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Review article

Emerging role of orexin antagonists in insomnia therapeutics: An update on SORAs and DORAs

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ABSTRACT

The pharmacological management of insomnia has lately become a challenge for researchers worldwide. As per the third International Classification of Sleep disorders (ICSD-3) insomnia can be defined as a state with repeated difficulty in sleep initiation, duration, consolidation, or quality that occurs despite adequate opportunity and circumstances for sleep, and results in some form of daytime impairment. The conventional treatments approved for management of insomnia were benzodiazepines (BZDs) (estazolam, quazepam, triazolam, flurazepam and temazepam) and non-BZDs, also known as z-drugs (zaleplon, zolpidem, and eszopiclone), tricyclic antidepressant (TCA) doxepin as well as melatonin agonists, e.g. ramelteon. But the potential of these agents to address sleep problems has been limited due to substantial side effects associated with them like hangover, dependence and tolerance, rebound insomnia, muscular atonia, inhibition of respiratory system, cognitive dysfunctions, and increased anxiety. Recently, orexin neuropeptides have been identified as regulators of transition between wakefulness and sleep and documented to aid an initial transitory effect towards wakefulness by activating cholinergic/monoaminergic neural pathways of the ascending arousal system. This has led to the development of orexin peptides and receptors, as possible therapeutic targets for the treatment of sleep disorders with the advantage of having lesser side effects as compared to conventional treatments. The present review focuses on the orexin peptides and receptors signifying their physiological profile as well as the development of orexin receptor antagonists as novel strategies in sleep medicine.

Contents

Abbreviations: DR, dorsal raphe; DMH, dorsomedial hypothalamus; GPCR, G protein coupled receptor; GABA, gamma amino butyric acid; LDT, laterodorsal tegmental nucleus; LC, locus coeruleus; LPC, lysophosphatydylcholine; NMDA, N-methyl-D-aspartate; NSCC, non-selective cationic channels; OX_1R, Orexin receptor 1; OX_2R, orexin receptor 2; PPT, pedunculopontine nucleus; PUFAs, polyunsaturated fatty acids; VTA, ventral tegmental area; RAS, reticular activating system; VLPO, venterolateral preoptic; 5-HT, 5-hydroxy tryptamine.

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Introduction

Insufficient sleep is considered as a public health epidemic. Approximately 65 million adults in the USA (36% of total population) complain of poor sleep, and out of these, 25% suffer from insomnia on chronic basis. As per the third International Classification of Sleep disorders (ICSD-3) insomnia can be defined as a state with repeated difficulty in sleep initiation, duration, consolidation, or quality that occurs despite adequate opportunity and circumstances for sleep, and results in some form of daytime impairment [1].

The sleep–wake cycle is controlled by a reciprocal inhibitory interaction between the wakefulness-promoting orexinergic, noradrenergic, serotoninergic, and cholinergic neural systems of the ascending reticular activating system (RAS) and sleep promoting venterolateral preoptic (VLPO) region. The reciprocal inhibitory control between the arousal areas and the VLPO neurons establishes a feedback loop that regulates the sleep wake homeostasis [2,3].

Orexins hold an important role in the wakefulness promoting ascending arousal system by having an excitatory effect on almost every wake promoting neuronal group of RAS. During the past few years many clinical and preclinical studies as well as reviews have focussed on hypothalamic neuropeptides 'orexins' (orexin A and B) for characterising their effects on central nervous system (CNS). Counteracting their initial effects on appetite regulation, recent research has established orexins as the critical modulators of the sleep wake cycle homeostasis [4,5]. These findings have brought about the possibility of development of novel therapeutic agents targeting the orexin cascade (receptors and peptides) for treatment of sleep disorders. These agents in turn were also expected to be associated with lesser adverse effects unlike the conventional treatments for insomnia like benzodiazepine receptor agonists (BzRAs), non benzo-diazepines (e.g. zolpidem, zaleplon), sedating antidepressants such as trazodone, amitriptyline, and doxepin and melatonin and the melatonin agonists. The present review focusses on neuropeptides orexin A and B, their receptor pharmacologies, the role played by them in modulating sleep/wake homeostasis and exploring orexin receptors as therapeutic targets for treating sleep disturbances.

The orexin cascade

Orexin peptides

The history of orexin peptides can be accorded way back to the time when orexins were independently isolated by two different groups of researchers. While one of the groups was exploring hypothalamic neuropeptides, the other was researching upon possible endogenous ligands of the then categorised 'orphan G protein coupled receptors' (GPCR) (ligands to these receptors remain unknown), delineated today as orexin receptor 1 (OX_1R) [7,8]. Both orexin A and B are derived by enzymatic action of convertases, according a post translational modification of a common precursor called prepro-orexin [6,8]. While orexin A is chemically characterised by a 33-amino acid peptide chain, with N-terminal cyclized with a pyroglutamyl residue, two intra-chain disulphide bonds and C-terminal amidation, orexin B is a 28-amino acid, C-terminally amidated linear peptide which probably forms two alpha helices. No doubt, concentration of orexin B in the brain is 2–5 times higher in comparison to orexin A, but the stability of orexin A in the cerebrospinal fluid and blood as well as its behavioural effects are more distinguished as compared to orexin B [4,8].

The orexin peptides are produced by a cluster of orexinergic neurons localised in the perifornical area and the lateral and posterior hypothalamus areas of the brain. The estimated number of these neurons has been found to be around 3000–4000 in rat brains and 70,000 in human brains [5,9]. The orexinergic neurons send extensive input projections to nuclei that regulate arousal and motivation, like the noradrenergic neurons of the locus coeruleus (LC), the histaminergic neurons of the tuberomammillary nucleus (TMN), and the serotonergic neurons of the raphe nuclei as the cholinergic and noncholinergic neurons of the basal forebrain. They also send afferents to the dopaminergic neurons of the ventral tegmental area (VTA) that control wakefulness, attention and REM sleep, the nucleus accumbens, the substantia niagra and VTA regions that control motivation, reward, feeding and locomotion.

These orexin neurons receive a variety of neural signals from different brain areas as well. They receive strong inputs from regions like the amygdala and insular cortex found to be responsible for mediating responses to stress and autonomic tone and the nucleus accumbens and VTA nucleus that regulate reward and motivation supply. Moreover, they are innervated by neurons originating from serotoninergic raphe hypothalamus (DMH), which are responsible for supplying information related to circadian rhythms and the timing of wakefulness. The orexinergic neurons receiving such innervations, exemplify signal information from these diverse inputs, and appropriately promote arousal [5,9].

Orexin receptors

Orexins play an important role in increasing the depolarisation and excitability of the neurons. Their action is mediated *via* two different G protein coupled receptors: the orexin receptor 1 and orexin receptor 2 (OX_1R and OX_2R). The OX_1R is selective for orexin-A while OX_2R is non-selective, showing binding affinities for both orexin-A and B [8,10]. The OX_1R is thought to couple to Gq protein and its excitation causes activation of phospholipase Cβ (PLCβ) pathway, further enabling the release of calcium ions from endoplasmic reticulum and subsequent depolarisation. The intracellular Ca^{2+} concentration also increases by an alternate means, i.e. *via* influx from specific non-selective cationic channels (NSCC) located in the cell membrane that get opened with the help of Gq receptors activation. OX_1R may also activate phospholipase A2 leading to the production of lysophosphatydylcholine (LPC) and polyunsaturated fatty acids (PUFAs), which further mediate Ca^{2+} influx by acting as ligands for the opening of NSCC. This net