Jana Janockova et al., J Neurol Disord 2018, Volume 6
DOI: 10.4172/2329-6895-C4-035

Orexin receptor 2 modulators in the treatment of narcolepsy

Jana Janockova, Tereza Kobrlova, Eva Mezeiova, Rafael Dolezal, Ondrej Soukup and **Jan Korabecny**
University Hospital Hradec Kralove, Czech Republic

The neuropeptides orexin A and orexin B (also known as hypocretins) are produced by hypothalamic neurons and belong to ligands for orphan G-protein coupled receptors, OX1-R and OX2-R mapped on human chromosomes 1p33 and 6cen respectively. The localization of orexins in humans is limited to the dorso lateral hypothalamus with comprehensive dense projection to the locus coeruleus, basal forebrain, amygdala, dorsal raphe nuclei, cholinergic brainstem and spinal cord. Generally, the primary role of orexins is to act as excitatory neurotransmitters and regulators of the sleep process. Several studies have suggested that loss of orexin neurons may lead to the sleep disorder narcolepsy. Narcolepsy is a chronical neurological disorder of alertness characterized by a decrease of ability to manage a sleep-wake cycles which is demonstrated as abnormal daytime sleeping periods, hypersomnia, interrupted nocturnal sleep, cataplexy and rapid eye movement. Recent studies showed that the major pathophysiology characteristic for human narcolepsy is the autoimmune-mediated loss of neurons producing the orexin neuropeptides. Currently, patients with narcolepsy are treated symptomatically with amphetamine-like stimulants and antidepressants, but it was shown a higher risk of potential addiction. An alternative to treatment of narcolepsy with cataplexy would be a direct orexigenic system-targeted therapy. The discovery of orexin receptors, modulators and their casual implication in narcolepsy is the most important advance in sleep-research. The presented work is focused on the evaluation of compounds (L1-L11) selected by virtual screening for their ability to modulate orexin receptors in comparison to standard agonist orexin A. We used a Fluo-3–based Ca2+-mobilization assay to assess the efficiency of studied ligands on the OX-2R. We have also predicted their blood-brain barrier permeability. We can conclude that studied compounds possess the affinity towards the OX2-R. However, the compounds do not have intrinsic activity; behave like the antagonists of this receptor. It was shown that L4 was the most potent antagonist and displayed the IC50 value of 2.2 μM..

Recent Publications

1. Etori K, Saito Y C, Tsujino N and Sakurai T (2014) Effects of a newly developed potent orexin-2 receptor selective antagonist, compound 1 m, on sleep/wakefulness states in mice. Frontiers in Neurosciences 8:1-13.
2. Inutsaka A and Yamanaka A (2013) The physiological role of orexin/hypocretin neurons in the regulation of sleep/wakefulness and neuroendocrine. Frontiers in Endocrinology 4:1-10.
3. Sakurai T (2013) Orexin deficiency and narcolepsy. Current Opinion in Neurobiology 23:760-766.
4. Nishino S, Okuro M, Kotorii N, Anegawa E, Ishimaru Y, Matsumura M and Kanbayashi T (2010) Hypocretin/orexin and narcolepsy: new basis and clinical insights. Acta Physiologica. 198:209-222.
5. Yin J, Mobarec J C, Kolb P and Rosenbaum D M (2015) Crystal structure of human OX2 orexin receptor bound to the insomnia drug suvorexant. Nature 519:247-250.

Biography

Jana Janockova completed her PhD in the Department of Biochemistry, P J Safarik University in Kosice, Slovakia in 2015. Currently, she is a Postdoctoral fellow at Biomedical Research Center (BRC), University Hospital Hradec Kralove, Czech Republic and is responsible for *in vitro* testing and identification of biochemical and pharmacological properties and cytotoxicity evaluation of newly synthetized potential therapeutics for Alzheimer´s disease, narcolepsy or as antidotes in organophosphate intoxication.

jana.janockova@gmail.com