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Orexin Receptor Antagonists

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Abstract

Purpose of Review This paper focuses on the role of orexin receptors in sleep as evidenced in recent preclinical and clinical work. Orexin A and B and their two receptors (OX_1R and OX_2R) play essential roles in arousal and sleep/wake regulation, addiction, and stress. The absence of orexin producing cells in the lateral hypothalamus or of orexins in the CSF results in narcolepsy with cataplexy in humans. This finding and others on sleep phenotypes in orexin or orexin receptor knockout mice have triggered drug discovery programs on orexin receptor (OXR) antagonists for the treatment of insomnia and other disorders.

Recent Findings Several OXR antagonists, most of which are dual OX_1R/OX_2R antagonists (dual orexin receptor antagonists (DORAs)), have now reached phase II/III clinical trials. Suvorexant (Belsomra®), recently registered in Japan, USA, and Australia for insomnia, is the first orexinergic hypnotic principle of this new class. DORAs promote sleep primarily by increasing REM sleep, with little effect on slow wave sleep (SWS). Based on rodent studies, it is clear that the OX_2R is the primary target mediating sleep promotion by DORAs. We briefly review preclinical and clinical data of OXR antagonists in situations of unperturbed and perturbed sleep, e.g., insomnia and various neurological diseases.

Summary We propose that REM sleep enhancement by DORAs may provide opportunities to treat specific neurological disorders. By contrast, OX_2R antagonists such as seltorexant (JNJ-54717793/MIN-202) or MK-1064 may have broader applications as they appear to promote balanced sleep architecture in preclinical models and should, in theory, have a lower narcoleptic/cataplectic potential. These concepts require further validation as more OXR antagonists move beyond early stages of clinical development.

Keywords Orexin · Hypocretin · Orexin receptors · Antagonists · Hypothalamus · Sleep · Feeding · Reward · Addiction · Insomnia · Narcolepsy/cataplexy

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Introduction

The first clinical data on an orexin receptor antagonist developed for the treatment of insomnia were presented in 2007 [1], just 9 years after the initial publications describing the two orexin peptides and their two receptors (OX_1R and OX_2R) [2, 3]. This short time frame between discovery and clinical data is unheard of, at least in the field of low molecular weight compounds, where a normal development program can take up to 15 years from preclinical research to regulatory submission and more than 30 years from initial drug target discovery to market entry. The first orexin receptor antagonist in the clinical setting was almorexant [1], developed by the Swiss Biotech Actelion; initially alone, then in collaboration with

Glaxo Smith Kline (GSK). Almorexant reached phase III clinical studies and was eventually stopped for undisclosed reasons, most likely a safety issue [4]. Orexin (OX), a neuropeptide that comes in two forms (OXA and OXB), was discovered independently by two groups. One team was at Scripps in La Jolla, led by G. Sutcliffe. They reported the discovery of two peptides in January 1998, which they named hypocretins (HCRT1 and HCRT2), since their structure was reminiscent of incretins [2, 3] and because the 3000–7000 cells in rodent brain producing hypocretins are exclusively located in the lateral hypothalamus (LH). One month later, in February 1998, a group led by M. Yanagisawa (Howard Hughes Medical Institutes/Dallas) reported the deorphanization of two G-protein-coupled receptors (GPCRs): these were named OX_1R and OX_2R and their endogenous ligands named orexin A and B [3]. The name orexin, from the Greek "orexis" for appetite, was related to the observation that when orexins were applied intracerebroventricularly, food intake was increased [5–7]. Orexins were also produced exclusively by LH cells, and their sequence identical to that of HCRT1 and HCRT2, respectively; being, as they were, the same peptides as hypocretins.

Ultimately, it was decided that the genes would be named hypocretin and the gene products, i.e., peptides and receptors, named orexin [8, 9]. There are approximately 70,000 cells producing orexin in the human brain, all located in the LH [10], whereas OX_1R and OX_2R have a wide brain distribution [11, 12]. One year after the initial discovery of orexins, orexin peptide knock out mice were reported to have rapid transitions between wake and REM sleep [13]; such transitions do not occur normally, except in patients suffering from narcolepsy with cataplexy. Indeed, post mortem brain analysis showed that such patients lacked orexin-producing LH cells [10, 14–16], possibly as the result of an autoimmune disorder [17, 18]. Thus, CSF orexin levels are extremely low or below detection limit in patients suffering from narcolepsy with cataplexy [14, 19–21]. On the other hand, orexin levels are relatively normal in a number of neurological or psychiatric diseases, e.g., depression and narcolepsy without cataplexy, whereas in Alzheimer's disease, CSF orexin levels tend to be elevated [22, 23]. The OX_2R is non-functional in dogs suffering from narcolepsy with cataplexy [24, 25], but there is no evidence for an orexin receptor (OXR) defect in human patients. Furthermore, LH orexin-expressing cells actively fire during wake periods, with a peak preceding sleep onset; whereas, firing attenuates almost completely during sleep, to start again in the next wake state; and there is also a reduced firing rate during quiet wake in comparison to active wake [26].

Collectively, these findings supported that the orexin system is strongly involved in sleep wake regulation and arousal [27–32]. By 2005, it was agreed by an expert committee that narcolepsy with cataplexy is due to the absence of orexin A in the brain and that the very low CSF levels of the peptide can be used as a biomarker of the disorder [33–35]. Orexin KO mice show behaviors reminiscent of narcolepsy with cataplexy, which is triggered by strong positive (e.g., food, sex) or negative emotional triggers (e.g., fear), as is the case in human patients [13, 36]. Orexin KO mice show reduced locomotion and food intake, but increased body mass [36, 37]. Orexin receptor KO mice have different sleep phenotypes [38–41]: OX_1R KO shows almost no sleep disturbances, whereas OX_2R KO has a moderate phenotype with mildly fractionated sleep and wakefulness, and the appearance of, albeit rare, fast transitions from wake to REM sleep. By contrast, double OX_1R/OX_2R KO mice, like orexin KO mice, show frequent cataplexy attacks, a greater number of rapid transitions from wake to REM sleep and highly fragmented sleep throughout the light and dark phases. The narcolepsy phenotype of such mice can be corrected by orexin gene transfer [42, 43] or by applying orexin intranasally: this approach was also tried in humans suffering from narcolepsy with cataplexy, but with limited success given the pharmacokinetic liabilities of the orexin peptide [44]. Based on the sleep and feeding phenotypes in various murine models, Biotech and Pharma companies started drug development programs soon after the discovery of orexin, which were initially aimed at food intake and obesity, with, e.g., OX_1R antagonists [45]. However, the results observed in animal models did not translate into a clinical setting, and this approach has apparently been abandoned. Concomitantly, dual OXR antagonists were investigated in sleep, e.g., at Actelion, Glaxo, and Merck. Thus, candidate drugs such as almorexant, SB-649868, suvorexant, and filorexant, all dual OXR antagonists, reached phase II/III clinical development within the last few years [1, 46–48] (and see [49–52]). Suvorexant is the first OXR antagonist registered for the treatment of insomnia in Japan, the USA, and Australia, with other applications pending [53–55]. We shall describe these efforts below. Further research is also actively ongoing in the addiction field, since orexin and OXR play a role in drug addiction, e.g., alcohol, cocaine, and others, with either OX_1R and/or OX_2R as the main targets [56–59] (see also [60]).

The Role Orexin and Orexin Receptors in Sleep/Wake Regulation

At Novartis, given that OX_1R KO mice have almost no sleep phenotype and OX_1R/OX_2R KO replicate the narcolepsy/cataplexy phenotype observed in orexin KO and in humans, we initially investigated the respective contributions of OX_1R and OX_2R in sleep regulation. We tested almorexant in mice lacking either the peptide or the receptors, namely OX_1R, OX_2R and both OX_1R/OX_2R [61]. Almorexant dose-dependently induced sleep in wild-type (WT) and OX_1R KO

mice, whereas it was devoid of effects in OX_2R KO or double OXR KO mice. Thus, the data indicated that the OX_1R receptor did not contribute to almorexant-induced sleep, that the sleep effects were entirely OX_2R-dependent, and furthermore, that no other receptors were responsible for the effects of almorexant. Interestingly, almorexant had a clear effect on total sleep time in WT mice, whereby REM was increased more than NREM sleep [61]. A closer look at the OX_1R KO mice suggested that almorexant disproportionately increased REM sleep in this mutant, albeit without increasing total sleep time (TST). Interestingly, C. Dugovic and colleagues at Janssen reported that a combination of OX_1R and OX_2R antagonists [62, 63] produced more marked effects on REM sleep than OX_2R blockade alone. Indeed, this team commonly uses REM sleep as a marker for OX_1R receptor engagement [64] (see also [65]). Different roles for OX_1R and OX_2R in REM and NREM sleep have thus been advocated [66–68].

The logical consequence of these findings is that a selective OX_2R antagonist would probably induce sleep to the same extent as dual antagonists, but with a reduced potential for incurring cataplectic attacks, an issue raised early on by M. Tafti [69]. This hypothesis was rejected by most teams working on dual OXR antagonists, as no spontaneous attacks have been documented in normal animals (rodents, dogs, non-human primates) treated with any of the current OXR antagonists. However, as we shall describe below, suvorexant is contra-indicated in patients suffering from narcolepsy with cataplexy, as it produces cataplectic attacks in narcoleptic dogs [54••]. Similarly, almorexant induces cataplexy in sensitive mice [70]. In any case, we and others took the route to develop OX_2R selective antagonists (see [49, 71–73]). One of the main arguments for that path is that dual antagonists induce REM/NREM sleep imbalance and sleep onset REM (SOREM), whereas OX_2R antagonists produce a more physiologically balanced sleep. Whether a high level of REM sleep is detrimental can be discussed at length [74, 75]; however, we felt convinced that SOREM, which can be seen with dual antagonists, is not desirable in any patient population (see also [76, 77]). In contrast, enhancing REM sleep may ultimately prove beneficial in patients where there is a REM sleep insufficiency or disruptions such as fragmentation, as seen in a number of neurological or psychiatric diseases, including post-traumatic stress disorder (PTSD) and Alzheimer's disease (see [78, 79]).

Clinical Status of Dual Orexin Receptor Antagonists

Almorexant

Almorexant, ACT 078573, is a dual receptor antagonist with high affinity and almost equal nanomolar potency at OX_1Rs and OX_2Rs [1]. Almorexant was the first dual antagonist to be tested in insomnia patients [80]. Almorexant dose-dependently induced sleep in various species, increasing both NREM and REM sleep, in contrast to zolpidem, which reduced REM sleep profoundly; both drugs had similar effects on total sleep time (TST) [1]. Almorexant, unlike other hypnotics, does not show drug-drug interactions with alcohol and a number of other drugs and importantly, does not affect memory, in contrast to $GABA_A$ receptor modulators [81–84]. Another interesting feature of the antagonist is that animals treated with almorexant are easily woken up and return to sleep readily, whereas under zolpidem, waking is more difficult [1, 85](see also [86•, 87]). These points indicate that orexin receptor antagonism is not subject to the same limitations as benzodiazepines and Z drugs (memory impairment, alcohol, and other drug-drug interactions). Furthermore, almorexant shows no evidence of withdrawal effects or drug-dependency potential after treatment cessation. On the contrary, orexin receptor antagonists may be good candidates for various forms of addiction [60].

Almorexant has been investigated in clinical studies for efficacy, pharmacokinetics (PK) and pharmacodynamics (PD), formulation, abuse potential, and drug-drug interactions. There are seven published studies evaluating almorexant's potential as a hypnotic, four in healthy subjects, including one in elderly [1, 88–90] and three in insomnia patients, one of which was also in elderly subjects [80, 91•, 92]. In single ascending dose studies, almorexant was tested at 1, 5, 25, 50, 100, 200, 400, and 1000 mg in healthy male subjects: effects on wake and sleep became prominent at 200 mg, with a marked decrease in latency to stage 2 (S2) sleep [1, 88]. A 2012 multiple ascending dose study revealed significant effects in polysomnography (PSG) outcomes, with almorexant reducing latency to REM and increasing REM sleep duration [89]. Two phase III clinical studies have only recently been published. In 709 insomnia patients, almorexant (100 and 200 mg) was compared to zolpidem (10 mg) and placebo over 16 days. Wake after sleep onset (WASO) and latency to persistent sleep (LPS) were reduced and TST increased by 200 mg almorexant [92]. PSG showed increases particularly in S2 and REM sleep on day 1–2 of treatment vs baseline, although only REM sleep was increased as a percentage of TST. Latency to stage 1 (S1), S2, and REM sleep were all reduced on days 1–2, but not SWS, with latency to REM sleep more affected than other stages (− 15 and − 18 min by 100 and 200 mg doses, respectively). The effect on latency to REM sleep was similar after 15–16 days of dosing, while the effects on other sleep stages were lost [92].

Almorexant was also tested in a phase III study in elderly patients with primary insomnia [91•] at 25, 50, 100, and 200 mg in groups of up to 100 patients each. Almorexant dose-dependently increased sleep, with a marked effect on wake after sleep onset (WASO; up to − 46.5 min/night) and a small reduction in LPS. There was a clear increase in S2 (up

to 20 min/night) and especially REM sleep, (up to 25 min/night), but no increase in slow wave sleep (SWS). Latency to stage 1 or SWS was hardly affected, whereas latency to REM sleep was reduced by up to 30 min. Thus, almorexant (like other DORAs) increases sleep by affecting S2 and REM, but not slow wave sleep (see Fig. 1). As stated in Roth et al., 2017: "Similar to previous data with the dual orexin antagonist SB-649868, almorexant consistently increased the amount of total time spent in REM and reduced latency to REM." [91•]. The incidence of side effects in the elderly subjects study was comparable to the placebo group, although somnolence and fatigue are mentioned. Special attention was paid to muscle weakness and cataplexy, which were not observed in the study, an important consideration in the elderly, given the higher propensity for falls in this population. Almorexant was stopped after phase III (see [4, 89]).

SB-649868

SB-649868 is also a dual OXR antagonist [48], which binds with high affinity and shows almost equal nanomolar potency at OX_1R and OX_2R in calcium mobilization assays. SB-649868 was discovered at Smith Kline Beecham (SKB) and with the successive mergers, ended up in the Glaxo development pipeline, since the discovery of orexin receptors by Yanagisawa's team was supported by the SKB orphan receptor program [3]. SB-649868 has been tested in various clinical settings: in healthy volunteers subjected to sleep deprivation (10–80 mg); in situational insomnia (10 and 30 mg, compared to zolpidem 10 mg), and eventually in patients with primary insomnia (10, 30, and 30 mg) [93, 94, 95••]. All studies were performed in male subjects. In healthy volunteers, SB-649868 dosed at 30 and 60 mg produced sleep, but had no effect on stage 1 or SWS; SB-649868 affected only REM sleep. It had clear effects on WASO and LPS, again primarily by reducing latency to REM sleep, with one and seven subjects showing sleep-onset REM sleep (SOREM) at 30 and 60 mg, respectively (see Table 1). As stated by the authors "A dose-dependent increase in absolute and percent REM sleep and reduction in REM sleep latency was observed mainly at the 60-mg dose" [95••]. Sleep architecture when analyzed as percentage of TST revealed that NREM, S1, and SWS were significantly reduced, whereas the proportion of REM sleep was dose-dependently increased. Although a dual antagonist, our kinetic studies suggest that dissociation of SB-649868 from OX_1Rs is slower than from OX_2Rs [96], suggesting some OX_1R selectivity at equilibrium, which may explain the pronounced effects on REM sleep duration and latency.

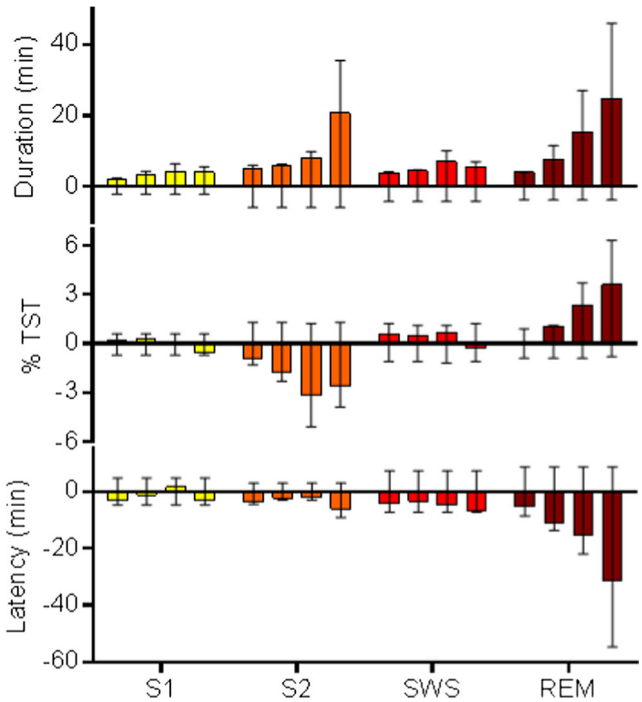

Fig. 1 Effects of almorexant in elderly patients suffering from insomnia. The data are from the supplementary information of Roth et al., 2017 [91•] and show duration and percentage of, as well as latency to stages 1 and 2, SWS and REM sleep (95% confidence intervals) at the increasing doses of 25, 50, 100, and 200 mg. Note the main effects on S2 and especially on REM sleep

The PK of SB-649868 has been determined in healthy volunteers at 5, 15, and 30 mg: Tmax was at 1–3 h or more with a lipid-rich meal, and T½ ranged from 4 to 7 h. Therefore, in clinical studies, the compound was administered 90 min before bedtime. When given for 15 days, Cmax and AUC of SB-649868 increased, indicating accumulation. Side effects were moderate, with evidence of next morning somnolence, fatigue, and dizziness in a dose-dependent manner. Seven subjects out of 19 at 30 mg showed SOREM (REM latency < 15 min) in the phase I study. The compound had no negative effects in a series of cognitive tasks performed the next morning, except for the word recall test. Hallucinations, sleep paralysis, and cataplexy were not noted [95••]. SB-649868 appeared to be stopped after phase II for undisclosed reasons (although there were no announcements to that effect).

Suvorexant

Suvorexant from Merck, also known as MK-4305 or Belsomra® [47, 97, 98], is the most widely tested sleep drug in the world [53, 99–107, 108••, 109] (reviewed in [51]). Suvorexant is a dual OXR antagonist, with high affinity and almost equal nanomolar potency at OX_1R and OX_2R. The compound has been tested in a number of species: rats, mice, dogs, and non-human primates. Across all, there is good evidence for sleep inducing effects, although with little effect on SWS. Suvorexant induced sleep in a purely OX_2R receptor-dependent manner, in that, no sleep enhancing effects are seen in OX_2R KO mice, and like all dual OXR antagonist, suvorexant drives essentially REM sleep, e.g., as stated in Herring et al., (2012): "…increases in TST for suvorexant

Table 1 Effects of SB-649868 in adult males with primary insomnia

PSG parameter	Placebo	SB-649868 10 mg	SB-649868 30 mg	SB-649868 60 mg
LPS (min)	54.8 (38.4)	29.3 (22.9)	21.8 (21.6)	10.6 (10.3)
REML (min)	82.8 (34.3)	78.3 (36.5)	60.9 (31.3)	52.4 (30.1)
TST (min)	367.9 (45.7)	390.4 (46.8)	417.9 (30.5)	438.1 (19.8)
WASO (min)	63.6 (33.9)	66.3 (42.0)	44.8 (26.9)	34.6 (18.6)
REM (min)	77.6 (19.6)	82.5 (26.2)	95.7 (25.2)	109.6 (23.3)
S1 (min)	61.3 (21.8)	61.4 (21.8)	64.0 (21.5)	65.0 (22.5)
S2 (min)	201.1 (41.8)	221.3 (35.6)	231.7 (33.2)	235.2 (29.2)
SWS (min)	28.0 (30.4)	25.1 (27.6)	26.5 (26.4)	28.3 (30.4)
REM (%)	20.8 (4.7)	20.8 (5.5)	22.8 (5.9)	24.9 (5.0)
SEI (%)	76.6 (9.5)	81.3 (9.7)	87.1 (6.4)	91.3 (4.1)
S1P (%)	17.3 (6.5)	16.0 (5.8)	15.6 (5.9)	15.0 (5.7)
S2P (%)	54.2 (8.0)	56.9 (7.9)	55.4 (7.6)	53.7 (6.7)
SWSP (%)	7.7 (8.3)	6.3 (6.8)	6.2 (6.1)	6.4 (6.8)

The data are from Bettica et al., 2012 [95••] and describe latency to persistent sleep—*LPS*, latency to REM—*REML*, total sleep time—*TST*, wake after sleep onset—*WASO*, rapid eye movement sleep—*REM*, sleep stages 1 and 2—*S1* and *S2*, slow wave sleep—*SWS*, as well as the different sleep phases in percentage of total sleep and sleep efficiency index—*SEI%*, determined using polysomnography—*PSG* (standard deviation), in groups treated with placebo or SB-649868 10, 30, or 60 mg. Note the absence of effect on SWS, compared to S2 and REM sleep

compared with placebo were mainly attributable to greater time spent in REM sleep and, to a lesser degree, stage-2 sleep" [103]. There were no negative effects on cognition or synergism with alcohol (although monkey data submitted to the US Food and Drug Administration (FDA) suggest a slight interaction) or withdrawal or dependence. Normal animals showed no muscle weakness or cataplectic attacks [110•, 111–113]. This may not be surprising, since cataplexy tends to occur in situations of strong positive or negative stimuli [69]; thus, narcoleptic dogs may show an enhanced propensity for cataplectic attacks when suvorexant is given in combination with a food presentation challenge (see [53]). Thus, the FDA recommended suvorexant not to be prescribed to narcolepsy with cataplexy patients. Suvorexant was subjected to extensive phase II trials in primary insomnia patients at 10, 20, 40, and 80 mg. During phase III, suvorexant was tested at 15, 20, 30, and 40 mg in adult and elderly insomnia patients, during 3 months and then up to 12 months, with a large number of patients—up to 600 patients per arm. Suvorexant dose-dependently increased sleep and reduced WASO and LPS, with no evidence of withdrawal symptoms, cognitive impairment or reduced efficacy after 1 year of administration, in the longest investigator-driven study of a hypnotic to date. Similar to almorexant, suvorexant affected REM sleep and to a lesser degree stage 2 sleep with no effect on SWS [103]. Suvorexant, especially in the high doses, reduced latency to REM sleep and produced SOREM in a dose-dependent manner in some patients. Suvorexant has been submitted for registration in Japan, USA, and Australia. Japan accepted the submission, whereas the US FDA rejected the first application in 2012–2013, recommending to abandon the high doses, and to start dosing at 10 mg (or even 5 mg depending on CYP interactions and obesity), with 15 and 20 mg as the highest doses, given once per night. Suvorexant was then approved by the FDA in 2014. Australia rejected the first application, but a revised submission was successful in late 2016. Interestingly, the Australian TGA (Therapeutic Goods Administration) accepted the higher doses, in contrast to the FDA, as the Australian agency was not convinced of the efficacy of the 10 mg dose.

The PK of suvorexant is rather slow, with a Tmax between 2 and 3 h and a terminal half-life of 12–19 h, with longer half-life noted especially in obese subjects, and particularly obese women [54••]. Plasma suvorexant levels reach steady state after 4–5 days of repeated dosing, although it is only administered at bedtime. In addition suvorexant, like almorexant, SB-649868 and filorexant, dissociates very slowly from orexin receptors once bound [61, 96]. Thus, traditional PK may underestimate target engagement, as suvorexant may occupy receptors longer than expected from the PK data.

Suvorexant is generally considered to be well tolerated; the main side effect was dose-dependent next morning somnolence, which explains why the FDA rejected the 30 and 40 mg doses, as this was also seen to affect the driving ability of patients. Although suvorexant was in general as good as the comparators, there were still patients who showed a worsening of driving skills, as highlighted by the assessment of Dr. Farkas of the FDA (see [54••, 114]). Indeed, the FDA's response to suvorexant is in line with their recent unilateral decision to reduce the dosage of a number of sleeping pills, including Z-drugs [115, 116]. Other side effects of suvorexant are strange dreams and hallucinations, and there may be some muscle weakness in certain subjects. Altogether, based on

these finding, the the U S Food and Drug Administration (FDA) recommended 10 mg as a starting dose (or 5 mg for obese patients) with the possibility to increase to 15 and maximally 20 mg/night. Suvorexant prescribing information recommends the compound to be taken when already in bed (to avoid potential falls), only once per night and with at least 7 h of sleeping time available before wake time. It is also recommended not to drive the next morning, and as stated above, suvorexant is contra-indicated in patients suffering from narcolepsy with cataplexy.

Filorexant

Filorexant, or MK6096 [46, 98], was Merck's backup candidate to suvorexant; it went into phase II clinical studies. In contrast to suvorexant, filorexant has a relatively short T½ of 3–6 h [117]. The compound has been tested in various species [98], and in essence, filorexant replicates the effects of suvorexant, both in preclinical models and in the clinic [46, 117, 118]. In a phase II trial [117], filorexant was tested at 2.5, 5, 10, and 20 mg in primary insomnia adult male and female patients vs placebo for 4 weeks. Filorexant at 10 and 20 mg clearly increased LPS, WASO, and sleep efficiency. As with other dual OXR antagonists, TST, REM latency and duration, and S2 sleep represented the primary effects as measured by PSG; SWS was hardly affected by filorexant, even after 4 weeks' treatment. Somnolence was dose-dependently increased, but there were no major other side effects, nor was there any adverse signs following treatment cessation, i.e., no rebound insomnia [117]. Filorexant is currently not listed in the Merck development portfolio.

Lemborexant

Lemborexant, or E2006, from Esai is a dual OXR antagonist with nanomolar affinity at both receptors [119]. Functionally, lemborexant is about tenfold selective for OX_2R over OX_1R (0.44 vs 5.7 nM in calcium mobilization assays, respectively). In preclinical studies, it produces sleep with effects on both NREM and REM sleep, although there appears to be a dose-dependent increase at REM sleep at the doses tested (10 and 30 mg/kg), whereas NREM was already at ceiling responses [119]. Lemborexant is in phase II/III for the treatment of insomnia (ClinicalTrials.com ID: NCT01995838, NCT02952820, NCT03001557), with an abstract published on one study which investigated 1, 2.5, 5, 10, 15, and 25 mg or placebo administered for 15 nights [120]. PSG was conducted at baseline and on treatment days 1/2 and 14/15. Lemborexant induced sleep and reduced WASO during the second half of the night, although a detailed clinical study remains to be published. Lemborexant was apparently well tolerated, with moderate adverse events, e.g., headache and dose-related somnolence.

Act-462206

ACT-462206 is the second dual OXR antagonist from Actelion [121, 122]; it has been tested in healthy male volunteers at doses between 5 and 1500 mg. The compound had rather slow PK features in humans, with dose-dependent half-lives from 5.3 to 12.4 h and a Tmax of 1.5 to 4 h. In contrast, in rodents, the compound shows a rapid absorption and elimination, with a T½ of less than 2 h, suggesting interesting PK features. The pharmacodynamic effects investigated in the clinical setting were vigilance and attention, alertness, and motor coordination, which lasted less than expected from the PK, whereas effects on sleep by PSG are not documented. At the highest tested doses, significant plasma concentrations of ACT-462206 were still present 48–72 h after administration, clearly too long to avoid the next morning somnolence that has been a concern to FDA with a number of sleep-inducing pills over the recent past [115, 116]. ACT-462206 has apparently been discontinued after the phase I trials.

Selective Orexin Receptor Antagonists

Seltorexant

JNJ-42847922, also known as JNJ-922, MIN-202 or seltorexant, is a high-affinity antagonist with about 100-fold selectivity for OX_2R [72, 73]. The compound is in co-development by Janssen/Johnson & Johnson and Minerva Neurosciences; it is promoted as producing balanced sleep in insomnia and depression. In rats, seltorexant (3–30 mg/kg) dose-dependently reduced latency to NREM and prolonged NREM sleep, whereas it affected REM sleep minimally. Seltorexant's effects on sleep were maintained upon 7-day repeated dosing (30 mg/kg). Like other OXR antagonists, it had no effect in OX_2R knockout mice [64]. In a single ascending dose study in healthy subjects, seltorexant (10, 20, 40, and 80 mg) increased somnolence and displayed a favorable PK and safety profile [64]. The majority of subsequent clinical information about seltorexant is available only as press releases and a meeting abstract. A phase II trial was performed in 20 insomnia patients with major depressive disorder (MDD) stably treated with selective serotonin reuptake inhibitors (SSRIs) and serotonin/noradrenalin reuptake inhibitors (SNRIs) [123, 124]. The patients received placebo and seltorexant at 10, 20, or 40 mg in a cross-over design. Sleep onset was rapid and TST was increased up to 45 min, with a dose-dependent reduction in LPS as measured by PSG. Sleep was described as physiological or restorative [125]. In insomnia patients without psychiatric comorbidity, seltorexant was tested vs placebo over 7 days at 2 × 20 mg: the PSG data showed positive effects on LPS, TST, and WASO ([126] and NCT02464046). Side effects were somnolence and abnormal

dreams; the compound is otherwise reported as safe [127]. The compound (2 × 20 mg) was also tested against placebo and zolpidem (10 mg) in healthy volunteers on cognitive performance and simulated driving. The full reports are pending.

MK-1064

MK-1064 [128, 129] is a selective OX_2R antagonist (as are MK-3697 [130] and MK-8133 [131]). MK-1064 was in a phase I study in healthy volunteers [129], but the compound is not listed in the Merck development pipeline. MK-1064 at 50, 120, and 250 mg decreased LPS and WASO and increased TST and sleep efficiency. Both NREM and REM sleep were increased moderately. The human PK data shows that at these doses, significant plasma levels of MK-1064 are observed after 16–24 h. Overall, the team concluded that MK-1064 had no advantage over dual orexin receptor antagonists (DORAs) for either main or side effects, which were all moderate [129]. MK-1064 has not been tested in insomnia patients.

JNJ-54717793

JNJ-54717793 is a potent, brain penetrant, 50-fold selective OX_1R antagonist [64]. As expected, JNJ-54717793 has minimal effect on sleep in rats or WT mice. Interestingly, and along the lines elaborated above with regard to the summation of OX_1R and OX_2R antagonism enhancing REM sleep, JNJ-54717793 selectively promotes REM sleep in OX_2R knockout mice and reduces REM sleep latency, without changing NREM sleep [61–63, 65], although OX_1R antagonism in isolation has no sedative or hypnotic effects. JNJ-54717793 when tested in two rodent panic models attenuated CO_2 and sodium lactate-induced panic-like behaviors and cardiovascular responses. The compound was devoid of effects on baseline locomotor or autonomic activity or sleep. Its current development status is unclear, but the preclinical data are highly interesting.

Conclusions

There is no doubt that OXR antagonists produce sleep in patients with insomnia. This is true for both dual antagonists (suvorexant, almorexant, filorexant, SB-649868, and lemborexant) as well as the OX_2R antagonist seltorexant. Rodent PSG studies with OXR antagonists have proven highly translational across species in this regard, accurately predicting the effects of the drugs in humans, including patients with insomnia. Of note, suvorexant and most dual OXR antagonists have been tested in patients with "primary insomnia" as defined by DSM IV, although primary and secondary insomnia is not distinguished in DSM V [132]. Interestingly, seltorexant is apparently also efficacious in insomniacs who suffer from MDD (see [123–125]), although peer-reviewed reports are not yet available.

Dual OXR antagonists affect primarily REM and S2 sleep, with signs of SOREM with some agents, whereas OX_2R antagonists seem to induce a more balanced NREM/REM sleep. It is unclear what the consequences of increasing primarily REM sleep are, compared to the enhancement of both REM sleep and SWS; the long-term use of suvorexant and other dual OXR antagonists will clarify this matter. It is, however, obvious that the orexin receptor antagonist approach is different and indeed superior to benzodiazepines and Z drugs with regard to effects on sleep architecture. $GABA_A$ receptor modulators can reduce REM sleep, which is important for the consolidation of certain types of memory [133]. Indeed, a hypnotic that increases REM sleep may be of specific advantage in treating disorders where REM is reduced or disrupted. Addressing the orexin system may also be safer than the $GABA_A$ system with regard to side-effects and drug-drug interactions. Benzodiazepines and Z drugs show profound interactions with alcohol and lead to a general inhibition of the brain activity, like anesthetics; in addition, it is difficult to reverse the hypnotic state produced by these agents. OXR antagonists, in contrast, block the arousal, wake-promoting and motivated behavioral effects of orexin. They do not generally dampen the brain function, and thus allow treated subjects to awaken rapidly in case of need and to fall back to sleep as long as the active agent remains on board.

Currently, suvorexant is the only approved orexin receptor antagonist and only in USA, Japan, and Australia. More dual OXR antagonists are in development, as well as selective OX_2R antagonists (e.g., seltorexant). There are also a number of additional clinical trials under way with suvorexant and other OXR antagonists in patients with various psychiatric and neurodegenerative disorders, including Alzheimer's disease, where an orexin receptor antagonist may have beneficial effects, not only due to its direct effects on sleep, but also indirectly via the reduction of beta amyloid levels in the brain [134–136] (see ClinicalTrials.com study IDs NCT02750306 and NCT03077620). A study on Parkinson's disease is also reported to be recruiting patients, which may determine whether or not any residual, subclinical sleep paralysis induced by OXR antagonists may be capitalized upon for the treatment of REM sleep behavior disorder which occurs in this disorder (ClinicalTrials.com ID: NCT02729714). The potential of OXR antagonists in various addictions has not been addressed here, but is certainly promising [60, 137]. The many clinical studies underway will determine what potential OXR antagonists may have as a disease modifying agent in these indications. In the meanwhile, the future of orexin receptor antagonists as hypnotics appears to be well assured.

Compliance with Ethical Standards

Conflict of Interest Daniel Hoyer and Laura H. Jacobson declare no conflicts of interest.

Human and Animal Rights and Informed Consent This review article does not contain any studies with human or animal subjects.

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