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REVIEW ARTICLE

The orexin story, sleep and sleep disturbances

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Summary

The orexins, also known as hypocretins, are two neuropeptides (orexin A and B or hypocretin 1 and 2) produced by a few thousand neurons located in the lateral hypothalamus that were independently discovered by two research groups in 1998. Those two peptides bind two receptors (orexin/hypocretin receptor 1 and receptor 2) that are widely distributed in the brain and involved in the central physiological regulation of sleep and wakefulness, orexin receptor 2 having the major role in the maintenance of arousal. They are also implicated in a multiplicity of other functions, such as reward seeking, energy balance, autonomic regulation and emotional behaviours. The destruction of orexin neurons is responsible for the sleep disorder narcolepsy with cataplexy (type 1) in humans, and a defect of orexin signalling also causes a narcoleptic phenotype in several animal species. Orexin discovery is unprecedented in the history of sleep research, and pharmacological manipulations of orexin may have multiple therapeutic applications. Several orexin receptor antagonists were recently developed as new drugs for insomnia, and orexin agonists may be the next-generation drugs for narcolepsy. Given the broad range of functions of the orexin system, these drugs might also be beneficial for treating various conditions other than sleep disorders in the near future.

KEYWORDS
insomnia, narcolepsy, orexin/hypocretin, sleep disturbances

1 | INTRODUCTION

Orexin (ORX)-A and ORX-B (or hypocretin; Hcrt-1 and -2) are neurotransmitters, cleaved from a single precursor peptide (prepro-ORX or prepro-Hcrt), which were discovered simultaneously by two research groups in 1998 (de Lecea et al., 1998; Sakurai et al., 1998). One group was searching for specific hypothalamic neurotransmitters, and named these peptides Hcrts given the specific expression in neurons located in the dorso-lateral hypothalamus together with amino-acid similarities with the gut hormone secretin (de Lecea et al., 1998). Hcrt-producing neurons showed widespread projections within the hypothalamus, as well as to the thalamus and brainstem, and one peptide had an excitatory effect on cultured hypothalamic neurons (de Lecea et al., 1998). The other group disclosed that these neuropeptides stimulated food consumption and were upregulated during fasting, thus being a central feedback mechanism for the regulation of feeding behaviour (Sakurai et al., 1998). For their role in promoting feeding, the authors named the neurotransmitters ORXs (Sakurai et al., 1998).

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ORX-A binds selectively to ORX-1 receptor (ORX1R), whereas both ORX-A and ORX-B bind to ORX-2 receptor (ORX2R), non-selectively. ORX1R and ORX2R are two G-protein-coupled receptors. ORXs are exclusively produced by a group of neurons localized in the lateral and dorsomedial hypothalamus (Peyron et al., 2000). In humans the number of Hcrt-producing neurons is estimated to be between 15–20 000 and 50–80 000 depending on the techniques used (in situ hybridization for prepro-ORX versus immunocytochemistry with anti ORX-A antibody; Fronczek et al., 2005; Peyron et al., 2000), and in the lateral hypothalamus they are intermingled with melanin-concentrating hormone-producing neurons (Aziz et al., 2008). Orexinergic projections are widespread throughout the central nervous system (Peyron et al., 1998), and thus are now known to be involved in a variety of functions and disorders (Jacobson et al., 2022). Across species, especially in mice and dogs, a disrupted ORX signalling leads to a narcoleptic phenotype with sleepiness, sleep instability and fragmentation, and cataplexy, unravelling a key role of ORXs in the regulation of sleep–wakefulness states (Saper et al., 2005). Despite ORX-A injection inducing feeding, it does not increase overall food consumption and body weight (Yamanaka et al., 1999), but conversely it plays a key role in reward mechanisms and motivational behaviour (Harris et al., 2005). Indeed, ORX-A secretion increases not only in relation to the wakefulness–sleep state, but maximally during positive emotion, social interaction and anger, thus modulating to complex human behaviours (Blouin et al., 2013; Sakurai, 2014). The ORX system is also involved in the hypothalamic regulation of several basic functions, such as autonomic control (Grimaldi et al., 2014), thermoregulation (Kuwaki, 2015) and energy homeostasis (Sakurai & Mieda, 2011), thus playing an important role in several human functions and disorders not limited to those affecting the central nervous system. In this review we will summarize the role of the ORX system in sleep and sleep disorders.

2 | SLEEP AND SLEEP DISTURBANCES

2.1 | ORX and normal sleep

The discovery of the ORX system led to a revolution on the conceptualization of sleep regulation. Indeed, the two-process model of sleep physiology included the integration of a homeostatic process (Process S) controlled by a circadian pacemaker (Process C) able to explain neurophysiological experimental data obtained in humans up to predict the time course of the sleep–wake rhythms and behavioural performances (Borbély et al., 2016). From the brain circuitry standpoint the regulation of sleep stands on the interaction between an ascending arousal system promoting wakefulness with different neuronal components located from the pons to the hypothalamus and thalamus and secreting several aminergic neurotransmitters and acetylcholine, and the opposite role of γ-aminobutyric acid (GABA)ergic modulation from the ventrolateral preoptic nucleus able to inhibit different targets (such as the locus coeruleus, dorsal raphe nucleus and tuberomammillary nucleus) of the arousal system. The discovery of orexinergic neurotransmission added a key point in sleep regulation as long as ORXs conceptualized from basic experimental evidence as neurotransmitters able to promote wakefulness, but also to stabilize the "sleep" or "wake" state as long as the condition is established resulting in a "flip-flop" switch model (Saper et al., 2005). ORX neurons have strong projections to the wake–active brain areas, such as the locus coeruleus, dorsal raphe nucleus and tuberomammillary nucleus and others, and form the external stabilizer for this switch. Accordingly, the complete loss of ORX neurotransmission (as in narcolepsy type 1) results in state boundary dyscontrol (Broughton et al., 1986), with an inability to maintain wakefulness during daytime (Broughton et al., 1988) and to stabilize sleep during nighttime (Barateau et al., 2020; Maski et al., 2022), with the peculiar feature of increased sleep–wake transitions during nighttime in patients of all ages (Maski et al., 2020; Pizza et al., 2015). Moreover, sleep duration and continuity change across the life span, with frequent awakening during nocturnal sleep in the healthy elderly (Dijk et al., 2000) that is associated with a decline in sleep quality and quantity (Ohayon et al., 2004). Despite cerebrospinal fluid (CSF) levels of ORX not showing significant changes across ages (Kanbayashi et al., 2002a, 2002b), a reduction of the number of ORX neurons in the tuberal hypothalamic area was disclosed when comparing older subjects with infants and young adults (Hunt et al., 2015), thus indirectly suggesting that a decrease in ORX neurotransmission might play a role in sleep problems in the elderly. Recent experimental data showed that in aged mice ORX neurons are hyperexcitable and show more frequent activity leading to increased wake bouts, a finding possibly paving the way to therapeutic options (Li et al., 2022).

2.2 | ORX and sleep disturbances: Central disorders of hypersomnolence

After the discovery of the ORX system, its key role in the pathogenesis of primary sleep disorders was demonstrated, with narcolepsy being newly defined into narcolepsy type 1 (NT1, former narcolepsy with cataplexy) and narcolepsy type 2 (NT2, former narcolepsy without cataplexy) on the basis of having evidence of disrupted ORX system (American Academy of Sleep Medicine, 2014). The ORX system was therefore immediately a key pathophysiological and diagnostic element to dissect the spectrum of central disorders of hypersomnolence, and accordingly several studies reported the evidence obtained from CSF analyses in the different primary hypersomnolence disorders. As a result, we now look at central disorders of hypersomnolence dissecting them in orexinergic (i.e. NT1) and non-orexinergic (NT2, Kleine-Levin syndrome, idiopathic hypersomnia) ones, and a scientific debate is ongoing on how to better classify these disease entities (Fronczek et al., 2020; Lammers et al., 2020).

2.2.1 | NT1 and NT2

Narcolepsy is a rare sleep disorder, now split into two disease entities that are lumped by the neurophysiological evidence of rapid

occurrence of rapid eye movement (REM) sleep at sleep onset (SOREMP; Dement et al., 1966), a disease fingerprint well documented by the Multiple Sleep Latency Test (MSLT; Arand & Bonnet, 2019; Krahn et al., 2021).

Narcolepsy type 1 is clinically marked by a pentad of symptoms: excessive daytime sleepiness (EDS), sleep paralysis, hypnagogic/hypnopompic hallucinations, disturbed night sleep and cataplexy. Cataplexy is the pathognomonic symptom of NT1, and is characterized by a sudden occurrence of muscle weakness triggered by strong, most commonly positive, emotions (Kornum et al., 2017). While cataplexy phenotype is wide, with also subcontinuous weakness at disease onset in children possibly making its recognition challenging (Pillen et al., 2017), in NT2 it should be absent by definition (American Academy of Sleep Medicine, 2014). After the discovery of the ORXs, several scientific evidence discoveries connected their role to the pathophysiology of narcolepsy: first, a mutation in the gene coding for ORX2R was found as the cause of canine narcolepsy (Lin et al., 1999); second, in humans, ORX-producing neurons were found to be almost absent in the hypothalamus of deceased narcolepsy with cataplexy patients (Peyron et al., 2000; Thannickal et al., 2000). These data were associated with the possibility to document in vivo the deficiency of ORX-A in the CSF (defined as a level below 110 pg ml^{-1}) by means of a dedicated radioimmunoassay in narcolepsy with cataplexy (Nishino et al., 2000; Ripley et al., 2001), thus making this biological marker an exclusive diagnostic tool for narcolepsy with cataplexy. The evidence that ORX deficiency may forerun cataplexy occurrence (Andlauer et al., 2012) further contributed to the current definition of NT1 where cataplexy and ORX deficiency are considered equivalent (American Academy of Sleep Medicine, 2014). Conversely, ORX-A should be present in the CSF of NT2, together with the absent evidence of cataplexy (Bassetti et al., 2003; Dauvilliers et al., 2003; Heier et al., 2007), two key points that are shared by NT2 and the other central disorders of hypersomnolence (Baumann et al., 2014; Fronczek et al., 2020; Lammers et al., 2020). However, patients with NT2 may show a partly reduced number of ORX-producing neurons in the hypothalamus (Thannickal et al., 2009), despite CSF ORX levels comparable to those of healthy controls (Dauvilliers et al., 2003; Mignot et al., 2002). Recent data also showed that NT1 may be preceded by several years by EDS with SOREMPs before the occurrence of cataplexy (Pizza et al., 2014), and that CSF levels of ORX may decrease over time in a subset of narcolepsy patients with genetic predisposition (HLA DQB1*06:02) initially presenting with clinical features of NT2 (Lopez et al., 2017a; Pizza et al., 2014). Therefore, the exact role of ORX in determining NT2 is currently under debate, as well as the most appropriate cut-off (i.e. 110 versus 200 pg ml^{-1}) to identify ORX deficiency (Andlauer et al., 2012; Postiglione et al., 2022; van der Hoeven et al., 2022). At the same time, caution should be taken when diagnosing NT2 given the frequent occurrence of SOREMPs in patients with other sleep disorders (e.g. insufficient sleep syndrome, circadian rhythm sleep disorders) or under medications (Arand & Bonnet, 2019; Goldbart et al., 2014), thus making the role of careful clinical assessment and differential diagnosis crucial (Baumann et al., 2014).

While NT1 and NT2 are definite sleep–wake disorders occurring in otherwise healthy subjects, several neurological, genetic and paraneoplastic disorders may cause secondary narcolepsy (Kanbayashi et al., 2011; Nishino & Kanbayashi, 2005). Secondary narcolepsy may be related to inflammatory (e.g. multiple sclerosis) or tumoural lesions of the hypothalamus associated with EDS, and can have a favourable course along with resolution of the primary brain damage, as well as with antibody-mediated disorders such as neuromyelitis optica with anti-aquaporin-4 antibodies or limbic encephalitis of undetermined origin responsive to immunological approaches (Kanbayashi et al., 2011; Nishino & Kanbayashi, 2005). Otherwise, secondary narcolepsy can be paraneoplastic and tell-tale the presence of a tumour located outside of the central nervous system (Dauvilliers et al., 2013; Landolfi & Nadkarni, 2003; Overeem et al., 2004; Vitiello et al., 2018), with the link between the primary neoplasm (e.g. testicular, pulmonal) and the onset of narcolepsy being the presence of specific antibodies such as anti-Ma2 or anti-Hu (Dauvilliers et al., 2013; Landolfi & Nadkarni, 2003; Overeem et al., 2004; Vitiello et al., 2018) or unknown (Rossi et al., 2021). In most of these paraneoplastic cases narcolepsy occurs in patients not carrying the genetic predisposition (HLA-DQB1*06:02), may have variable levels of CSF ORX-A up to clear deficiency, and the evolution of the disease is frequently variable and linked to that of the primary disorder. Other causes of secondary narcolepsy may be genetically determined disorders occurring at different ages of life. In young children, and more rarely adults, Niemann Pick type C disease should be clinically suspected when sleepiness or cataplexy are associated with hepatosplenomegaly, vertical supranuclear saccadic palsy, ataxia, dystonia and dementia (Imanishi et al., 2020; Kandt et al., 1982). The evidence of cataplexy, as well as of mildly reduced CSF levels of ORX-A, in patients with other neurological signs and symptoms may therefore lead to prompt diagnosis of the autosomal recessive storage disorder, thus paving the way to treatment able to modify disease evolution (including the progression of ORX deficiency; Imanishi et al., 2020). Finally, there are autosomal-dominant familial pedigrees where narcolepsy with cataplexy progressively occurs (about 30–40 years of age) within a widespread neurological involvement including cerebellar ataxia and deafness (Autosomal-Dominant Cerebellar Ataxia, Deafness and Narcolepsy; ADCA-DN) leading to premature death (Melberg et al., 1995), a neurodegenerative condition that includes evidence of ORX-A deficiency in the CSF (Melberg et al., 2001). Mutations in DNMT1 gene encoding for a DNA methyltransferase involved in the epigenetic modulation of gene expression in different tissues have been recently linked to ADCA-DN (Winkelmann et al., 2012), as well as with another autosomal-dominant disorder characterized by peripheral neuropathy, hearing loss, premature dementia and in some cases narcolepsy without cataplexy (Hereditary Sensory and Autonomic Neuropathy with Dementia and Hearing loss type IE; HSAN IE; Moghadam et al., 2014). While optic atrophy and daytime sleepiness with SOREMPs may lump these two neurodegenerative conditions, cataplexy is typical of ADCA-DN and associated with evidence of reduced levels of ORX-A in the CSF confirming the role of the orexinergic system in the pathophysiology of cataplexy across different diseases (Moghadam

et al., 2014). Unfortunately, even if pathophysiological research is ongoing on disease mechanisms leading to neurodegeneration in DNMT1-related disorders (Maresca et al., 2020), no curative approach is available to date. As a whole, secondary narcolepsy should be suspected when the disease occurs in familial cluster, in association with other neurological symptoms/signs, and in the absence of typical biological fingerprints (genetic predisposition, intermediate CSF levels of ORX-A).

2.2.2 | Idiopathic hypersomnia

Idiopathic hypersomnia is a central hypersomnolence disorder characterized by EDS, long non-refreshing naps, sleep inertia at awakening (Roth, 1981) and prolonged nocturnal sleep, as well elevated time spent asleep across the 24 hr (Evangelista et al., 2018; Vernet & Arnulf, 2009). Idiopathic hypersomnia is formally differentiated from narcolepsy for the occurrence of SOREMPs at the MSLT (Arand & Bonnet, 2019; Krahn et al., 2021), an unstable neurophysiological fingerprint given the low test–retest reliability of the test itself in non-cataplectic hypersomnolence disorders (Lopez et al., 2017b; Ruoff et al., 2018; Trotti et al., 2013). Accordingly, the diagnostic criteria have changed over time leading to heterogeneous case series published in the literature, and currently a prolonged (conventionally established above 11 hr) 24-hr sleep time is accepted as objective neurophysiological confirmation (American Academy of Sleep Medicine, 2014), despite different protocols used worldwide to quantify sleep needs across the 24 hr (Fronczek et al., 2020; Lammers et al., 2020). Few data addressed CSF levels of ORX-A in idiopathic hypersomnia, and there is no evidence to date pointing to a reduction of the neurotransmitter in these patients compared with otherwise healthy, or subjectively sleepy, controls (Dauvilliers et al., 2003; Kanbayashi et al., 2002a, 2002b; Mignot et al., 2002; Pizza et al., 2015). Therefore, if any, the role of the orexinergic system in idiopathic hypersomnia seems limited, and warrants further research.

2.2.3 | Kleine-Levin syndrome

Kleine-Levin syndrome is a peculiar central disorder of hypersomnolence characterized by recurrent episodes of hypersomnolence with long sleep duration for days associated with behavioural, cognitive, perceptual and eating disturbances, and separated by periods with normal alertness, cognition, mood and behaviour (American Academy of Sleep Medicine, 2014). The disorder generally arises in adolescence, and most frequently resolves spontaneously over time with acute attacks becoming progressively shorter as well as less intense, and intermixed by normal alertness for more prolonged periods up to spontaneous resolution (Arnulf et al., 2012; Lavault et al., 2015). CSF ORX-A levels were reported within the normal range in between hypersomnia episodes, but when retested in the same patients during the episodes a significant decrease was reported in several case series (Dauvilliers et al., 2003; Lopez et al., 2015; Podestá et al., 2006; Usuda et al., 2018; Wang et al., 2016). CSF ORX-A level fluctuations appeared within values considered above the diagnostic cut-off for NT1 in most patients (Podestá et al., 2006; Usuda et al., 2018), but in some cases also a reduction up to below 110 pg ml^{-1} was reported (Lopez et al., 2015; Wang et al., 2016). It is therefore unclear the relation between hypersomnia episodes and CSF ORX levels, whereas a recent study disclosed that polymorphisms of the TRANK1 gene (already associated with bipolar disorder and schizophrenia) constitute a genetic predisposition to the disorder (Ambati et al., 2021).

2.2.4 | ORX-based therapies

Current treatments of narcolepsy are symptomatic, but often not sufficient and even with treatment patients have reduced quality of life. In this context and because of the specific pathophysiology of NT1, ORX-based therapies are the most promising treatment for NT1, and possibly also for other patients with EDS. Accordingly, since the discovery of ORX deficiency in narcolepsy, several approaches have been considered: intranasal administration of ORX peptides, development of ORX-receptor agonists, ORX neuronal transplantation, transforming stem cells into ORX neurons and ORX gene therapy (Table 1). The activation of ORX2R was particularly expected to promote wakefulness, as narcolepsy-like phenotypes (with wakefulness fragmentation) are observed in ORX2R knockout mice, but not in ORX1R knockout mice.

Orexin replacement therapy has remained complicated so far, as both peptides poorly cross the blood–brain barrier (Fujiki et al., 2003). ORX administration (per os and intravenous) in animal models of NT1 was almost unsuccessful because of this impermeability. Nevertheless, the direct administration of ORX intraventricularly suppressed narcoleptic symptoms in a mouse model (ORX/ataxin-3 neuron-ablated; Mieda et al., 2004). Furthermore, slow infusion of ORX delivered via a chronically implanted intrathecal catheter in another mouse model (ORX knockout mice) decreased cataplexy and SOREMPs (Kaushik et al., 2018). A few preclinical and clinical studies showed the promising effect of a non-invasive method via intranasal administration of ORX, targeting drugs almost "directly" to the brain along the olfactory and trigeminal neural pathways (Deadwyler et al., 2007; Weinhold et al., 2014). Non-peptide ORXR agonists, currently under development, are very promising to treat narcolepsy. A first study showed that systemic administration of a selective ORX2R agonist improved symptoms in mice models of narcolepsy, with the suppression of cataplexy and the promotion of wakefulness, providing a proof of concept for a mechanistic therapy of NT1 by ORX2R agonists (Irukayama-Tomobe et al., 2017). However, this compound had a limited in vivo efficacy, and was finally not suitable for clinical development. Then another ORX2R-selective agonist (TAK-925) showed a major wake-promoting effect in wild-type mice and non-human primates when injected intravenously, and increased wakefulness and suppressed cataplexy in ORX/ataxin-3 transgenic mice (Suzuki et al., 2018; Yukitake et al., 2019). It also attenuated the body weight gain, without

TABLE 1 Overview of ORX/Hcrt-based therapies tested (and published) in animal models of narcolepsy and in human narcolepsy (adapted from Barateau & Dauvilliers, 2019)

ORX-based therapy	Administration, methods	Animal/human subjects	Impact on symptoms	References
ORX-A replacement	IV (very high doses) and intrathecal ORX-A	ORX-ligand- deficient narcoleptic dog	IV administration: transient reduction of cataplexy, no effect on sleep; intrathecal: no effect	Fujiki et al. (2003)
	Intracerebroventricular ORX-A	ORX-neuron-ablated mice	Reduction of cataplexy and sleepiness	Mieda et al. (2004)
	Intranasal ORX-A	Sleep-deprived rhesus monkeys	Reduction of the effectsof sleep deprivation on cognitive performances	Deadwyler et al. (2007)
	Intranasal ORX-A	$n = 8$ patients with NT1	No effect on cataplexy Reduction of REM sleep quantity, stabilizationof REM sleep (reduced direct wake-to-REM transitions)	Baier et al. (2011)
	Intranasal ORX-A	$n = 14$ patients with NT1	No effect on cataplexy Reduction of REM sleep duration, stabilization of REM sleep (less wake–REM sleep transitions)	Weinhold et al. (2014)
Non-peptide selective ORX2R agonist	Intracerebroventricular and intraperitoneal (YNT- 185)	Models of narcoleptic mice	Reduction of sleepiness and cataplexy (also promotes wakefulness in wild-type mice, IV administered)	Irukayama-Tomobe et al. (2017)
	Subcutaneous administration of TAK-925 (full agonist)	Wild-type mice, models of narcoleptic mice	Promotion of wakefulness in wild-type mice, but not in ORX2R-KO mice	Yukitake et al. (2019)
ORX cell transplantation	Implantation of ORX neurons in the lateral hypothalamus	Neurotoxin-ablated ORX neuron rats	Reduction of sleepiness	Arias-Carrión and Murillo-Rodríguez (2014)
ORX gene therapy	Overexpression of prepro-ORX transgene	Models of narcoleptic mice	Reduction of cataplexy, stabilization of REM sleep, slight effect on sleepiness	Blanco-Centurion et al. (2013) ; Kantor et al. (2013)
	Transient expressionof ligand in the lateral hypothalamus with herpes simplex vector	ORX–KO mice	Reduction of cataplexy, increased REM sleep	Liu et al. (2008)
	Delivery of the ORX gene into brain areas using recombinant adeno-associated viral vectors	Models of narcoleptic mice	Reduction of cataplexy	Liu et al. (2011, 2016)

Notes: IV, intravenous; KO, knockout; NT1, narcolepsy type 1; ORX, orexin/hypocretin; REM, rapid eye movement.

changing the daily food intake (Kimura et al., 2019). Of interest, the persistence of the effect after a 14-day period of chronic administration suggested an absence of ORX2R desensitization. Other new promising non-peptide ORXR agonists (TAK-994 and TAK-861) with per os administration are also currently under development (Ishikawa et al., 2019; Ishikawa et al., 2020). The development of ORX2R agonists could also be of interest in patients with sleepiness and normal CSF ORX-A levels: NT2, idiopathic hypersomnia or even hypersomnolence in other conditions such as sleep apnea (ClinicalTrials.gov identifiers: NCT04091425, NCT04091438). Other ORX-based therapies were tested with success in rodents, such as cell replacement technique using ORX neurons derived from pluripotent stem cells (Arias-Carrión & Murillo-Rodríguez, 2014), and could eventually be an option for very severe or pharmaco-resistant patients (Barateau & Dauvilliers, 2019). At last, ORX gene therapy improved symptoms in narcoleptic mice, but those findings remain preliminary (Blanco-Centurion et al., 2013; Kantor et al., 2013; Liu et al., 2008; Liu et al., 2011, 2016).

3 | INSOMNIA AND ORXR ANTAGONISTS

The discovery of the Hcrt system opened a new era of development of new drugs in the field of sleep medicine. Indeed, besides the research of ORXR agonists and in general orexinergic agents for the treatment of NT1, and hopefully for its natural borderland, impressive research focused on the development of Hcrt-R1/Hcrt-R2 antagonists (Brisbare-Roch et al., 2007). These drugs aim at competitively binding

ORXRs to blunt the orexinergic-mediated maintenance of wakefulness. To date, five drugs targeting both orexinergic receptors (namely dual ORX receptor antagonists; DORAs) have been used in clinical trials: suvorexant (Herring et al., 2012; Herring et al., 2016; Herring et al., 2020; Michelson et al., 2014); almorexant (Black et al., 2017; Hoever et al., 2012; Roth et al., 2017), filorexant (Connor et al., 2016); lemborexant (Kärppä et al., 2020; Murphy et al., 2017; Rosenberg et al., 2019); and daridorexant (Dauvilliers et al., 2020; Mignot et al., 2022; Zammit et al., 2020). These drugs proved efficacious against placebo on several objective sleep parameters, including sleep efficiency, total sleep time and wakefulness after sleep onset (Xue et al., 2022). Almorexant reached clinical trials phase 3, but was later discontinued due to liver enzyme increase, while suvorexant and lemborexant have been approved by FDA for the treatment of insomnia in 2014 and 2019, respectively, and daridorexant completed the phase 3 trials obtaining the FDA approval and is currently under evaluation by EMA. DORAs did not show main side-effects on memory and cognition, and the most commonly reported side-effects are somnolence, abnormal dreams, fatigue and dry mouth (Xue et al., 2022).

More recently, selective ORX receptor-2 antagonists (2-SORAs) have been developed and applied in clinical samples (Brooks et al., 2019; De Boer et al., 2018), opening new avenues in our comprehension of the role of ORX signalling manipulation (and role) in patients with insomnia (Clark et al., 2020). Indeed, when comparing the effect of DORAs and 2-SORAs on sleep architecture, both approaches increased total sleep time, but acted differently on sleep architecture in healthy subjects and in patients with insomnia. DORAs increased total sleep time mostly by increasing REM sleep, an effect more evident in patients with insomnia compared with healthy subjects given the potential near-ceiling levels of total sleep time and REM sleep time in healthy sleepers (Clark et al., 2020). Conversely, 2-SORAs increased total sleep time by means of increasing both non-REM and REM sleep, a finding that needs further research also in experimental models and healthy sleepers (Gotter et al., 2016). This evidence paves the way to better phenotyping insomnia patients, also taking into account psychiatric comorbidity, and to obtain key information on the role of the orexinergic system dysfunction in the determination of insomnia itself.

4 | CONCLUSIONS

The ORX system discovery is new in the field of sleep medicine. Its role is crucial in the regulation of sleep and wakefulness, as well as in modulating several behaviours and function in humans. While a complete defect of the ORX system is causal of narcolepsy, other central disorders of hypersomnolence may be influenced directly (lesion) or indirectly (immune-mediated) by processes affecting altering orexinergic neurotransmission. Accordingly, new drugs replacing ORX function are highly promising for the treatment of central disorders of hypersomnolence. On the other side, recent evidence in patients with insomnia showed different impacts in sleep architecture of drugs blocking ORX2R or ORX2R/ORX1R, possibly leading to a better comprehension of the orexinergic role in sleep maintenance. Overall, the manipulation of the orexinergic system will unravel complex relations between sleep and sleep disorders in healthy subjects, in patients with sleep disorders and other conditions affecting the central nervous system from a neurological and psychiatric standpoint.

CONFLICT OF INTEREST

The authors declare no conflicts of interest related to this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in [repository name] at [URL/DOI], reference number [reference number]. These data were derived from the following resources available in the public domain: [list resources and URLs]

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