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# Orexin Receptor Antagonism: A New Principle in Neuroscience

Christoph Boss*, Catherine Brisbare-Roch*, Francois Jenck, Hamed Aissaoui, Ralf Koberstein, Thierry Sifferlen, and Thomas Weller

*Abstract:* Orexins are hypothalamic neuropeptides interacting with G-protein coupled receptors in the brain. They play a role in the regulation of sleep–wake cycles in mammals, as suggested by the deficits in orexinergic function that are associated with rodent, canine and human narcolepsy. Selective or dual orexin1-receptor and/or orexin2-receptor antagonists or agonists that cross the blood-brain-barrier (BBB) may be of therapeutic interest for disorders of disturbed arousal and alertness. This article summarizes recent research to identify and characterize orexin receptor antagonists and their therapeutic potential for normalizing sleep in insomnia patients.

**Keywords:** G-protein coupled receptors · Medicinal chemistry · Neuroscience · Orexin receptor antagonists · Sleep–wake cycle

## 1. Introduction and Biological Background

Orexins (orexin A and orexin B, also named hypocretin 1 and 2, respectively) are peptides discovered in the brain in 1998 by two independent research groups as the result of systematic and intensive research programs on orphan G-protein-coupled receptors.[1,2] Orexins bind to two receptors (orexin1/$OX_1$ and orexin2/$OX_2$ receptors, also named HCRT1 and HCRT2 receptors, respectively) and are proteolytically derived from a single precursor peptide in a discrete population of neurons of the lateral hypothalamus. $OX_1$ receptors have preferential affinity for orexin A whereas $OX_2$ receptors do not discriminate between both neuropeptides *in vitro*. $OX_1$ or $OX_2$ activation produces intracellular $Ca^{2+}$ increases *via* functional coupling involving a Gq mechanism of transduction.[3] This ultimately results in slow membrane depolarization and in neuronal activation found to involve different ionic conductances in various brain regions in the rat, such as potassium conductance in locus coeruleus[4] or calcium current in tuberomammilary nucleus.[5]

The orexin system is well conserved across mammalian species. Orexin A is similar in rat, mouse, pig, and man and contains two disulfide bridges. Orexin B in rat and mouse differs by only one amino-acid (S18N) from porcine and human orexin B; it is a linear, non-lipophilic, less stable peptide than orexin A. Both orexins are derived from a single precursor peptide coded on human chromosome 17q21-24, which is syntenic with mouse chromosome 11.[6] High structural and functional homology is also reported for rat and human $OX_2$ and $OX_1$ receptors. The *in vitro* pharmacology of human and rat orthologs of $OX_1$ is very similar.[7] The human $OX_1$ receptor is coded on chromosome 1p33 and contains seven exons, the human $OX_2$ receptor is coded on chromosome 6p11-q11 containing seven exons over 108439 base pairs. In the mouse, splice variants of $OX_2$ are distributed in a tissue-specific manner.[8]

Following original observations that orexins have a role in appetite and food intake, most recent evidence suggests that orexins play a determinant role in functions beside the regulation of appetite. Orexins may thus be important in food intake only under particular circumstances, *e.g.* in response to hypoglycemia and/or in the regulation of circadian food intake.[9] Nerve fibers from orexin neurons are widely distributed in the brain suggesting that orexins exert multiple functions, in particular as regulators of behavioral arousal, sleep and wake states. Indeed, hypothalamic neurons have dense projections[10] to the basal forebrain, limbic structures and brainstem regions, in particular those related to waking and rapid eye movement (REM) sleep regulation. Enhanced behavioral activity, increased attention, prolonged latency to the first occurrence of REM, maintenance of cortical activation and activated cell firing in thalamic or reticular regions such as the locus coeruleus have been consistently reported following intracerebroventricular (icv) infusion of orexins in the rat.[11,12]

Since many homeostatic processes in mammals (*e.g.* food intake, body temperature, hormone release) are intimately linked to sleep and arousal, it is likely that orexins link sleep and arousal to these processes. It remains to study the orexin circuitry that is disturbed under states such as sleep loss, night or shift work, jet lag, aging, affective disorders and endocrine diseases. Manipulation of the orexin peptide-receptor system using brain-penetrant orexin receptor antagonists or full, partial, or inverse agonists may prove therapeutically useful in the treatment of those medical and psychiatric conditions associated with sleep disturbances. The relative brain distribution of $OX_1$ *versus* $OX_2$ receptors and their

*Correspondence: Dr. C. Boss, Dr. C. Brisbare-Roch
Actelion Pharmaceuticals Ltd
Drug Discovery and Preclinical Research & Development
Gewerbestrasse 16
CH-4123 Allschwil / BL
Tel.: +41 61 565 6561
Fax: + 41 61 565 6500
E-mail: christoph.boss@actelion.com
E-mail: catherine.brisbare@actelion.com

contribution to diverse neurobiological effects implies that different biological effects might be expected from drugs acting in the brain selectively at either $OX_1$ or $OX_2$ receptors or both.

## 2. Synthetic Orexin Receptor Ligands: Recent Patents on Antagonists

Several companies are working in the field of orexin receptor antagonism. Analysis of the recent patent literature shows that Merck & Co, Sanofi-Aventis and Actelion Pharmaceuticals seem to be very active in the field. A literature search going further back shows that GlaxoSmithKline (GSK) was very active in the field until 2004. Since then, no new patents have appeared authored by GSK, claiming orexin receptor antagonists. In the following sections a short summary of the patent literature is given. The authors do not claim completeness.

The patent literature generally implies the importance of orexin receptors to diverse pathologies, the most important being eating and appetite disorders, sleep disorders, depression, anxiety, or addictions. The different disorders seem to have different relationships to the orexin system. For treatment of certain diseases selective orexin receptor antagonists, either $OX_1$- or $OX_2$-selective compounds might be suitable, as for treatment of other pathologies dual $OX_1$-/$OX_2$-antagonists might be necessary. With clinical investigations of further compounds exhibiting different selectivity profiles, some of the questions about an optimal selectivity profile may be answered.

### 2.1. *Orexin Receptor Antagonists from Merck & Co*

A search in the Integrity® database (Prous Science) in the patents section, with the keywords 'Orexin AND Merck' resulted in the following hits, describing compounds from the classes depicted in Fig. 1.

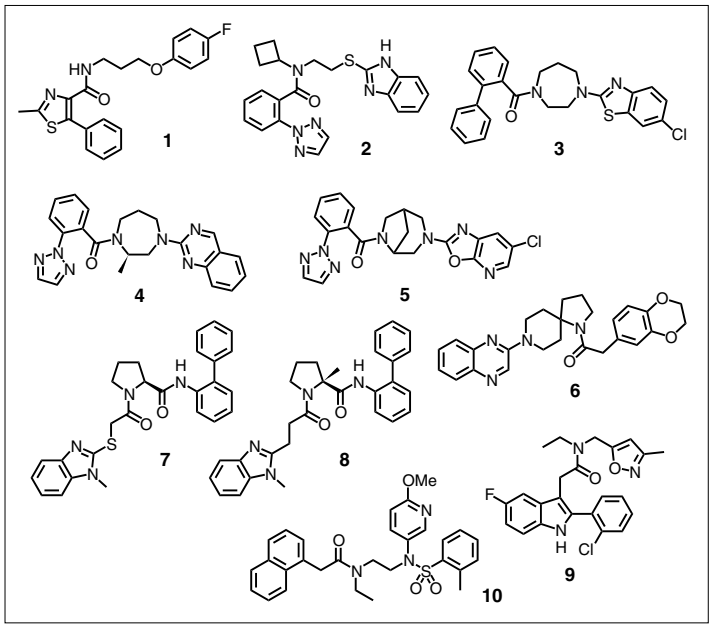


Fig. 1. Structures of orexin receptor antagonists from Merck & Co

Scientists at Merck & Co have so far mainly worked on structural classes related to earlier work done at GlaxoSmithKline (see Section 2.4.). The general structure of the majority of Merck's orexin receptor antagonists can be described as consisting of two aromatic systems connected by a linker of three or four bonds in length (**1** to **6**) Fig 1. Derivatives **1** and **2** are based on a linear chain linker.[13,14] One of the substituents is usually an *ortho*-biphenyl unit or a system which is structurally closely related, *e.g.* 5-aryl-thiazoles or 2-heteroaryl-phenyl-groups. With respect to the second aryl-unit, the receptors seem to be quite tolerant, as one can find simple phenyl-rings as well as a diversity of bicyclic, fused heteroaromatic systems. With respect to orexin antagonistic activity, no specific statements were made in any of Merck's patents. In general, the compounds inhibit both orexin receptors with an $IC_{50}$ < 50 μM. Preferred compounds show an $IC_{50}$ < 100 nM on at least one of the orexin receptors. Compounds **3**, **4**, and **5** represent examples from very recent patents. They are closely related to **1** and **2** but contain a diazepan ring system which can additionally be bridged or substituted, linking the two substituents together.[15–17] Depending on which way one follows the path from the first N-atom to the second N-atom, we either have a linker of two or of three atoms. These derivatives can therefore be considered as a combination of **1** and **2**. Derivative **6** connects the two aromatic units with a spiro-diamine unit.[18] This type of linkage seems to tolerate a new type of substituents, since the *o*-biaryl residues have been replaced by phenyl acetic acid residues. The proline derivatives **7** and **8** represent yet another group of dual orexin receptor antagonists.[19,20] The patent literature does not give insight into the activity pattern of this class of compounds, but it seems to be necessary to separate the two aromatic units by a different linker arrangement. A major difference as compared to the former classes of orexin receptor antagonists is the inversion of the amide connecting the *o*-biaryl unit to the template and the addition of a spacer of two bonds between the carbonyl group and the second aryl system. A more detailed picture of these compounds was recently published indicating that **7** has a $K_i(OX_1)$ of 3 nM and a $K_i(OX_2)$ of 0.2 nM as well as a suitable pharmacokinetic profile and substantial brain penetration after i.p.-administration to rats.[21] In addition the compounds were assessed for their potential as P-gp-substrates. It could be shown that **7** was only a moderate substrate. *In vivo* activity of the compounds was assessed in a rat model inducing locomotion by icv injections of ADL-orexin B peptide. It could be shown that pretreatment of rats with a dual orexin receptor antagonist, *e.g.* **7**, could suppress increased locomotor activity of ADL-orexin B challenged rats.

Further structural classes of orexin receptor antagonists developed at Merck are the 2-aryl indole-based compounds represented by **9** and the sulfonamide derivatives exemplified by **10**.[22,23]

### 2.2. *Orexin Receptor Antagonists from Actelion Pharmaceuticals Ltd*

A search in the Integrity® database (Prous Science) in the patents section, with the keywords 'Orexin AND Actelion' resulted in the following hits, describing compounds from the classes depicted in Fig. 2. The major efforts in the field of orexin receptor antagonists undertaken at Actelion Pharmaceuticals are mentioned in Section 3 describing the pharmacology of almorexant (**11**, ACT-078573) which is in phase III clinical development for the treatment of primary insomnia.

Compounds like **12** and **13** are obviously structurally very closely related to almorexant (**11**). In **12** the phenyl ring of the phenethyl side chain of almorexant (**11**) is replaced by a pyridine ring.[24,25] The compound is described to show *in vivo* activity in electrophysiological measures of sleep parameters (explained below, Section 3) and to have a favourable cytochrome inhibition profile. Compound **13** is an example of a series of primary amides structurally

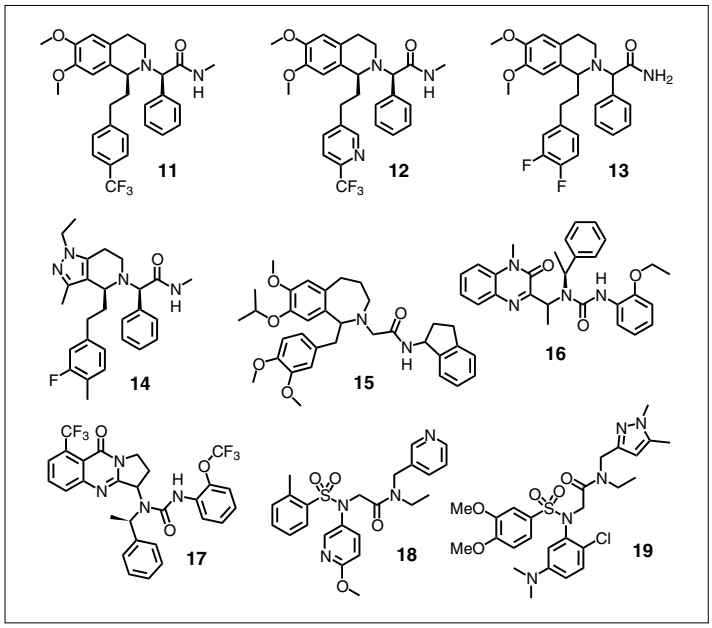


Fig. 2. Structures of orexin receptor antagonists from Actelion Pharmaceuticals Ltd

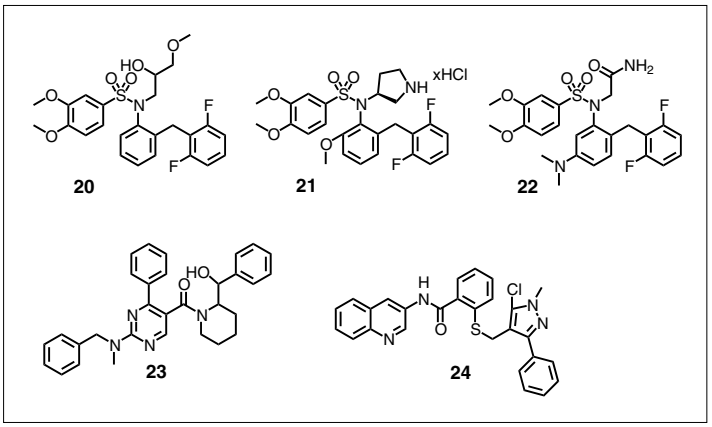


Fig. 3. Structures of orexin receptor antagonists from Sanofi-Aventis

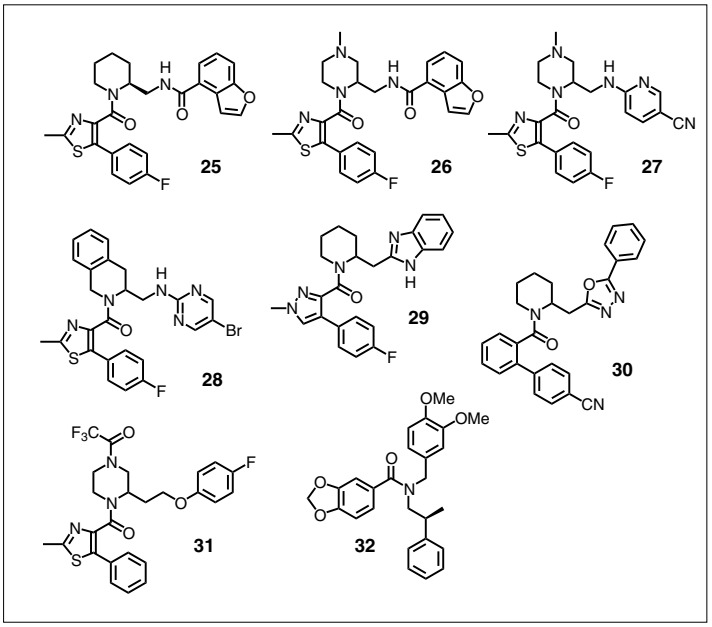


Fig. 4. Structures of orexin receptor antagonists from GlaxoSmithKline

closely related to almorexant (**11**).[26] Most examples in this patent are described as being dual orexin receptor antagonists. The patent does not indicate any preferred stereochemistry and as well allows for benzyl substituents as replacements of the phenethyl substituent depicted in **13**. In another patent, Actelion Pharmaceuticals describes tetrahydro-pyrazolo-pyridine derivatives as novel orexin receptor antagonists.[27] As an example of this group of orexin receptor antagonists, compound **14** is given (Example 32 from the patent with an $IC_{50}(OX_1)$ = 49 nM and an $IC_{50}(OX_2)$ = 2 nM). The derivatives related to **14** are described to be very potent orexin receptor antagonists with a tendency of being more active on the $OX_2$-receptor. Another group of antagonists is represented by the benzazepine derivative **15**.[28] The activity of the specific compound (Example 68 from the patent) is given with an $IC_{50}(OX_1)$ of 12 nM and an $IC_{50}(OX_2)$ of 174 nM, respectively. The benzazepine-based group of orexin receptor antagonists, according to the activity table in the patent, seems to represent a class of rather $OX_1$ selective derivatives. Further structurally different classes of compounds are reflected by **16** (quinoxalin-3-ones) and **17** (quinazolinones).[29,30] Both groups are described as being dual $OX_1/OX_2$ receptor antagonists with activities of 1 nM < $IC_{50}$ < 100 nM for **16** and $IC_{50}(OX_1)$ = 12 nM / $IC_{50}(OX_2)$ = 16 nM for **17**. A last group of Actelion orexin receptor antagonists are the sulfonamides **18** and **19**.[31,32] Compound **18** is a representative of a class of $OX_2$ selective antagonists ($IC_{50}(OX_1)$ > 10000 nM and $IC_{50}(OX_2)$ = 2 nM), whereas **19** represents a differently substituted sulfonamide from a class of highly potent dual orexin receptor antagonists ($IC_{50}(OX_1)$ = 6 nM and $IC_{50}(OX_2)$ = 11 nM). The selectivity profile seems to depend on the specific substitution pattern of the (hetero)aromatic groups contained in the molecules.

### 2.3. *Orexin Receptor Antagonists from Sanofi-Aventis*

A search in the Integrity® database (Prous Science) in the patents section, with the keywords 'Orexin AND Sanofi-Aventis' resulted in the following hits, describing orexin receptor antagonistic compounds from the classes depicted in Fig. 3.

The orexin receptor antagonists belonging to Sanofi-Aventis can be divided into two groups. The first group, the sulfonamides, is represented by **20**, **21** and **22**.[33–35] The compounds represent $OX_2$ selective antagonists with $IC_{50}$ values of 37 nM ($OX_2$) for **20**, 9 nM ($OX_2$) and 103 nM ($OX_1$) for **21**, and 9 nM ($OX_2$) and 1870 nM ($OX_1$) for **22**. The structures from all three patent applications only differ in the non-aromatic substituent connected to the sulfonamide N-atom. The aromatic substituents from all three groups of antagonists allow the same possibilities and variations. In addition to the sulfonamides, **23** represents a pyrimidine-based orexin receptor antagonist.[36] No hints to activities were disclosed for any representative of this class. Compound **24**, a pyrazole based, moderately potent dual orexin receptor antagonist ($IC_{50}$(OX1) = 33 nM; $IC_{50}$(OX2) = 156 nM) is an example from a patent application describing either orexin-1-selective or dual orexin receptor antagonists.[37]

### 2.4. *Orexin Receptor Antagonists from GlaxoSmithKline*

A search in the Integrity® database (Prous Science) in the patents section, with the keywords 'Orexin AND Glaxo' resulted in the following hits, describing compounds from the antagonist classes depicted in Fig. 4.

GSK holds a large group of patents describing potent, dual orexin receptor antagonists. Many of the compounds are based on 2-aminomethyl-aza-cycloalkanes such as 2-aminomethyl-piperidine, -pyrrolidine, piperazine, -morpholine, -tetrahydroisoquinoline, or tetrahydroquinoline.[38–49] The vast majority of the GSK-compounds contains a 5-aryl-thiazole- or *o*-biphenyl- or another structurally similar substituent connected to the ring-N-atom *via* an amide bond. Substituents at the exocyclic N-atom may be of benzamide type or heteroarylamine type forming a 2-amino-pyridine or a 2-amino-pyrimidine subunit. Compound **25** is specifically claimed in a patent application and some of its pharmacological effects are described below in comparison to almorexant (**11**). Derivatives **26** and **27** are structurally closely related to **25**. In **26** the central 2-aminomethylpiperidine is replaced by a 4-methyl-2-aminomethylpiperazine. In addition to this change, in **27**, the exocyclic benzofuranoyl-unit is replaced by a substituted pyridine group in order to replace one of the amide groups with a heteroaryl moiety. Another group of structurally related orexin receptor antagonists are summarized by **28**, a 3-aminomethyltetrahydroisoquinoline derivative. In addition, this example shows a further possible replacement of the exocyclic benzoyl substituent by a 5-bromo-2-pyrimidin-2-yl unit. Further changes not only in the exocyclic substituent but also in the 5-aryl-thiazole-group are possible as demonstrated with the benzimidazole derivative **29**, the oxadiazole derivative **30**, or the aryl ether **31**. Compounds **29** (4-aryl-pyrazole-unit) and **30** (*o*-biphenyl-unit) as well indicate possible variations and replacement options for the formerly almost ubiquitous 5-aryl-thiazole groups. A different group of orexin receptor antagonists is represented by **32**. This class, according to the statements made in the literature, represents dual and $OX_1$- or $OX_2$-selective receptor antagonists of astonishingly low structural complexity. With respect to activity the patents disclose average activity ranges of pKi values from 6.4 to 7.4 (equals $IC_{50}$ values of approximately 500–50 nM).

### 2.5. *Miscellaneous Orexin Receptor Antagonists*

Formula **33** (Fig. 5) represents an example of an orexin receptor antagonist from Biovitrum AB. The compounds are described as dual $OX_1$/$OX_2$-receptor antagonists.[50] Activities indicated as $IC_{50}$ values are between 30 nM and 2 μM. Compound **34** is described as a selective $OX_2$-receptor antagonist with a pKi value of 8.3 at the $OX_2$-receptor and a selectivity factor of 600.[51,52] The last compound depicted in Fig. 5, **35**, is a representative from an early class of $OX_1$ selective receptor antagonists.[53,54]

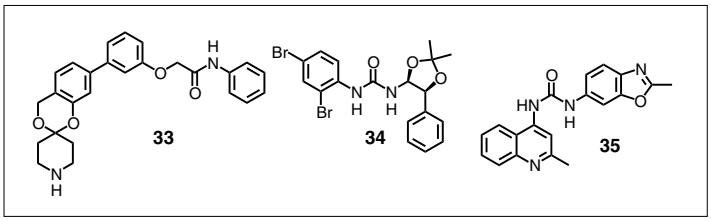


Fig. 5. Miscellaneous structures of orexin receptor antagonists

$OX_1$ selective antagonists are said to decrease food intake in rats with a high fat diet after i.p. administration.[55] Other reports from the scientific literature speculate about the importance of the orexin system with respect to memory acquisition and consolidation again in combination with the $OX_1$ selective antagonist **35**.[56] Regarding the clinical potential of either type of selective or dual orexin receptor antagonists, with the exception of insomnia, we can only speculate at the moment. Future clinical trials will hopefully deliver answers.

## 3. Biological and Pharmacological Effects of Two Orexin Receptor Antagonists

Effects of two orexin receptor antagonists with good systemic and brain bioavailability were investigated on sleep and wake cycles in rats: almorexant (**11**, ACT-078573) developed by Actelion Pharmaceuticals Ltd. and compound **25** taken from a GlaxoSmithKline patent application.

Almorexant (**11**) is a competitive orexin receptor antagonist active on both human $OX_1$ and $OX_2$ receptors.[7] It inhibited the intracellular $Ca^{2+}$ increase induced by 10 nM human orexin-A in Chinese hamster ovary cells overexpressing human $OX_1$ and $OX_2$ receptors. The concentrations of almorexant necessary to inhibit 50% of the response ($IC_{50}$) for the $OX_1$ receptor were 13 ± 1 nM (n=8) and 8 ± 1 nM (n=8) for the $OX_2$ receptor. It was more than 600-fold selective for orexin receptors when tested in 89 receptor-binding or enzyme activity assays including hepatic enzymes.

Compound **25** is also a dual $OX_1$ and $OX_2$ receptor antagonist. The $IC_{50}$ of this compound measured under the same conditions as almorexant (**11**) were 2 ± 0.2 nM (n=8) and 2.7 ± 0.4 nM (n=8) for the $OX_1$ and $OX_2$ human receptors, respectively.

Both almorexant (**11**) and compound **25** cross the blood-brain-barrier (brain/plasma ratio between 33 and 57%, respectively) (Table 1).

Both compounds present the same pattern of activity on electrophysiological measures of sleep parameters made in freely moving Wistar rats implanted with miniature radiotelemetric probes over several 12-h light-dark cycles.

When given orally at the beginning of the active dark phase in the rat (when intracerebral orexin levels are high), dual orexin receptor antagonists increase the time spent in REM (rapid-eye-movement) and non-REM sleep and decrease the time spent in home cage activity and active wake in a dose-dependent manner (Fig. 6 and 7, 10–300 mg/kg p.o.). At approximately bioequivalent dose (100 mg/kg for almorexant (**11**) and 30 mg/kg for compound **25**), home cage activity measured over the 12 h night period, is decreased by 52% and 55% (Fig. 6) and active wake by 25% and 23% for almorexant (**11**) and compound **25**, respectively (Fig. 7). Total sleep time, over the 12 h night period, was increased by 27% for almorexant (**11**) and 26% for compound **25**. These results correspond to a non-REM sleep increase of 25% and 23%

Table 1. Brain and systemic concentration measured 3 and 6 hours following oral administration of $OX_1$/$OX_2$ receptor antagonists to male Wistar rats

| | Plasma concentration [ng/ml] | Brain concentration [ng/g] | Brain/plasma ratio [%] |
|---|---|---|---|
| 100 mg/kg almorexant **11** (n=8) | | | |
| 3 hours | 3088 ± 463 | 1009 ± 194 | 33% |
| 6 hours | 2598 ± 319 | 864 ± 174 | 33% |
| 30 mg/kg Compound **25** (n=3) | | | |
| 3 hours | 1846 ± 999 | 1055 ± 427 | 57% |
| 6 hours | 2115 ± 593 | 944 ± 287 | 45% |

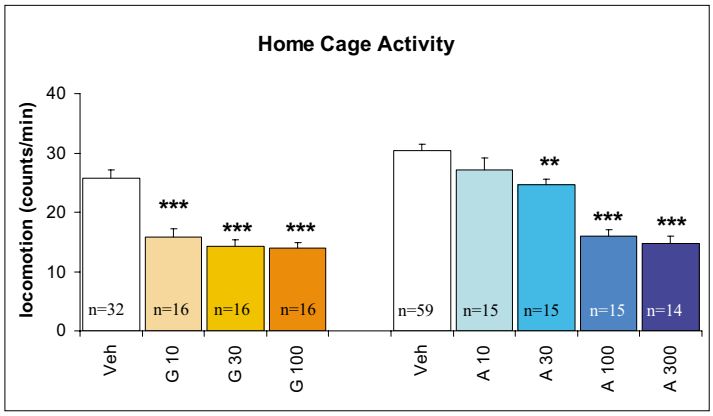


Fig. 6. Dose response for the effects of $OX_1/OX_2$ receptor antagonists (almorexant (**11**) or A and compound **25** or G) on home cage activity. Data are represented as mean +/- s.e.m. * p <0.05, ** p <0.01, *** p <0.001.

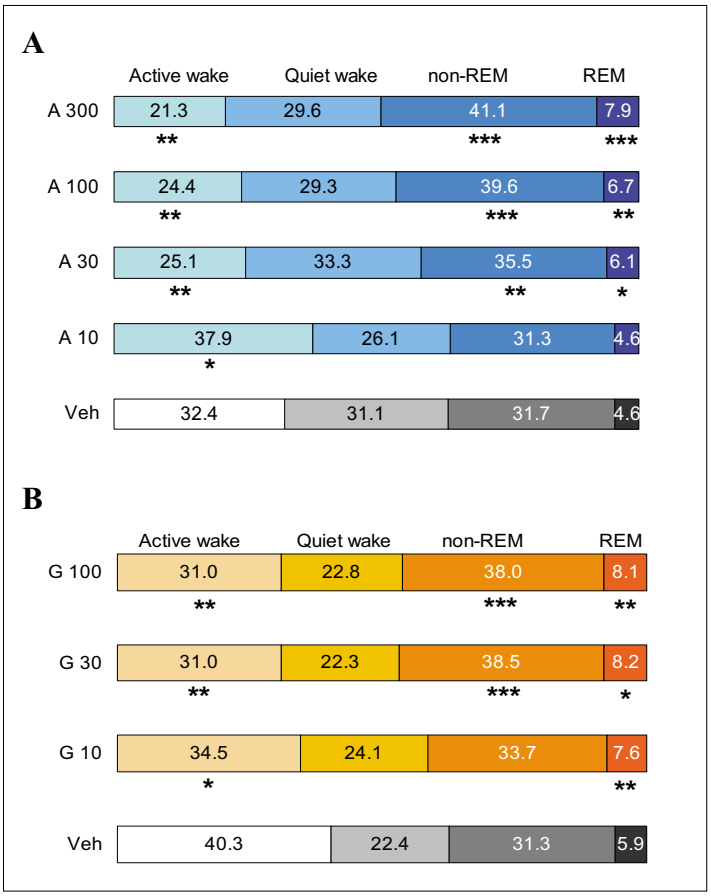


Fig. 7. Values represent the percentage of time spent in each sleep or wake stage over the 12 h night period following administration, n = 15 for A 10, A 30, A 100; n = 14 for A 300; n = 59 for Veh in A panel; n = 16 for G 10, G 30, n = 14 for G 100; n = 31 for Veh in panel B. * p <0.05, ** p <0.01, *** p <0.001. A = almorexant (**11**); G = compound **25**

and a REM sleep increase of 46% and 39% for almorexant (**11**) and compound **25**, respectively.

A unique characteristic of these dual $OX_1/OX_2$ receptor antagonists is that the relative proportion of time spent in non-REM and REM sleep over the total sleep time in the 12 h night period remains unchanged (Table 2).

Table 2. Proportion of non-REM and REM sleep over the total sleep time of the 12 h night period.

| | % of total sleep time | |
|---|---|---|
| | time spent in non-REM sleep | time in REM sleep |
| veh / almorexant (**11**) | 87% / 86% | 13% / 14% |
| veh / compound **25** | 84% / 82% | 16% / 18% |

## 4. Discussion and Perspective

When transient reduction of orexin function was induced by dual orexin receptor antagonists such as almorexant and compound **25**, decreased alertness was observed dose-dependently in rats. Dual orexin receptor antagonists appear to mimic a physiological state of sleep that occurs when orexin release is decreased during the sleep phase. The maintenance of a natural sleep architecture differs from what is usually seen with $GABA_A$ receptor modulators such as zolpidem that decrease REM sleep.

Immunoreactivity for orexin A shows diurnal variations in areas of the brain involved in the regulation of sleep, arousal and circadian hormone release. For example, hypothalamic orexin A concentrations are significantly higher during active waking than during slow-wave sleep. This has been observed in cats and rats and extends to humans. Current hypotheses on the role of orexins in the CNS sleep system are influenced by the findings that many different types of neurons, including noradrenergic, serotonergic, histaminergic, glutamatergic and cholinergic neurons (in *e.g.* basal forebrain, perifornical hypothalamus, locus coeruleus) are strongly innervated by orexin neurons originating in the hypothalamus. This indicates a potentially prominent role of orexins in sleep-wake regulation within certain brain structures. Hypothalamic neurons are under the control of incoming circadian signals from suprachiasmatic nuclei (biological clock). Sleep disorders such as primary insomnia are thus possibly related to dysfunctions of the orexin system; this has been recently confirmed in a phase II clinical trial using almorexant (**11**) in primary insomnia patients.[57]

Since the full pathophysiology and clinical pictures of orexin dysfunctions is largely unknown, the possibility for therapeutic opportunities in human or veterinary medicine remains largely open. The relative contributions of $OX_1$ versus $OX_2$ receptors to diverse neurobiological effects and their brain distribution suggests that different physiological effects might be expected from drugs acting in the brain selectively at either $OX_1$ or $OX_2$ receptors or at both receptors in parallel. This will be investigated experimentally using selective and dual orexin antagonists emerging from various medicinal chemistry programs.

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