Dual orexin receptor antagonists – promising agents in the treatment of sleep disorders

Artur Pałasz, Damien Lapray, Christelle Peyron, Ewa Rojczyk-Golębiewska, Rafał Skowronek, Grzegorz Markowski, Beata Czałkowska, Marek Krzystanek and Ryszard Wiaderkiewicz

1 Department of Histology and Embryology, Medical University of Silesia, Katowice, Poland
2 Laboratory of Sensory Processing, Brain Mind Institute, Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland
3 Lyon Neuroscience Research Center, Team 'Sleep', Faculty of Medicine Laënnec, Claude Bernard University, Lyon, France
4 Department of Glottodidactic and Distance Learning, Institute of Romance Languages and Translation Studies, University of Silesia, Sosnowiec, Poland
5 Faculty of Life Sciences, Institute of Biotechnology, University of Manchester, Manchester, UK
6 Department and Clinic of Psychiatry and Psychotherapy, Medical University of Silesia, Katowice, Poland

Abstract

Insomnia is a serious medical and social problem, its prevalence in the general population ranges from 9 to 35% depending on the country and assessment method. Often, patients are subject to inappropriate and therefore dangerous pharmacotherapies that include prolonged administration of hypnotic drugs, benzodiazepines and other GABA_A receptor modulators. This usually does not lead to a satisfactory improvement in patients’ clinical states and may cause lifelong drug dependence. Brain state transitions require the coordinated activity of numerous neuronal pathways and brain structures. It is thought that orexin-expressing neurons play a crucial role in this process. Due to their interaction with the sleep–wake-regulating neuronal population, they can activate vigilance-promoting regions and prevent unwanted sleep intrusions. Understanding the multiple orexin modulatory effects is crucial in the context of pathogenesis of insomnia and should lead to the development of novel treatments. An important step in this process was the synthesis of dual antagonists of orexin receptors. Crucially, these drugs, as opposed to benzodiazepines, do not change the sleep architecture and have limited side-effects. This new pharmacological approach might be the most appropriate to treat insomnia.

Introduction

Sleep is a physiological state that has been shown to be necessary to maintain homeostasis, proper body functioning and mental health in humans. The control of sleep and wakefulness is a complex process involving the coordinated activity of numerous neuronal circuits. It is thought that a fundamental role in this phenomenon is played by a relatively small group of hypothalamic neurons that synthesize and release orexins (also known as hypocretins).

In humans, the orexinergic cell population is formed by ~80,000 neurons that are exclusively localized in the perifornical nucleus and the lateral and posterior hypothalamic area (Peyron et al., 1998). They are therefore in an ideal position to influence both sleep and wakefulness. Similar to other neuropeptides, orexins have a broad spectrum of regulatory effects in the central nervous system. They influence the physiology of virtually all brain functions, from sleep and homeostasis to memory, emotions and reward (Sakurai and Mieda, 2011).

Many reviews have been written in the last 10 yr on orexin neurons and their role in the regulation of sleep and wakefulness (e.g. Sakurai, 2007; Bonnavion and de Lecea, 2010; Nishino 2011). Animal models have been of great use to explore the mechanisms involved. Therefore, we will only briefly report the general knowledge on this issue to aid understanding of our
main focus. This review aims at reporting and discussing recent evidence highlighting a key role of orexinergic neurons in the context of pathogenesis of insomnia and the development of new treatments targeting this system.

Orexinergic innervation: the source of sleep–wake cycle modulation

Orexins were independently isolated in 1998 by two groups searching either for neuropeptides specifically expressed in the hypothalamus (de Lecea et al., 1998) or for endogenous ligands of orphan receptor HFGAN72, defined today as orexin receptor 1 (OX1R; Sakurai et al., 1998). They belong to the G-protein-coupled receptor family. They are composed of two peptides: orexin A and B. They are derivatives of one polypeptide precursor called prepro-orexin and are generated following post-translational activity of convertases. Orexin A and B are peptides with fundamentally different characteristics, well preserved among vertebrates.

Orexin A is composed of 33 amino acids with two disulphide bridges (Cys6–Cys12 and Cys7–Cys17) in its molecule. It is characterized by a higher stability in the cerebrospinal fluid and in blood than orexin B. On the other hand, orexin B is a linear molecule composed of 28 amino acids and its concentration in the brain is 2–5 times higher in comparison to orexin A (Sakurai et al., 1998).

Orexins act via two receptors, known as OX1R and OX2R, belonging to the G-protein-coupled receptor family. They are composed of seven transmembrane domains encoded by separate exons and show significant homology among mammals. They show diverse affinity to orexins: OX1R has higher affinity to orexin A, whereas OX2R is equally sensitive for both peptides. Their activation always induces excitation of target neurons through cascades of secondary transmitters (Kukkonen, 2013; Fig. 1).
Orexinergic cells, which co-express glutamate and dynorphin, are projection neurons that target multiple brain regions involved in the execution of sleep/wake cycles (Peyron et al., 1998). Many of these targets are reciprocally connected to orexinergic cells providing feedback and feed-forward information (Sakurai et al., 2010; Fig. 2). The main orexinergic projections target wakefulness-promoting regions such as the histaminergic tuberomammillary nucleus in the posterior hypothalamus, the cholinergic neurons of the basal forebrain and the brainstem, the monoaminergic neurons in the brainstem such as the locus coeruleus (LC) and the raphe nuclei. Moreover, they are innervated by neurons originating from serotoninergic raphe nuclei and noradrenergic LC cells. Both monoamines have inhibitory effects on orexinergic neurons. An additional source of inhibition is indirectly mediated by dopamine from the ventral tegmental area via α2-adrenoreceptors and glycineergic inhibitory fibres (Yamanaka et al., 2003; Hondo et al., 2012). Importantly, orexinergic cells receive excitatory cholinergic inputs from the basal forebrain (Sakurai, 2007). In agreement with the observed widespread orexin action in the central nervous system, their receptors have been identified in various brain regions (Trivedi et al., 1998; Marcus et al., 2001).

**Involvement of orexinergic signalling in sleep–wake cycle regulation**

Accumulating data highlight the role of orexins in the transition from sleep to wakefulness (de Lecea et al., 2012). Intracerebroventricular infusion or local micro-injections of orexins into the LC result in a large increase in waking time and a decrease in paradoxical sleep (PS) periods (Hagan et al., 1999; Bourgin et al., 2000). Activation of orexin neurons using optogenetic tools drastically increases the transition from sleep to wakefulness (Adamantidis et al., 2007). Recent studies have also shown that optically inhibiting LC neurons during orexinergic stimulation block orexin-dependent sleep to wake transitions. Conversely, when the same LC perikarya were photo stimulated, concomitant activation of orexinergic neurons increased the probability of the aforementioned switches compared with orexin stimulation alone. These findings have emphasized the crucial role of orexin-LC neuronal interplay in the regulation of non-rapid eye movement sleep/wake cycles (Carter et al., 2012).

In addition, a defect in the orexinergic system (prepro-orexin knockout mice (Chemelli et al., 1999) leads to a narcolepsy phenotype as translated by sleep fragmentation, a shortened PS latency and direct...
transition from wakefulness into PS, as seen in human narcolepsy, suggesting a key role of orexinergic signaling in the genesis of this pathology (Nishino and Mignot, 2011). In accordance with these results, post-mortem analysis of brains from narcoleptic patients have revealed an extreme reduction in the number of orexin-expressing neurons (Peyron et al., 2000) associated with undetectable levels of orexin A in the cerebrospinal fluid (Nishino et al., 2000). Interestingly, slow-wave sleep (SWS) could be induced in mice with acute inhibition of the orexinergic cells expressing a light driven ion pump halorhodopsin (Tsunematsu et al., 2011). Similarly, pharmacogenetic inhibition of orexinergic neurons also increased the length of SWS episodes in mice (Sasaki et al., 2011).

Sleep and wakefulness are two very distinct brain states that cannot coexist. While the structures responsible for one are activated, the others must be under constant inhibition until a switch in this balance occurs (Saper et al., 2001). The network involved in the regulation of the sleep–wake cycle is very complex and requires an interaction between many brain structures (Fort et al., 2009). Sleep-active neurons seem to be located mainly in the anterior hypothalamus and, more specifically, in the ventrolateral preoptic nucleus and the median preoptic nucleus (Gvilia et al., 2006). Ventrolateral preoptic nucleus neurons express γ-aminobutyric acid (GABA) and galanin and send numerous inhibitory projections to wake-mediating cells (Sherin et al., 1998; Gervasoni et al., 2000; Steininger et al., 2001; Lu et al., 2002; Uschakov et al., 2007). In addition, the activity of these cells is suppressed by noradrenaline – noradrenergic neurons being active only during wakefulness – and acetylcholine. Interestingly, orexin neurons have been shown to have an excitatory effect on every wake-promoting neuronal group tested so far (Sakurai et al., 2010).

The synchronized activity of the tuberomammillary nucleus, LC and dorsal raphe neurons is thought to play a fundamental role in the maintenance of the arousal state. These cells, characterized by tonic firing during arousal, are less active during SWS and quiescent during PS, similar to the activity of orexinergic neurons. Some studies have demonstrated that orexins excite noradrenergic neurons of the LC, dopaminergic neurons of the ventral tegmental area, serotonergic neurons of the dorsal raphe and histaminergic neurons of the tuberomammillary nucleus as well as arousal of active cholinergic neurons of pedunculopontine tegmental nucleus (Mileykovskiy et al., 2005).

### Dual antagonists of orexin receptors: preclinical and clinical studies

The participation of orexinergic transmission in the physiological regulation of sleep–wake cycles and its disturbances is a potential site for pharmacological modulation. Pharmaceutical companies have therefore started intensive studies on orexinergic receptor antagonists (Roecker and Coleman, 2008; Sullivan and Guilleminault, 2009; Hoever et al., 2010; Coleman et al., 2011). Among the numerous compounds studied, the most advanced have been applied to the antagonists that act on both orexin receptors, known as dual orexin receptor antagonists (DORAs) such as almorexant (Actelion), suvorexant (Merck & Co), SB-649868 (GlaxoSmithKline) and MK-6096 (Merck & Co.; Fig. 3).

**Almorexant (ACT-078573)**

Almorexant is by far the most studied of the DORAs and has been shown to induce somnolence and promote sleep in rats, dogs and humans (Brisbare-Roch et al., 2007; Table 1). Binding to both orexin receptors in nanomolar concentration, almorexant prevents their activation. Malherbe et al. (2009) revealed that almorexant is a competitive antagonist of OX1R and a non-competitive antagonist of OX2R. When bound to OX1R, this drug is characterized by a fast association and dissociation rate, in contrast to the significantly slower dissociation rate with OX2R. Recent studies in mice have shown the crucial role of OX2R blockage in almorexant-dependent sleep induction (Mang et al., 2012). These results suggest that its action might be mainly carried out through this latter process.

When administered during the subjective day, almorexant decreased active wake and locomotor activity and increased sleep in a dose-dependent manner (Brisbare-Roch et al., 2007). In contrast to GABA_A-receptor modulators such as zolpidem, the time spent in PS was significantly increased and these effects were not observed when the drug was administered during the subjective night. The subjective day is the time during which the organism is normally active, whereas the subjective night is the period of inactivity and sleep, e.g. the subjective night of nocturnal species occurs during the astronomical day (Pace-Schott and Hobson, 2002). In order to assess the level of tolerance and side-effects induced by chronic treatment, almorexant or vehicle was administered once per day to rats at the beginning of the dark-active period over 6 wk (Brisbare-Roch et al., 2010). A decrease of motor activity and wakefulness was observed over the first 6 h of every night,
associated with an increase of SWS and PS without any alterations in their ratio. Importantly, no cataplexy with PS intrusions was recorded and animals returned to normal sleep–wake cycles after cessation of treatment. No traditional long-term, non-desirable outcomes of the pharmacotherapy such as the rebound effect and tolerance were reported (Brisbare-Roch et al., 2010).

In healthy subjects, the drug caused both objective (electrophysiological measurements) and subjective sleep symptoms (Brisbare-Roch et al., 2007; Hoever et al., 2010). Almorexant was administered orally to participants in the morning hours in doses between 1 and 1000 mg and quantitative electroencephalogram (EEG) signals were recorded for 25 min starting 90 min post-administration (Brisbare-Roch et al., 2007). The authors reported a dose-dependent reduction of latency to SWS stage 2, total sleep time (TST) and amount of time in stage 2. These effects lasted >6 h for the higher dose (1000 mg) associated with an increase in EEG δ and θ band frequency power (the extent of this increase being unknown). Almorexant was well tolerated with no episodes of cataplexy but some adverse effects have been reported. Almorexant has also been tested on sleep variables in patients suffering from primary insomnia (at doses 50, 100, 200 and 400 mg) and was shown to improve sleep efficiency (TST divided by time in bed), decreased sleep initiation and the time spent in SWS stage 1 (Hoever et al., 2012b). The drug also had an effect on sleep architecture with a normalization of SWS distribution over the course of the night and an increase in the PS duration to normal values. The safety profile was favourable for the lower doses, some adverse events were evident only for the 400 mg dose; however, no symptoms of narcolepsy or cataplexy were observed (Hoever et al., 2012b). Some concerns have been raised that almorexant might improve insomnia by inducing narcoleptic-like symptoms, such as direct transition from wakefulness to rapid eye movement sleep rather than promoting physiological sleep. It has also been suggested that almorexant may cause a reduction in muscle tone (Tafti, 2007). This controversy indicates that further studies are needed to find out whether almorexant is a safer hypnotic agent than traditional drugs. In 2008, clinical trials of almorexant (Restore Physiological Sleep with the Orexin Receptor Antagonist Almorexant) started with a study involving 709 patients with chronic primary insomnia. This polysomnographic evaluation was focused on the efficacy and safety of 16-d oral administration of almorexant (200 and 100 mg) in adults. According to the results reported by Actelion (www.actelion.com, www.sleepreviewmag.com/sleep_report/2010-01-13_03.asp), the study has shown a superiority of almorexant compared to placebo on objective and subjective wakefulness after sleep onset (WASO). A recent finding in healthy subjects has shown that lower doses (100 and 200 mg) of almorexant were well tolerated. From 200 mg, some adverse effects, e.g. headache, fatigue, blurred vision, were reported more frequently for the almorexant than placebo. One case of sleep paralysis was described at the highest (1000 mg) dose only (Hoever et al., 2012a).
Insomnia is often associated with neuropsychiatric disorders such as depression resulting in putative dangerous drug interactions. Despite the inhibitory effect of almorexant on CYP2D6, an isoform of cytochrome P450 engaged in metabolism of many psychiatric drugs, it has been shown that the concomitant action of almorexant and desipramine (an antidepressant) did not modify the expected effects of almorexant alone (Cruz et al., 2010). Interestingly, a recent study on mice suggested that almorexant might even present antidepressive properties (Nollet et al., 2011) and could indicate an involvement of the orexinergic system in the pathophysiology of major depression. Supporting this assumption almorexant has been shown to induce a robust antidepressant-like effect and the restoration of stress-related dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis independently of a neurogenic action (Nollet et al., 2012). However, it is worth noting that narcoleptic patients also present depressive symptoms (Peyron et al., 2000; Jara et al., 2011).

Since 2008, Actelion and Glaxo Smith Kline have conducted phase II studies on almorexant. However, at the beginning of 2011, they unexpectedly discontinued these studies due to unfavourable safety and tolerance profiles of the drug (actelion.com). Both companies do not reveal the detailed causes and therefore no information is available for potential continuation of these studies in the future.

SB-649868

SB-649868 is a DORA with similar affinity to OX1R and OX2R with a 3–6 h half-life (di Fabio et al., 2011; Bettica et al., 2012c; Table 2).

When administrated to rats, SB-649868 was able to reduce sleep latency and wakefulness with a concomitant increase of TST and PS time without any motor coordination impairment (di Fabio et al., 2011; Piccoli et al., 2012). These results were confirmed by studies in healthy humans or patients suffering from insomnia (Bettica et al., 2012a, b, c). In most cases, these effects were dose-dependent, especially for TST. When compared with zolpidem, SB-649868 has a greater ability to decrease TST and WASO (Bettica et al., 2012b).

Objective hypnotic activities of SB-649868 were in accordance with subjective sleep quality improvements assessed by questionnaires and by pharmaco-EEG showing an increase of $\theta$ and decrease of $\alpha$ and $\beta$ waves 1 and 2h after drug dosing (Bettica et al., 2012a, b).

Analysis of sleep phases revealed that the duration of PS was augmented after the SB-649868 administration while an opposite effect of zolpidem was
SB-649868 was shown to dose-dependently inhibit CYP3A4 using simvastatin as a known drug metabolized by this enzyme. After administration of SB-649868, exposure to simvastatin was increased, suggesting CYP3A4 attenuation (Bettica et al., 2012c). It is worth mentioning that CYP3A4 is known to metabolize SB-649868 (Renzulli et al., 2011), so an inhibition of self-metabolism may occur.

SB-649868 seemed to be quite well tolerated with side-effects mostly related to the sleep-promoting mechanism of action (Bettica et al., 2012a, b, c). However, a dose-related cognitive impairment was observed 2 h after drug administration with no residual effects in the morning several hours later (Bettica et al., 2012c).

**Suvorexant (MK-4305)**

Suvorexant, like almorexant, is a dual antagonist of orexin receptors and is currently in phase 3 clinical trials (Table 3). Changes in sleep behaviour after 30 mg/kg treatment were observed in rats (Cox et al., 2010). It has also been shown to induce a transient decrease in locomotor activity, dose-dependently promote sleep and to positively modify sleep architecture in rats, dogs and rhesus monkeys (Cox et al., 2010; Winrow et al., 2011).

Randomized, double-blind clinical trials focused on the efficacy and tolerance of suvorexant in patients suffering from primary insomnia. Polysomnographic studies involved two 4-wk sessions of oral administration of suvorexant at doses of 10, 20, 40 and 80 mg. The treatment was shown to have significant dose-related effects for sleep induction and maintenance parameters. In general, the drug was well tolerated with only one patient suffering from side-effects in the form of hypnagogic hallucinations and daytime sleepiness (Herring et al., 2012).

**MK-6096**

MK-6096 is a highly potent and selective antagonist of both orexin receptors in humans and rats, with equivalent potency for OX1R and OX2R (Winrow et al., 2012). It represents a new series of DORAs, a 2,5-disubstituted piperidine with a molecular structure slightly different to that of almorexant and suvorexant. MK-6096 has been shown to dose-dependently promote sleep in rats and dogs (Coleman et al., 2012; Table 3). In rats, a reduction in active wakefulness has been observed associated with an increase in SWS and PS and a decrease in latency for both states. This sleep-promoting effect was less evident after almorexant administration and, in this case, no changes in SWS and PS latencies were observed (Winrow et al., 2012). Moreover, in contrast to almorexant (revealing lower efficacy in somnolescence induction), MK-6096 treatment in dogs led to a significant dose-dependent decrease in active wakefulness.

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**Table 2. Pharmacokinetic parameters after single and repeated dosing with SB-649868 in humans**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Doses (mg)</th>
<th>Values</th>
<th>References</th>
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<tbody>
<tr>
<td>AUC (ng · h/ml; 0–24 h)</td>
<td>5</td>
<td>843.0</td>
<td>(Bettica et al., 2012c)</td>
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<tr>
<td></td>
<td>10</td>
<td>1930.9</td>
<td>(Bettica et al., 2012a)</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>4308.0</td>
<td>(Bettica et al., 2012c)</td>
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<tr>
<td></td>
<td>30</td>
<td>7229.0</td>
<td></td>
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<tr>
<td></td>
<td>60</td>
<td>8300.0 (0–∞) (Renzulli et al., 2011)</td>
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<tr>
<td></td>
<td></td>
<td>6734.1 (Bettica et al., 2012a)</td>
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<tr>
<td>Cmax (ng/ml)</td>
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<td>158.0</td>
<td>(Bettica et al., 2012c)</td>
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<td></td>
<td>10</td>
<td>281.7</td>
<td>(Bettica et al., 2012a)</td>
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<tr>
<td></td>
<td>15</td>
<td>624.0</td>
<td>(Bettica et al., 2012c)</td>
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<tr>
<td></td>
<td>30</td>
<td>964.0</td>
<td></td>
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<tr>
<td></td>
<td>60</td>
<td>1200.0 (Renzulli et al., 2011)</td>
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<tr>
<td></td>
<td></td>
<td>775.5 (Bettica et al., 2012a)</td>
<td></td>
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<tr>
<td>tmax (h)</td>
<td>5</td>
<td>2.5</td>
<td>(Bettica et al., 2012c)</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>1.5</td>
<td>(Bettica et al., 2012a)</td>
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<td></td>
<td>15</td>
<td>2.5</td>
<td>(Bettica et al., 2012c)</td>
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<td></td>
<td>30</td>
<td>4.0</td>
<td>(Renzulli et al., 2011)</td>
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<tr>
<td></td>
<td>60</td>
<td>4.0</td>
<td>(Bettica et al., 2012a)</td>
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<tr>
<td>t1/2 (h)</td>
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<td>3.47</td>
<td>(Bettica et al., 2012c)</td>
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<tr>
<td></td>
<td>60</td>
<td>4.80</td>
<td>(Renzulli et al., 2011)</td>
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OX1R and OX2R, orexin receptor 1 and 2 respectively; AUC, area under the curve.

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Observed (Bettica et al., 2012a, b). However, the duration of SWS was not affected by SB-649868 in a human model of noise-induced insomnia (Bettica et al., 2012b) or even decreased in patients and healthy subjects (Bettica et al., 2012a, c).

Interestingly, SB-649868 was also shown to dose-dependently inhibit CYP3A4 using simvastatin as a known drug metabolized by this enzyme. After administration of SB-649868, exposure to simvastatin was increased, suggesting CYP3A4 attenuation (Bettica et al., 2012c).
corresponding with an increase in light SWS phase 1 and deep δ SWS phase 2 as well as a trend increase in PS (Coleman et al., 2012; Winrow et al., 2012). SWS phase 1 and 2 latencies were reduced, whereas PS latency showed a tendency to decrease. In comparison to almorexant, MK-6096 has higher bioavailability and a cerebrospinal fluid:plasma ratio. In addition, it induces somnolence in dogs at markedly lower doses than almorexant. It is also noteworthy that MK-6096 binds human orexin receptors more rapidly (approx. 2-fold) than almorexant (Winrow et al., 2012). Although only few data are available yet, this novel DORA has a promising preclinical profile.

Conclusions

The present century has witnessed an increase of sleep-related disorders accompanied by efforts to produce more effective treatments than the traditional benzodiazepines, non-benzodiazepines (Z-drugs), antagonists of H1-histamine receptors and agonists of melatonin receptors. The ideal candidate would only promote sleep during night time with no sleep architectures disturbances. It would also provoke a negligible recurrence of insomnia on discontinuation of treatment and no rebound effects or withdrawal symptoms. Orexins have been shown to play a crucial role in sleep physiology and seem the correct target for novel therapies for insomnia. The recent development of DORAs has shown very promising results in animal models and humans, although some concerns regarding their safety have been raised. Furthermore, orexins not only play a role in sleep–wake cycle regulation, but are also involved in a wide variety of neurological functions. These include the control of energetic homeostasis, the regulation of biological rhythms, pain reception, the activity of the HPA axis, the reward system as well as learning, motivation and addiction. Orexin receptors show a wide distribution in the central nervous system and are all modulated by the different DORAs; therefore, going far beyond a simple sleep regulator effect. For instance, orexins are able to activate the HPA both via adrenocorticotropic hormone release promotion and direct OX1R-mediated stimulation of adrenal cortex secretion (Kuru et al., 2000; Spinazzi et al., 2006). There are also suggestions that HPA stimulation by orexin A could be mediated through the release of neuropeptide Y (Russel et al., 2001). Although the HPA system may probably be involved in sleep modulation, data concerning its role in this process are rather conflicting (Katayama et al., 2010; Lattova et al., 2011). Glucocorticoid effects seem to be dose dependent, low doses decrease

<table>
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<th>Doses (mg/kg)</th>
<th>Values</th>
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<td></td>
<td>3</td>
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<td>(Winrow et al., 2012)</td>
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<tr>
<td>Cmax (μM)</td>
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<td>(Coleman et al., 2012)</td>
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<tr>
<td></td>
<td>3</td>
<td>0.5</td>
<td>(Winrow et al., 2012)</td>
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<tr>
<td>t1/2 (h)</td>
<td>2</td>
<td>0.5</td>
<td></td>
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OX1R and OX2R, orexin receptor 1 and 2 respectively; AUC, area under the curve.
wakefulness and increase SWS content (Friess et al., 2004), in contrast to higher ones that act conversely (Vazquez-Palacios et al., 2001). Moreover, recent evidence suggests that disturbances of the HPA system in patients suffering from sleep disorders are independent of its negative feedback mechanism (Lattouva et al., 2011). Supporting these results, recent studies also show that almorexant does not affect the HPA in rats (Steiner et al., 2013). Therefore, it could be concluded that orexin signalling plays a non-essential role in HPA function, suggesting that the effect of DORAs on this system is rather doubtful. Interestingly, long-term PS deprivation in rats results in HPA axis activation and increased orexin levels in the hypothalamus (Galvao Mde et al., 2009).

Some studies reported a potential anorexinergic effect of DORAs (Piccoli et al., 2012) through the blockage of orexin-related excitatory action on type 1 cannabinoid receptors (CB₁). This parameter should be carefully monitored in the future among other possible side-effects that the short-term studies have not yet revealed. On the other hand, a novel potential method in the treatment for compulsive eating disorders may be taken into consideration. Some noteworthy findings suggest that CB₁ activation could also induce sleep promotion (Santucci et al., 1996; Murillo-Rodriguez et al., 2011). It may suggest the existence of an alternative mode of the DORAs' hypnotic action in the brain. Despite some legitimate concerns, DORAs seem to be a promising alternative in the pharmacotherapy of insomnia. Their lack of myorelaxation and sedative effects is desirable but, more importantly, their non-addictive properties and their beneficial effect on sleep architecture are definitely in their favour. Putative application of DORAs in the treatment of depression and migraine, which are diseases often accompanying insomnia, are also of potential interest.

A greater understanding of the role of orexins in brain function and sleep–wake disorder mechanisms, together with pharmacological progress, may introduce selective antagonists of orexin receptors, which have only been used in basic studies so far. It has been suggested that central orexin insufficiency, which plays a key role in narcolepsy and cataplexy pathogenesis, can also be corrected by selective agonists of orexin receptors, e.g. OBT-9 (Lee et al., 2010). This hypothesis has already found its application in psychiatric practice, where modafinil, a psychostimulant used for narcolepsy treatment, proved to excite the orexinergic system (Ishizuka et al., 2012).

A new, more appropriate way to treat sleep disorders has been revealed and may also be a potential alternative in the design of new therapeutic strategies for other orexinergic mediated pathologies, such as drug addiction, obesity, eating and neuropsychiatric disorders. Nevertheless, there are still many questions related to the pharmacological effects of DORAs and many more detailed basic and clinical studies are needed to prove their potential usefulness for insomnia treatment.

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Statement of Interest

None.

References


