruption, and a variety of factors can worsen sleep (90). Insomnia is more prevalent in women and older adults and is common in people with depression, anxiety, dementia, substance abuse, and other psychiatric disorders. Maladaptive behaviors such as irregular bedtimes, heavy caffeine use, and alcohol dependency often contribute. Insomnia also occurs with disorders that disrupt sleep such as pain, sleep apnea, restless legs syndrome, and circadian rhythm disorders in which the internal body clock is out of synchrony with the desired bedtime. Occasionally, the insomnia has no obvious medical or psychiatric cause and is considered primary insomnia. Thus many clinicians focus first on treating the patient’s depression, counterproductive behaviors, or other aggravating factors (91), but these approaches are sometimes insufficient or impractical, and many patients benefit from sleep-promoting medications.

Current Treatments for Insomnia

Physicians frequently treat insomnia with benzodiazepine receptor agonists (BzRAs), which are positive allosteric modulators of $GABA_A$ signaling that widely inhibit neuronal activity. Nonbenzo-diazepines (e.g., zolpidem, zaleplon) differ in structure from the traditional benzodiazepines (e.g., lorazepam, diazepam), and some preferentially bind the α_1 subunit of the $GABA_A$ receptor. How they promote sleep is unknown, but they may enhance GABAergic inhibition of wake-promoting neurons and globally reduce cortical activity. BzRAs often hasten the onset of sleep, reduce the number of arousals from sleep, and can

increase the total amount of sleep. A few studies have also shown improvements in daytime alertness and well-being (92). Tolerance to BzRAs is uncommon, and two studies of nonbenzodiazepines have shown good efficacy for up to 6 months (92,93).

Sedating antidepressants such as trazodone, amitriptyline, and doxepin are also popular for treating insomnia, perhaps because they may improve concomitant depression and may be less likely to cause tolerance and dependency. How these drugs promote sleep is not well understood, but they may do so by blocking the effects of wake-promoting neurotransmitters such as serotonin, histamine, norepinephrine, and acetylcholine. Although antidepressants are among the most popular hypnotics, there is little clinical research on their efficacy and safety in insomnia (94).

A variety of other medications are used to treat insomnia. Melatonin and the melatonin agonist ramelteon are moderately effective at improving sleep onset and have few side effects besides occasional headache (95). Ramelteon has not been as widely prescribed as anticipated, perhaps because the improvements in sleep are modest and patients experience little of the sedation offered by BzRAs. Antipsychotics such as olanzapine can be very sedating, but they have a relatively high incidence of side effects. The antihistamine diphenhydramine is popular in over-the-counter sleeping aids, but as with the antidepressants, few studies have addressed the clinical effectiveness and safety of this and other older medications.

Limitations of Current Hypnotics

Most drugs used for the treatment of insomnia alter neurotransmission in widely acting GABA, monoaminergic, and cholinergic systems, so the fact that these medications can produce a variety of adverse effects is not surprising (Table 1). GABA is the primary inhibitory neurotransmitter in the brain, and it affects nearly every behavioral system, including those governing cognition, gait, balance, and mood. BzRAs are generally well tolerated, but sedation and mental fogginess in the morning can be bothersome, especially with longer-acting agents. Occasionally, patients may have amnesia for events around the time of dosing, and infrequently, BzRAs can lead to sleepwalking and similar behaviors. After a BzRA is stopped, rebound insomnia for one or two nights can occur, mainly with short-acting drugs. Respiratory depression is not a common concern with normal doses, but these sedatives can worsen sleep apnea. In older adults, falls, injury, and confusion are more common with both BzRAs and antidepressants (96,97). Dependence and abuse of BzRAs can be a concern, especially in patients with a history of substance abuse (98,99).

Some physicians perceive antidepressants to be safer than BzRAs, but in general, side effects are more common with the former. As with the BzRAs, side effects can include daytime sedation and confusion. Antidepressants with anticholinergic properties can cause dry mouth or urinary retention, and those that block noradrenergic signaling occasionally cause orthostatic hypotension. Weight gain and arrhythmias are also concerns. Antipsychotics can produce hypotension, weight gain, and extrapyramidal reactions, and antihistamines can cause lingering sedation, impaired cognition, and weight gain.

Because the orexin system mainly promotes arousal, orexin antagonists have the potential to selectively promote sleep and cause fewer side effects. Dependence and abuse should be less of a concern, as animal studies have shown that orexin antagonists actually reduce drug seeking (69,100–102). Imbalance and falls should not be a problem, as there is no evidence that the orexin system affects balance or gait directly. Consequences of an overdose should not be too concerning, as orexin antagonists should not significantly depress respiration or affect blood pressure. Potential side effects of orexin antagonists, including disinhibition of REM sleep, are discussed below, but overall, many researchers anticipate that these drugs

should promote sleep without many of the side effects encountered with current medications. Also, because orexin antagonists 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 orexin receptor antagonists.

PHARMACOLOGY OF OREXIN ANTAGONISTS

Several groups have rapidly developed and characterized small-molecule orexin antagonists (for reviews, see References 103–106). Many of these compounds potently increase sleep in rodents and dogs, and the OX1R/OX2R antagonists almorexant and MK-4305 promote sleep in humans (107,107a).

Preclinical Pharmacology

Just after the discovery of the orexins, GlaxoSmithKline (GSK) began to develop antagonists, including a series of heterocyclic urea compounds (108–110). Among these, the OX1R antagonist SB-334867 has been extensively studied because it has favorable preclinical pharmacokinetics and is readily available (Table 2). Its affinity for OX1R is ~50-fold higher than for OX2R, but some in vivo studies using high doses should be viewed cautiously because those doses may block both receptors. In addition, GSK has described other selective antagonists, including SB-408124 and SB-410220, which have ~50-fold selectivity for human OX1R in binding studies, and SB-674042, which is >100-fold selective (108,109,111,112). In 2009, GSK announced that SB-649868, a dual OX1R/OX2R antagonist, promoted REM and non-REM sleep in rats and marmosets (113). In-depth preclinical pharmacology data on this molecule have not been published, but SB-649868 has entered Phase II clinical studies (114).

In 2007, Actelion published a detailed description of almorexant (ACT-078573), a potent dual orexin receptor antagonist, with IC_{50} values of 13 nM and 8 nM in cell-based assays for human OX1R and OX2R, respectively (103,107). Almorexant appears to be a competitive antagonist of OX1R and a noncompetitive antagonist of OX2R (115). It is highly selective with little affinity for more than 90 other potential targets; it is ~99% protein bound in rat and human; it has low to moderate bioavailability with oral dosing in rats (8–34%) and dogs (18–49%); and it penetrates brain well. Almorexant has good absorption in dogs (T_{max} = 0.5–2 h) with an elimination half-life of 8–9 h. Oral administration of almorexant in rats dose-dependently increased non-REM and REM sleep when given during the active period, with no loss of effectiveness over 5 nights of treatment (107,116). In contrast, rats treated with zolpidem had more non-REM sleep but less REM sleep and developed tolerance over a few nights of dosing (107). However, when almorexant was given during the rest period, it had less effect on sleep, suggesting that the drug is most effective when orexin tone and wake drive are high (107,117) (but also see Reference 112). The effects of almorexant on autonomic tone are relatively small; in rats allowed to explore, it reduced heart rate and blood pressure slightly, but it had little effect in the rest period (75). In dogs, it reduced locomotor activity without significant effects on body temperature, blood pressure, or heart rate (107). With this favorable pharmacology and strong sleep-promoting effects in animals, Actelion then pursued clinical studies of almorexant, which are described below.

Merck has developed a range of orexin receptor antagonists in several distinct structural classes (104,105,118,119). DORA-1 is a potent, dual orexin receptor antagonist from a proline bis-amide series (120). It has favorable pharmacological properties in animals, has high affinity for both OX1R and OX2R, has good brain penetration, and is moderately bioavailable in rats. In vivo, DORA-1 blocks the increase in locomotion induced by orexin and dose-dependently promotes sleep in rats (121). Another orally bioavailable dual orexin

receptor antagonist, DORA-5, originates from a *N*,*N*-disubstituted-1,4-diazepane scaffold (118,122). This compound is potent in cell-based assays and antagonizes orexin-A-induced neuronal firing in rat dorsal raphe neurons. DORA-5 also reduced rat locomotor activity and efficiently reduced active wake while increasing REM and non-REM sleep (122). MK-4305 is a potent and selective dual orexin receptor antagonist from the diazepane series, exhibiting nanomolar antagonism in cell-based assays (OX1R IC_{50} = 50 nM, OX2R IC_{50} = 56 nM) and >6,000-fold selectivity against a panel of 170 receptors and enzymes. This compound is orally bioavailable, has good brain penetrance, and demonstrates orexin receptor occupancy in rat brain. In rodent sleep studies, MK-4305 dose-dependently reduced active wake and increased REM and non-REM sleep when administered orally at 10, 30, and 100 mg kg^{-1}. Supported by these encouraging preclinical results, MK-4305 has moved into clinical development (123).

Hoffmann–La Roche has developed a potent OX2R antagonist known as EMPA that exhibits >900-fold selectivity in binding to OX2R over OX1R (124). This compound reduces spontaneous locomotion and blocks the increase in locomotion induced by an orexin-B fragment, but its sleep-promoting effects have not been disclosed.

Researchers at Johnson & Johnson described potent substituted 4-phenyl-[1,3] dioxanes with >800-fold selectivity for antagonizing OX2R (125). This group recently reported that JNJ-10397049 (an OX2R antagonist) and almorexant significantly increased REM and non-REM sleep and reduced active wake (112). In contrast, the OX1R antagonist SB-408124 had no significant effects on sleep in rats, supporting the general observation that the wake-promoting effects of orexins are mainly mediated by OX2R or a combination of OX1R and OX2R.

Other companies have identified orexin antagonists, but the available data are limited mainly to in vitro characterization (see References 105 and 106 for reviews). Banyu Tsukuba Research Institute has described a series of tetrahydroisoquinoline amide compounds with 45- to 250-fold selectivity for OX2R over OX1R, with good solubility and selectivity against a panel of >50 receptors and enzymes (126). Sanofi-Aventis presented patents for several antagonists with selectivity ranging from 20- to 600-fold for OX1R, as well as more balanced antagonists with 5- to 20-fold selectivity for OX1R over OX2R. Biovitrum reported compounds with potencies ranging from 30 nM to 2 mM for OX1R.

Clinical Pharmacology

No orexin receptor antagonists have been submitted for approval by regulatory agencies, but Actelion, GlaxoSmithKline, and Merck have each reported active clinical development of orexin receptor antagonists for insomnia.

Actelion presented encouraging Phase I data on the sleep-promoting effects of almorexant in 2007 (107). In healthy, young men, almorexant was well tolerated up to 1000 mg with no serious adverse events (107). The compound displayed rapid absorption (T_{max} = 1.0 to 2.3 hours) and proportional increases in exposure based on plasma AUC measurements at doses from 100 mg to 1000 mg. Almorexant had biphasic elimination kinetics, with a half-life of 6.1 to 19.0 hours. Doses of 200 up to 1000 mg significantly reduced the latency to enter non-REM sleep, increased the amount of sleep, and increased subjective feelings of sleepiness (107).

In a Phase II, double-blind study of 147 patients with primary insomnia, 200 or 400 mg almorexant given just before the sleep period dose-dependently increased sleep efficiency from a baseline of ~75% to ~85% of the night (127). The same doses also had a tendency to improve wake after sleep onset by 35–55 minutes and shortened the latency to persistent

sleep. Subjective impressions of sleep latency and sleep amounts also tended to improve. As expected, the latency to enter REM sleep was slightly shortened, and the amount of REM sleep was slightly increased. Since 2008, Actelion has been conducting Phase III studies with Almorexant at doses of 100 mg and 200 mg.

GlaxoSmithKline reported that their OX1R/OX2R antagonist SB-649868 dose-dependently increased sleep at 10 and 30 mg in a model of insomnia in which the sleep of healthy volunteers was disrupted by noise (113). This compound also seemed to lack any residual morning sedation. Studies in insomnia patients showed that SB-649868 reduced latency to persistent sleep and wake after sleep onset, and increased total sleep time (114). Due to an undescribed preclinical toxicity, development of SB-649868 was placed on hold in late 2007 but is currently listed as being in Phase II development (128). GSK partnered with Actelion in 2008 to develop almorexant for insomnia.

MK-4305 is an OX1R/OX2R antagonist being developed by Merck for the treatment of insomnia. This compound has favorable pharmacokinetic properties and good preclinical efficacy (123). In 2009, Merck conducted Phase II studies with MK-4305 in insomnia patients, and in 2010, they announced that MK-4305 had entered into Phase III development.

These improvements in the initiation and maintenance of sleep with orexin antagonists provide important support for the development of orexin antagonists as a new treatment for insomnia. Several independently developed compounds show similar effects, with increases in non-REM and REM sleep that are distinct from the pattern seen with conventional hypnotics.

Potential Adverse Effects

Thus far, little information is publicly available on the adverse effects of orexin antagonists, but on the basis of the available evidence and the predicted effects of orexin blockade, one may anticipate that orexin antagonists will have a better adverse event profile than many currently available hypnotics (Table 1). Orexin antagonists may have their own unique set of concerns, and additional clinical data are needed. However, unlike BzRAs, they should have little potential for abuse or unsteady gait, and unlike sedating antidepressants, they are unlikely to cause autonomic side effects such as orthostasis.

Morning or daytime sleepiness may be a concern for drugs that continue to block orexin signaling upon awakening. Possibly, this sleepiness would present differently from how it presents with BzRAs because people with narcolepsy often feel alert upon awakening and then sleepy later in the day. Thus, in clinical trials, it will be important to monitor sleepiness during the entire day, not just in the morning.

Unlike other hypnotics, orexin antagonists may cause some dysregulation of REM sleep as is encountered in narcolepsy. Hypnagogic hallucinations and sleep paralysis could occur around the onset of sleep or upon awakening, although they have not been reported. In general, these symptoms are disturbing but fleeting, and they should be manageable with patient education and dose reduction. The potential for cataplexy is a bigger concern because a sudden fall could produce injury, yet people with narcolepsy rarely have cataplexy during their sleep period, and no cataplexy was observed with almorexant in rats, dogs, and humans despite high levels of receptor blockade (107). However, these studies may have overlooked a tendency for cataplexy because it is usually triggered by strong, positive emotions (e.g., laughing at a great joke) and it is hard to elicit in the lab (57,129). In addition, animals and subjects were allowed to sleep in most studies, which could have masked any tendency toward cataplexy. Most likely, cataplexy will be a concern only in

unusual circumstances inconsistent with intended clinical use, such as if a patient is wide-awake and socializing after taking a high dose of an orexin antagonist.

Considering that orexins promote wakefulness and suppress REM sleep, one might find it odd and surprising that some people with narcolepsy can have moderately fragmented sleep, sleepwalking during non-REM sleep, and movements during REM sleep known as REM sleep behavior disorder (130). Possibly, these symptoms are a consequence of chronic orexin deficiency or injury to neurons other than those producing orexins. As these symptoms are hard to explain with current models, predicting whether they may occur with orexin antagonists is difficult. However, in dogs, almorexant increased twitching of distal parts of the limbs during sleep (107), and clinical studies should monitor for movements or other disruptions of sleep.

Orexin signaling seems to enhance activity in the mesolimbic pathways that regulate reward and motivation, and reduced activity in this system could worsen mood or motivation. People with narcolepsy may have a higher prevalence of depression (131), although it is unknown if this is a direct consequence of reduced orexin signaling or a response to the challenge of having a chronic illness. Alternatively, better sleep in patients with depression could improve mood. As many patients with insomnia have depression, clinicians should watch for any changes in mood.

BzRAs can depress respiration and worsen obstructive sleep apnea or severe lung disease, and overdose can be fatal, especially if used in combination with alcohol or other sedatives. As orexin knockout mice have relatively normal baseline ventilation (132), it seems unlikely that orexin antagonists would significantly reduce respiratory drive. However, they may reduce the response to hypercarbia. High levels of CO_2 increase respiratory rate and tidal volume, and orexin antagonists can blunt this response, especially during wakefulness (132,133). Thus it may be wise to closely evaluate orexin antagonists in patients with hypercarbia, such as individuals with severe chronic obstructive pulmonary disease (COPD) or respiratory muscle weakness.

Whether orexin affects appetite or metabolism in humans remains unclear, but people and mice with narcolepsy tend to be slightly overweight despite apparently eating less than normal (35,80,81). Thus orexin deficiency may lower metabolic rate, and orexin antagonists could promote mild weight gain if administered chronically. In practice, orexin antagonists will be mainly given at night, and normal orexin signaling during the day should offset any reductions in metabolism or hunger at night.

BzRAs and sedating antidepressants can produce unsteady gait, dizziness, and falls, but these are unlikely to be concerns with orexin antagonists as the cerebellum and vestibular nuclei essentially lack orexin fibers and receptors (7,14). Orexin knockout mice run at a normal speed (51,83), and rats treated with EMPA or almorexant balance well on a rotating rod (124,134). Pilot studies of almorexant in humans have shown only small increases in body sway 1–3 h after dosing (135), so it seems unlikely that orexin antagonists will substantially increase the risk of falls.

Orexin antagonists should probably be avoided in patients with narcolepsy because they could worsen some of the patients' symptoms. These compounds might also have a higher risk of producing narcolepsy-like effects during the day in other disorders in which the orexin-producing neurons are injured, such as Parkinson's disease and severe traumatic brain injury (136–138). Thus in those patients, clinicians might consider initiating treatment with low doses.

Some researchers have questioned whether there is value in producing behavioral effects similar to narcolepsy (139), but overall, it appears that orexin antagonists should promote sleep with fewer and less harmful side effects than many current hypnotics. Ongoing clinical trials are watching closely for any symptoms related to dysregulation of REM sleep, and watching for fragmented sleep, movements during sleep, and worsening mood will also be important. Daytime sedation should not be much of a concern for compounds with favorable kinetics that permit normal orexin signaling during the day.

FUTURE DEVELOPMENTS

Which insomnia patients might benefit most from an orexin antagonist? We know of no evidence that people with insomnia have abnormally high orexin tone (49), but under most conditions, any reduction in orexin signaling should make it easier to fall asleep and to return to sleep. These drugs might be especially effective in shift workers or individuals with jet lag who are trying to sleep during their biological active period when orexin tone is high. They may also be helpful in the many insomnia patients who have high sympathetic tone (11) because high sympathetic tone delays the onset of sleep (140) and sympathetic activation may promote arousal by exciting the orexin neurons. Especially in elderly subjects, BzRAs can cause imbalance and confusion (141), so orexin antagonists may be a good choice for some older patients because they may be less likely to cause these side effects. On the other hand, drugs that block orexin signaling may be less effective in people suffering from insomnia caused by anxiety or pain; there is no evidence that orexin antagonists reduce anxiety or raise sensory thresholds as benzodiazepines do.

Orexin antagonists may also provide a novel approach for treating substance abuse and eating disorders such as bulimia and nocturnal eating because they can reduce activity in the mesolimbic reward system. In rats, self-administration of cocaine, alcohol, or nicotine is reduced by the OX1R antagonist SB-334867 (100–102). Conditioned place preference (moving to the site of drug administration) to morphine is much reduced in mice lacking the orexin neurons and in mice treated with SB-334867 (69). Recent work also suggests that SB-334867 reduces the motivation to work for rewarding, salient stimuli such as cocaine or high-fat food (142). Orexin antagonists may also help with drug withdrawal and with maintaining abstinence because the symptoms of morphine withdrawal are reduced in mice treated with SB-334867 and in orexin peptide knockout mice (143,144). In animals in which drug-seeking has been extinguished, reinstatement of drug-seeking by stress or other cues is reduced by an OX1R antagonist (68,145). SB-334867 also reduces intake of regular and high-fat food in rats, perhaps by blocking the same reward pathways (146,147). It may also enhance satiety and even promote weight loss in rodents (148). If the OX1R plays a similar role in humans, then a selective OX1R antagonist might reduce craving for drugs or food without too much sedation.

Conversely, development of orexin agonists could be immensely helpful for individuals with daytime sleepiness, especially those with narcolepsy. Development of a small-molecule orexin agonist may be challenging, but production of allosteric modulators that selectively enhance orexin signaling may be possible. If OX2R contributes little to mesolimbic activity, then a compound that selectively enhances OX2R signaling might promote wakefulness with little potential for addiction.

The discovery of the orexin system has provided many insights into the neurobiology of arousal and sleep, and the recent studies of orexin antagonists in animals and humans are encouraging. In the next few years, we expect to learn much more about the effectiveness of these compounds, their safety, and which patients with insomnia will benefit the most.

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Glossary

TMN	tuberomammillary nucleus
VTA	ventral tegmental area
DMH	dorsomedial nucleus of the hypothalamus
GIRK channel	G protein–regulated inward rectifier channel
NMDA	*N*-methyl-*D*-aspartate
Rapid eye movement (REM) sleep	a stage of sleep characterized by vivid dreams, cerebral cortical activation, saccadic eye movements, and general paralysis of skeletal muscles
Non-REM sleep	a stage of sleep with less vivid thoughts or complete unconsciousness, and slow cortical activity
CSF	cerebrospinal fluid
Hypnagogic hallucinations	dreamlike hallucinations around the onset or end of sleep
Sleep paralysis	an inability to move upon awakening or when dozing off
Cataplexy	partial or complete paralysis with preserved consciousness lasting a few seconds up to a few minutes; often triggered by strong positive emotions such as laughter
Locomotor sensitization	increased amounts of locomotion in response to the same dose of drug
Primary insomnia	insomnia that does not result from an obvious psychiatric or medical cause
BzRAs	benzodiazepine receptor agonists
Sleep efficiency	the percent of the time in bed spent asleep
Wake after sleep onset	the amount of time spent awake after sleep begins

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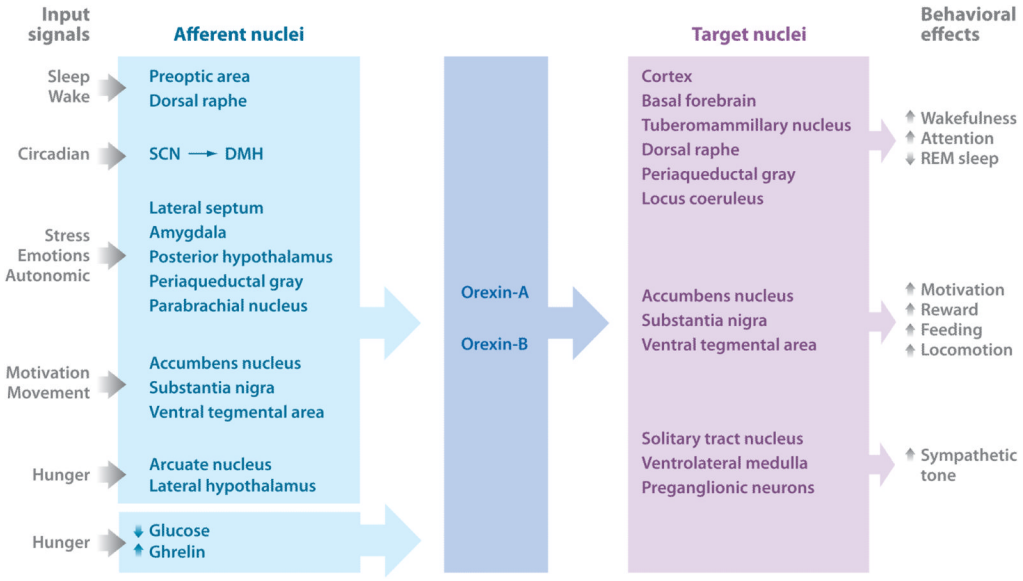

Figure 1.

The orexin system helps integrate motivating signals into arousal responses. This schematic summarizes putative pathways through which signals related to sleep, stress, motivation, and hunger activate the orexin neurons to drive various aspects of arousal. Circadian timing signals that arise in the suprachiasmatic nucleus (SCN) are probably relayed through the dorsomedial nucleus of the hypothalamus (DMH). Many input signals are neurally mediated, but the orexin neurons may also respond to humoral signals associated with hunger such as ghrelin or low glucose.

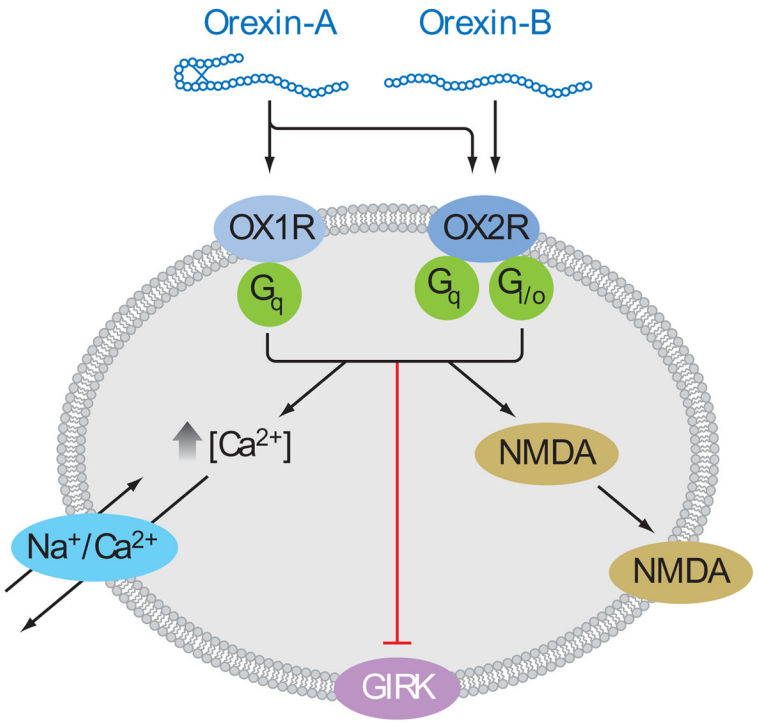

Figure 2.
Orexin signaling mechanisms. Orexin-A signals through both OX1R and OX2R, whereas orexin-B signals mainly through OX2R. Intracellular cascades mediated by G proteins increase intracellular calcium and activate the sodium/calcium exchanger, which depolarizes target neurons. These cascades also inactivate G protein–regulated inward rectifier (GIRK) channels. Increased expression of *N*-methyl-*D*-aspartate (NMDA) receptors on the cell surface produces long-lasting increases in neuronal excitability.

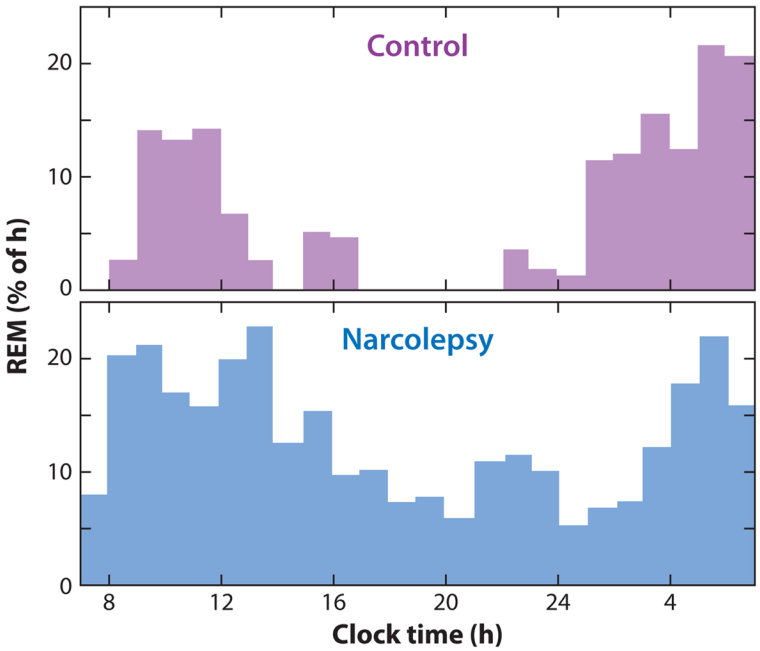

Figure 3.
Average amounts of rapid eye movement (REM) sleep in control and narcoleptic subjects on continuous bed rest for 24 h. Recordings were begun between 7 and 8 AM, and subjects were allowed to sleep ad lib (n = 10 in each group). Adapted from Reference 55 (methods described in Reference 150).

Table 1

Adverse effects of conventional hypnotics and potential effects of orexin antagonists. The side effects of conventional drugs are well documented, but little is known about the clinical effects of orexin antagonists. Some effects such as morning sedation may depend on the compound's pharmacokinetics. The frequency of these effects is indicated by the following symbols: ++, common; +, occasional; −, rare

	Benzodiazepines (e.g., clonazepam, lorazepam)	Nonbenzodiazepines (e.g., zolpidem, zaleplon)	Sedating antidepressants (e.g., trazodone, doxepin)	Orexin antagonists
Morning sedation	+	+	+	+
Hypnagogic hallucinations, sleep paralysis	−	−	−	+
Unsteady gait, falls	++	+	+	+/−
Confusion	++	+	++	+/−
Amnesia	+	+	−	−
Dependence and abuse	+	+/−	−	−
Rebound insomnia	+	+	−	−
Respiratory depression	+	+/−	−	−
Orthostasis	−	−	+	−
Anticholinergic effects	−	−	++/+	−

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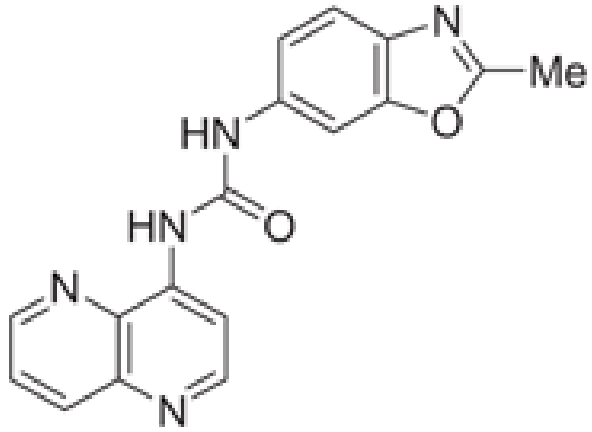
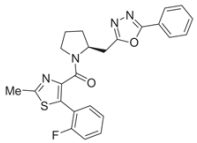
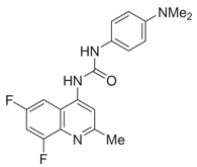
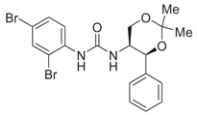
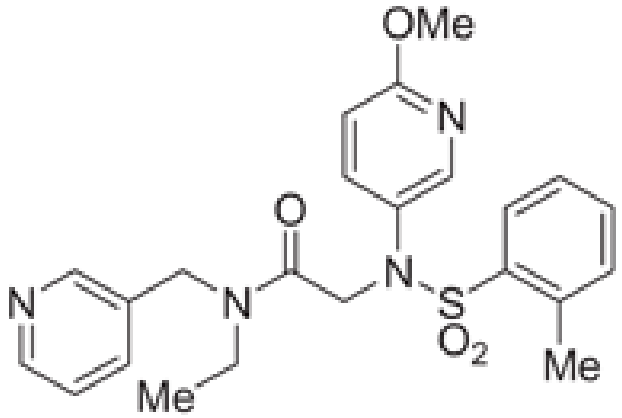
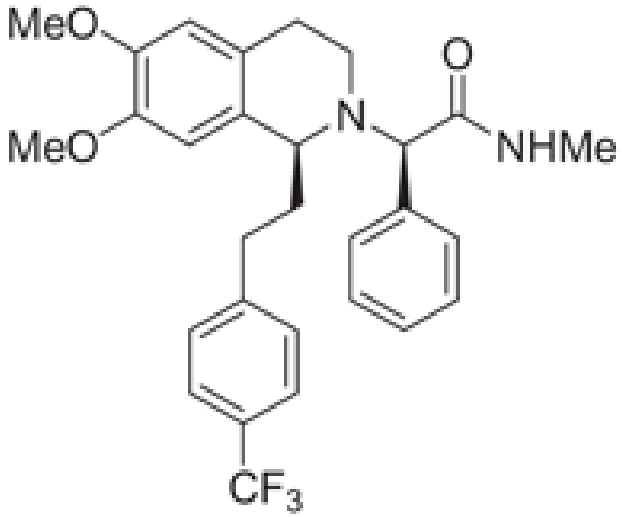
Table 2

Structures of some of the major orexin antagonists and their affinities for the OX1 and OX2 receptors

Compound	Selectivity	Potency		Reference
		OX1R	OX2R	
 SB-334867	OX1R (~50×)	K_b = 40 nM	K_b = 1995 nM	108,109
 SB-674042	OX1R (~130×)	K_b = 1nM	K_b = 129nM	111
 SB-408124	OX1R (~60×)	K_b = 22 nM	K_b = 1,405 nM	111
 JNJ-10394049	OX2R(~630×)	K_i = 3162 nM	K_i = 5 nM	112,125

Compound	Selectivity	Potency		Reference
		OX1R	OX2R	
 EMPA	OX2R(>900×)	K_i > 900 nM	K_i = 1 nM	124
 Almorexant (ACT-078573)	Dual	IC_{50} = 13 nM	IC_{50} = 8 nM	107

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Compound	Selectivity	Potency		Reference
		OX1R	OX2R	
MK-4305	Dual	K_i = 0.55 nM IC_{50} = 50 nM	K_i = 0.35 nM IC_{50} = 56 nM	123
Merck DORA-1	Dual	K_i = 0.2 nM IC_{50} = 4 nM	K_i = 3 nM IC_{50} = 17 nM	120
Merck DORA-5	Dual	K_i = 0.6 nM IC_{50} = 29 nM	K_i = 1.2 nM IC_{50} = 27 nM	122