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Selective orexin receptor antagonists

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ABSTRACT

The orexin, or hypocretin, neuropeptides (orexin-A and orexin-B) are produced on neurons in the hypothalamus which project to key areas of the brain that control sleep–wake states, modulation of food intake, panic, anxiety, emotion, reward and addictive behaviors. These neuropeptides exert their effects on a pair of G-protein coupled receptors termed the orexin-1 (OX1) and orexin-2 (OX2) receptors. Emerging biology suggests the involvement of these receptors in psychiatric disorders as they are thought to play a key role in the regulation of multiple systems. This review is intended to highlight key selective OX1 or OX2 small-molecule antagonists.

In 1998, de Lecea et al.[1] and Sakurai et al.[2] independently reported the existence of the orexin neuropeptides hypocretin-1 (Hcrt-1) and hypocretin-2 (Hcrt-2) which were also termed orexin-A and orexin-B.[3] These neuropeptides were shown to originate from the common precursor prepro-orexin which is produced by neurons in the hypothalamus that project widely to key areas of the central nervous system (CNS) hypothesized to control sleep–wake states, modulation of food intake, panic, anxiety, reward and addictive behaviors. The orexin neuropeptides mediate their effect by stimulating two distinct G-protein coupled receptors, orexin-1 (OX1) and orexin-2 (OX2). While orexin-A has near equal affinity for both OX1 and OX2, orexin-B preferentially binds to the OX2 receptor. The receptors are G-protein coupled with OX1 signaling through G_q and OX2 signaling through G_q or $G_{i/o}$.[4] Interestingly, OX1 and OX2 receptor mRNA are co-located or selectively located in certain areas of the CNS suggesting differentiated roles.[5] In fact, many regions of the brain have selective expression of the OX1 or OX2 receptors.[6] For example, the OX1 receptors are selective for the limbic system (bed nucleus of the stria terminalis and amygdala), cingulate cortex and noradrenergic neurons in the locus coeruleus. Conversely, OX2 receptors are the exclusive orexin receptor in the histaminergic neurons in the tuberomammillary nucleus which plays a critical role in wake promotion. In other brain regions, like the dorsal raphe, the ventral tegmental area or the prefrontal cortex the OX1 and OX2 receptors are co-expressed. The broad CNS distribution of orexin receptors, suggests involvement in a number of physiological functions, including feeding and metabolism, regulation of wakefulness and sleep, sympathetic activation, stress response and a key role in the regulation of motivation and reward.[7]

Several lines of evidence indicate that the orexin system is an important modulator of arousal. Rodents administered orexin intracerebroventricularly spend more time awake.[8] Orexin-mediated effects on arousal have been linked to orexin neuronal projections to histaminergic neurons in the tuberomammillary nucleus as indicated previously.[9] Rodents whose prepro-orexin gene has been knocked out, or whose orexigenic neurons have been ablated, display a phenotype of altered sleep/wake cycles similar to narcolepsy.[10] Canines reported to have mutant or nonfunctional OX2 receptors have a phenotype consistent with narcolepsy.[11] Orexin signalingas a target for sleep-promoting therapies was further validated clinically by findings of attenuated orexin levels and loss of orexinergic neurons in human narcoleptic patients.[12]

To date, the majority of research in the orexin field has focused on new sleep medications and to a large extent on dual orexin receptor antagonists (DORAs), (Fig. 1).[13] In 2007, Actelion reported sleep promotion in humans with the DORA Almorexant (**1**) which was later stopped from further clinical trials due to tolerability.[14] A second DORA, SB-649868 (**2**) has also entered clinical trials and was reported to promote sleep in male volunteers.[15] Subsequently, **2** was placed on clinical hold due to an adverse preclinical toxicology finding. More recently, Merck reported Suvorexant (**3**) which was demonstrated to improve subjective and objective measures of sleep and is currently in phase III clinical trials awaiting FDA approval.[16] As a back-up molecule to Suvorexant, Merck has also reported on MK-6096 (**4**),[17] a structurally distinct DORA which is reported to be in clinical trials for the treatment of primary insomnia, migraine prophylaxis and insomnia associated with major depressive disorders.[18]

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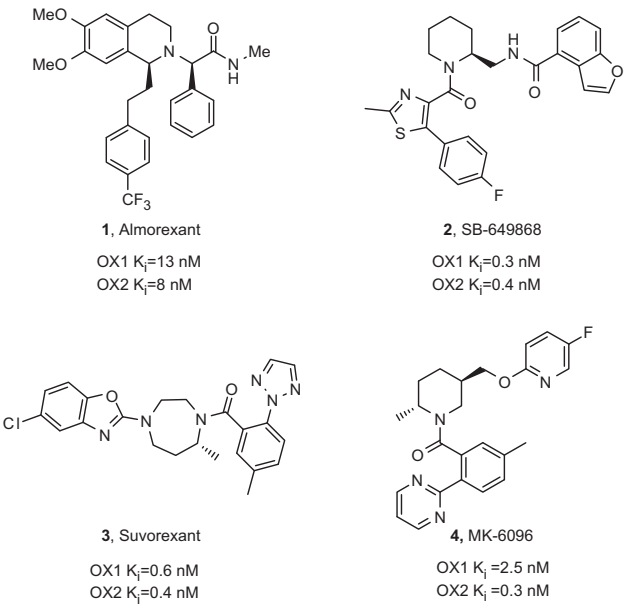

Figure 1. DORAs reported in clinical trials.

Beyond treatments for sleep disorders, evidence has alsoaccumulated that demonstrates an involvement of orexin signaling in reward pathways associated with drug dependence.[19] Based on the fact that orexinergic neurons send projections to the ventral tegmental area and other brain regions involved in reward processing, orexin ligands are thought to mediate reward behavior. Furthermore, antagonizing these effects with a selective OX1 receptor antagonist in various preclinical models of addiction has suggested that these actions are mediated through the OX1 receptor. Specifically, the selective OX1 antagonist SB-334867, vida infra, attenuates morphine conditioned place preference and reinstatement,[20] stress-induced cocaine reinstatement, cocaine-induced behavioral and synaptic plasticity,[21] intake, cue and stress-induced reinstatementof ethanol,[22] precipitated morphine withdrawal[23] and nicotine self-administration.[24] In addition, a recent study has also suggested a role for the OX2 receptor in the self-administration of ethanol.[25]

The role of orexin in more complex emotional behavior is also emerging.[26] Recent studies have demonstrated that orexin and glutamate interact at the synaptic level and that orexin facilitates glutamatergic actions.[27] Changes in orexin levels in patients with panic and post-traumatic stress disorders have been linked to differences in theprevalence of anxiety behaviors in narcoleptic patients.[28] Lactate infusion or acute hypercapnia, which causes panic in humans and are used as an animal model of panic, activates orexin neurons in the perifornical hypothalamus.[29] This activation correlates with anxiety in the social interaction test or open field test. Blocking orexin signaling with either siRNA or selective OX1 receptor antagonists attenuates panic-like responses to lactate.[30] Cerebrospinal fluid (CSF) levels of orexin are lower in depressed or suicidal patients, and levels of orexin inversely correlates with illness severity.[31] A positive correlation between OX1 receptor mRNA in the amygdala and depressive behavior in the forced swim testin mice has also been reported.[32]

As discussed above, the most advanced orexin antagonists in the clinic have been comprised of DORAs. Reviews on the various chemotypes, both selective (SORAs) and duals (DORAs), have appeared in the literature.[13] Recently, as will be illustrated here, a great deal of effort has been put forth into obtaining selective orexin receptor antagonists. In this review, we will highlight structural features, trends or SAR that afford selectivity over either of the two orexin receptors. The values reported here are comprised of either binding or functional data depending on the information available from original papers or patents.[33] The intent of this review is to show recent examples where selectivity was improved, obtained or eroded. While debatable, in our view the required selectivity in the orexin field or any other should be judged by considering drug receptor theory. Accordingly, in order to achieve 100% occupancy with 0% receptor occupancy of the undesired receptor, a molecule would theoretically need to possess 100-fold (2 log units) selectivity. At 50-fold selectivity, one would expect that 90% receptor occupancy of the desired target would result in 10% occupancy of the undesired receptor. While these theoretical values may serve as guidelines, other factors need to be considered, such as the receptor occupancy required to elicit a pharmacodynamic effect at both the desired or undesired receptor. Another aspect of selectivity that needs to be taken into account is the C_{max} of drug required to provide coverage over the determined efficacious drug concentrations. Selective orexin receptor antagonists with improved properties are of interest for the following reasons:

(1) Emerging literature[34] indicates that selective antagonism of the OX2 receptor is sufficient to initiate and prolong sleep.
(2) For the treatment of psychiatric disorders involving the OX1 receptor, one might see benefit in compounds which are selective over OX2 thus minimizing sedation.
(3) As the biology related to the orexin receptors emerges, selective compounds from multiple chemotypes will help to further understand the role and biology of each receptor in CNS disorders.

The first selective OX1 receptor antagonist to be reported was SB-334867(**5**), Figure 2.[35] Most of the in vivo and in vitro biology interrogating the OX1 receptor has utilized this compound. Although the original publication indicates 100-fold selectivity for **5** over a panel of GPCR's and ion channels, relevant off-target affinities have recently been reported by Merck.[3a] These include the adenosine A2A (K_i = 0.67 μM) and the 5-HT_{2C} (K_i = 1.2 μM) receptors. At higher concentrations, affinity for the monoamine and norepinephrine transporters, adenosine A3 and the 5-HT_{2B} receptor have also been documented. Another confounding factor is that, depending on the media, **5** has been reported to be hydrolytically unstable.[36] In particular the decomposition pathway was shown to be hydrolysis of the 2-methylbenzoxazole. While the major decomposition product has been shown to be inactive at OX1, in the absence of an evaluation of potential off-target activities

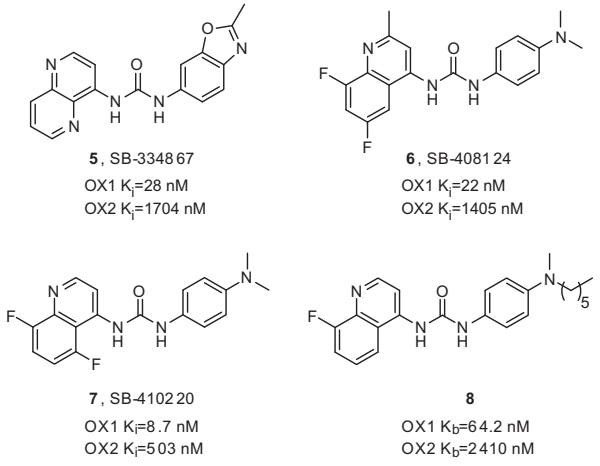

Figure 2. Diarylurea based selective OX1 receptor antagonists.