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Recent trends in orexin research—2010 to 2015

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ABSTRACT

Specific neurons in the lateral hypothalamus produce the orexin neuropeptides (orexin-A and orexin-B). The orexin-peptides are transported to areas of the brain regulating sleep-wake cycles, controlling food intake or modulating emotional states such as panic or anxiety. The orexin system, consisting of the two orexin-neuropeptides and two G-protein-coupled receptors (the orexin-1 and the orexin-2 receptor) is as well involved in reward and addictive behaviors. The review reflects on the most recent activities in the field of orexin research.

The orexin system consists of two G-protein coupled receptors (the orexin-1 (Ox1) and the orexin-2 (Ox2) receptor) and two neuropeptides, orexin-A and orexin-B which are both produced from prepro-orexin in the lateral hypothalamus by a cascade of enzymatic reactions.[1] Orexin-A is a 33 amino-acid peptide activating both Ox1 and Ox2 receptors with similar potencies whereas orexin-B, a 28 amino-acid peptide, is modestly selective for activation of the Ox2 receptors.[2] The Ox1 receptor signals mainly through Gq coupling whereas the Ox2 receptor signals through Gq or Gi/o coupling (Fig. 1).[3] The orexin neuropeptides were discovered and published in 1998 by the two research groups of Sakurai[4] and de Lecea[5] independently as the result of deorphanization programs focusing on brain orphan GPCRs. The orexin system is conserved across several mammalian species. On one hand, orexin-A, containing two disulfide bridges, is conserved in rat, mouse, pig, dog and man. On the other hand, the linear, non-lipophilic peptide, orexin-B from rat and mouse, differs by only one amino acid (S18 N) from the porcine, canine and human orexin-B.[6] Structural and functional homology between for example rat and human orexin receptors is high as well, resulting in reliably translatable pharmacology outcomes among species.

The orexin system is functionally related to physiological processes and roles as diverse as arousal[7], reward seeking behavior[8], energy homeostasis, sensory modulation, stress processing, or locomotion, cognition, endocrine functions as well as visceral functions.[9,10] Consequently, modulation of the orexin system could have a potential impact on various pathophysiological disorders including disturbances of the sleep-wake cycle, addiction, feeding disorders, stress and anxiety disorders or pain. Although there are only a small number of orexin-producing neurons localized in the hypothalamus, the orexin receptors are widely expressed throughout the CNS. And whereas many regions express both Ox1 and Ox2 receptors, others express mainly one out of the two orexin receptors suggesting potentially different functions. Significant receptor expression is found in brain regions linked with arousal and vigilance or stress and reward.[11–13]

Recent research activities in the field of orexin biology and pharmacology resulted in novel insights with respect to the interaction of orexin neurons with other neuromodulatory systems,[14] for example, interactions of the orexin system with cholinergic and monoaminergic neurons.[15] The efforts of many research teams toward the identification of small molecules as modulators of the orexin system, mainly antagonists, allowing for the investigation of the pharmacological consequences of antagonizing the orexin system with compounds exhibiting different selectivity profiles (dual antagonists versus antagonists selective for either receptor) as well as distinct binding kinetics (surmountable vs insurmountable).[16,17] First results have recently been published with respect to pharmacogenetic experiments on orexin peptides and their receptors which indicate the potential different physiological effects of polymorphisms.[18] This Letter will summarize the most recent achievements in the field of orexin biology, structural biology and recent results described with respect to small molecule orexin receptor antagonist research. The patent literature in the

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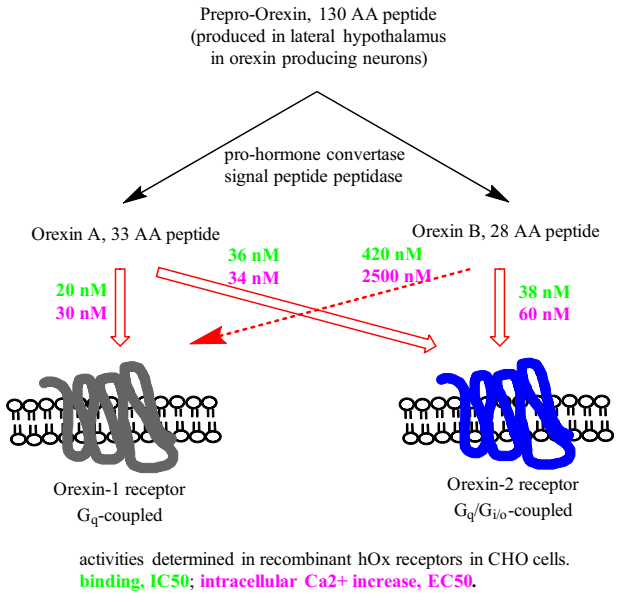

Figure 1. Orexin peptides and receptors. The precursor protein prepro-orexin (130 amino acids) is processed by signal peptide peptidase and vesicular pro-hormone convertase to result in the production of the sequence-related peptides orexin A (33 amino acids) and orexin B (28 amino acids). Orexin A contains two intramolecular disulfide bonds and interacts at low nanomolar concentrations with both orexin receptors whereas orexin B contains no disulfide bonds and exhibits a significant preference for the orexin 2 receptor. The signaling cascade of the orexin 1 receptor is Gq driven whereas the orexin 2 receptor signals through Gq as well as Gi/o coupling.

field of orexin receptor antagonists has recently been extensively reviewed and discussed.[9,10,19] Several orexin receptor antagonists have been in clinical trials (Fig. 2a) which finally resulted in the approval of suvorexant from Merck (**1**) by the US FDA in August 2014 for the treatment of primary insomnia.[20] Another antagonist with clinical development history is almorexant (**2**) which was the first dual orexin receptor antagonist (DORA) studied for the treatment of primary insomnia but was stopped due to tolerability issues.[21] The compound SB-649868 (**3**) was studied in male volunteers and was reported to promote sleep but was put on hold because of preclinical toxicology findings.[22] Merck's back-up compound filorexant (**4**, MK-6096), from a structurally different chemical class as compared to **1**, is reported to be investigated for the treatment of primary insomnia, migraine prophylaxis, painful diabetic neuropathy as well as adjunctive therapy in patients with major depressive disorders.[23,25] Recent press releases confirmed that Minerva Biosciences in collaboration with Janssen Pharmaceutica NV, successfully conducted phase I clinical trials with MIN-202, an Ox2 selective receptor antagonist (2-SORA) of which the structure is yet undisclosed. The compound shall be further clinically investigated for the treatment of sleep disorders.[24] Further orexin antagonists with recently reported ongoing clinical trial activities are lemborexant (**15**), ACT-462206 (**21**) or JNJ-42847922 (**67**), discussed in detail later in this article. The regulation of the sleep-wake cycles involves different neuronal pathways and is highly complex. An interesting and special aspect of the orexin system is that orexin neurons have an excitatory effect on every wakefulness promoting neuronal group tested so far. Therefore the orexin system seems to be an excellent target to correct imbalances in the sleep-wake cycle. In addition the clinically proven positive effects of DORAs on sleep efficacy in absence of sleep architecture modification clearly is in its favor.[26]

The advantage of a DORA for the treatment of insomnia as compared to other treatments is summarized in Figure 2b with the data acquired with almorexant (**2**) in a dose response experiment in telemetrized healthy male Wistar rats where the electroencephalogram (EEG) and electromyogram (EMG) are continuously

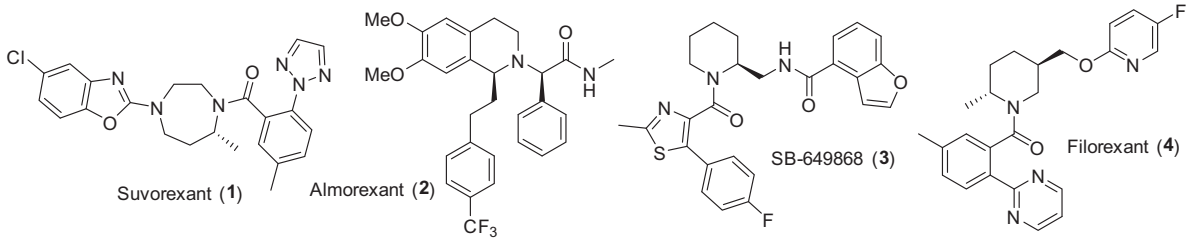

Figure 2a. Structures of orexin receptor antagonists with clinical development history.

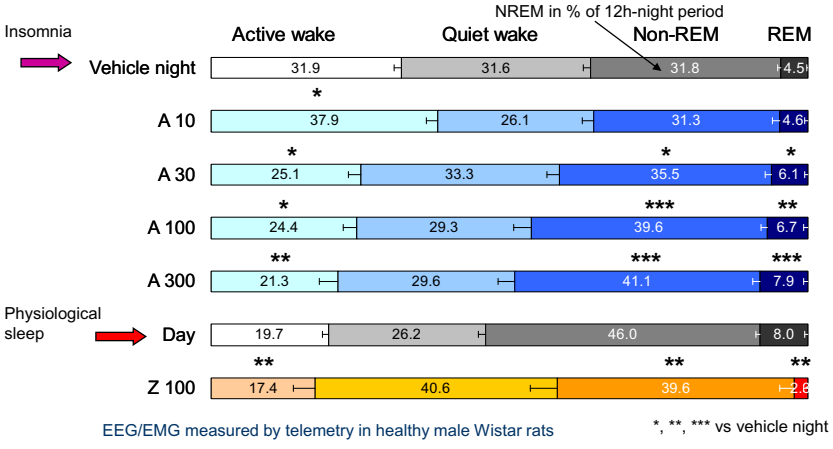

Figure 2b. Potential advantage of a dual orexin antagonist in the treatment of insomnia → Maintenance of a physiological sleep architecture (single administration of almorexant (**2**) increases time spent in NREM and REM sleep in natural REM to NREM proportions).