Role of the orexin system in the bidirectional relation between sleep and epilepsy: New chances for patients with epilepsy by the antagonism to orexin receptors?

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The role of the orexin system in the bidirectional relation between sleep and epilepsy: new chances for patients with epilepsy by the antagonism to orexin receptors?

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Orexin/hypocretin, epilepsy, sleep, treatment, dual orexin receptor antagonist

Abstract

Epilepsy is a common neurological disorder, affecting patients of all ages, reducing the quality of life and associated with several comorbidities. Sleep impairment is a frequent condition in patients with epilepsy (PWE), and the relation between sleep and epilepsy has been considered bidirectional since one can significantly influence the other, and *vice versa*. The orexin system has been described more than 20 years ago and is implicated in several neuro-biological functions, other than in controlling the sleep-wake cycle. Considering the relation between epilepsy and sleep, and the significant contribution of the orexin system in regulating the sleep-wake cycle, it is conceivable that the orexin system may be affected in PWE. Preclinical studies investigated the impact of orexin system on epileptogenesis and the effect of orexin antagonism on seizures in animal models. Conversely, clinical studies are few and propose heterogeneous results also considering the different methodological approaches to orexin levels quantification (cerebrospinal-fluid or blood samples). Since the orexin system activity can be modulated by sleep, and considering the sleep impairment documented in PWE, the recently approved dual orexin receptor antagonists (DORAs) have been hypothesized for treating sleep impairment and insomnia in PWE. Accordingly, sleep improvement can be a therapeutic strategy for reducing seizure and better managing epilepsy. The present review analyses the preclinical and clinical evidence linking the orexin system to epilepsy, and hypothesizes a model in which the antagonism to the orexin system by DORAs can improve epilepsy by both a direct and a sleep-mediated (indirect) effect.

Abbreviations and substances

4-AP, 4-aminopyridine

ACT-078573, dual orexin receptor antagonist

AD, Alzheimer's disease

Almorexant, dual orexin receptor antagonist

BBB, blood-brain barrier

CAP, cyclic alternating pattern

CNS, central nervous system

CSF cerebrospinal fluid

DORA, dual orexin receptor antagonist

EEG, electroencephalography

GABA, γ-Aminobutyric acid

GCSE, generalized convulsive status epilepticus

GTCS, generalized tonic-clonic seizures

HFOs high-frequency oscillations

ICV, intracerebroventricular injection

IEDs, interictal epileptic discharges

IP, intraperitoneal injection

N2, stage 2 of non-REM sleep

NREM, non-REM

NT1, type I narcolepsy

OX-A, orexin A

OX-B, orexin B

OX1R, orexin 1 receptor

OX2R, orexin 2 receptor

PD, Parkinson's disease

PTZ, pentylenetetrazol, a $GABA_A$ receptor antagonist used to induce chemical kindling in rodents

PWE, people with epilepsy

REM, rapid eye movement

SB-334867, OX1R antagonist

SE, status epilepticus

Stereo-electroencephalography, sEEG

Seltorexant, selective orexin (1 or 2) receptor antagonist

SORA, selective orexin (1 or 2) receptor antagonist

SUDEP, sudden unexpected death in epilepsy

Suvorexant, dual orexin receptor antagonist

TCS OX2 29, OX2R antagonist

WASO, wake after sleep onset

Introduction

Epilepsy is a neurological disorder characterized by recurrent, unprovoked seizures, that has a lifetime incidence of 1:26 people in the United States (Hesdorffer et al., 2011) and is associated with increased risk for many comorbid conditions, also counting sleep disorders (Gilliam et al., 2005; Manni and Terzaghi, 2010). Sleep impairment, and in particular sleep deprivation, has been associated with the increased risk of seizures in people with epilepsy (PWE) (Grigg-Damberger and Foldvary-Schaefer, 2021; Malow, 2004; Mattson et al., 1965). Therefore, the bidirectional link between epilepsy and sleep is known, and the mutual modulating effects have been widely described in clinical studies (Lehner et al., 2022; Nobili et al., 2022; Yeh et al., 2022). Consistently, seizures and sleep disorders have an interdependent relation where the occurrence of one can exacerbate the other. Sleep deprivation, also restricted to rapid eye movement (REM) sleep, and chronic sleep loss or insufficient sleep have been associated with worsening of seizure frequency and severity, thus possibly causing drug-resistant epilepsy (Grigg-Damberger and Ralls, 2014; Kotagal and Yardi, 2008). Therefore, the alteration in sleep quality and continuity can trigger a seizure and exacerbate epilepsy, thus significantly affecting patients' well-being and increasing the burden of comorbidities (Ng, 2017). Consistently, epilepsy-related comorbidities, such as cognitive deficits and neuropsychiatric symptoms, can be also affected by the sleep impairment (De Weerd et al., 2004; Jacoby et al., 2015; Killgore, 2010; Kotagal and Yardi, 2008; Malow et al., 1997; Plihal and Born, 1997; Rocamora et al., 2008; Steinsbekk et al., 2013). Therefore, sleep dysregulation in PWE not only may impact on seizure frequency but also on the management of the concomitant neuropsychiatric symptoms.

Although sleep and epilepsy can share several mechanisms, including brain networks, neurotransmitter activity, and circadian regulation, a complete picture of this close link remains partially unclear, and further hypotheses and studies are needed. To date, the scientific literature clearly highlighted the impairment of sleep architecture in patients with focal and generalized epilepsy; nevertheless, as shown in a recent review (Sudbrack-Oliveira et al., 2019), few studies compared the sleep structure of PWE with controls and there is no general agreement about objective

sleep impairment in PWE, because of the heterogeneity of patients included (considering type of epilepsy, type of seizure, aetiology of epilepsy) and the different methods for sleep recording and analysis. To increase the knowledge about sleep macrostructure in PWE, a very recent study documented the alteration of sleep stability and continuity in both focal and generalized epilepsy (Calvello et al., 2022). In this research, patients with focal epilepsy presented an increase in stage 2 of non-REM (NREM) sleep (N2) and wake after sleep onset (WASO) and a decrease in REM, with consequent fragmentation of the sleep structure, compared to controls (Calvello et al., 2022). Previous studies showed that REM sleep presents an antiepileptic effect due to the documentation of the reduction of ictal and interictal epileptic discharges (IEDs) in this sleep stage. It was consequently hypothesized the important role of REM sleep in regulating the epileptic spiking threshold and hampering the risk of seizures (Ng and Pavlova, 2013; Placidi et al., 2013; Shouse et al., 2000; Tavşanlı and Kınay, 2022). Therefore, a reduction in REM sleep and an increase in sleep instability in PWE may trigger epileptic seizures and cause, as a further effect, awakenings that can lead to sleep fragmentation (Gelinas et al., 2016; Parrino et al., 2006). Consistently, stereo-electroencephalography (sEEG) in patients with focal epilepsy showed that IEDs and epileptic bursts, particularly in the N2 stage, tend to increase before arousals (Peter-Derex et al., 2015). Epileptic manifestations during sleep can be thereupon mainly triggered by the frequent sleep stage shifting (Calvello et al., 2022). Hence, the microstructural assessment (cyclic alternating pattern - CAP - rate), identifying the sleep stability, is needed to add details on the intrinsic dynamics of the different NREM and REM stages in PWE and their relation to IEDs and seizures. Therefore, to better define the effect of REM sleep on seizures, IEDs, and high-frequency oscillations (HFOs), and to understand the increase in seizure propensity due to insufficient sleep, sleep deprivation, instability or fragmentation (Malow and Aldrich, 2000; Ochi et al., 2011), the investigation of further neurotransmitting systems involved in sleep regulation, namely orexin, can be useful in epilepsy research.

Hence, the present review aims at investigating the role of the orexin system in epilepsy from a translational point of view, including a detailed literature review of preclinical animal model studies

and clinical research, to test the clinical potential of modulating the orexin neurotransmission for controlling seizure generation and propagation. Moreover, this review proposes the opportunity to antagonize the orexin system in PWE for epilepsy management and treating sleep impairment and related comorbidities.

Orexin system and sleep

Neuropeptides orexin A and B (OX-A, OX-B), also called hypocretin 1 and 2, are released selectively by a population of neurons which projects widely to the entire central nervous system (CNS) but is localized in a restricted area of the tuberal region of the hypothalamus, caudal to the paraventricular nucleus. The orexin system prominently targets brain structures involved in the regulation of the wake–sleep state, switching and orchestrating multiple physiological functions. Orexinergic neurons maintain wakefulness by projecting to wake-promoting areas and influencing the monoaminergic and cholinergic systems (Scammell et al., 2001; Schwartz and Kilduff, 2015). Orexin activity is selectively highest during wake, whereas it decreases in slow-wave sleep and is completely absent in REM sleep (Schwartz and Kilduff, 2015; Tsujino and Sakurai, 2009) (Figure 1).

On the one hand, a strong orexinergic tone stimulates wakefulness with mild cortical desynchronization; on the other hand, a weak orexinergic tone fosters slow-wave sleep and thalamocortical synchronization. The orexin phasic bursts, finally, promote hyper-synchronized state transitions (Ng, 2017). Moreover, orexinergic neurons activity supresses REM sleep (Scammell, 2015). Conversely, the absence of orexinergic activity facilitates REM sleep and cortical desynchronization, which results in diminished spatial and temporal summation of aberrant neuronal activity (Frauscher et al., 2016; Shouse, 1986).

Animal model studies highlighted the importance of orexin on sleep, demonstrating that injection of OX-A into the laterodorsal tegmentum promotes wakefulness and suppresses REM sleep (Xi et al., 2001). Similarly, selective orexinergic activation of the ventral periaqueductal grey circuit suppresses REM sleep sparing NREM sleep in mice (Kaur et al., 2009). Moreover, REM sleep deprivation increases cerebrospinal fluid (CSF) orexin levels in rats (Pedrazzoli et al., 2004). Conversely, few

studies have been performed in humans to better characterize the impact of orexin on sleep and wake. Studies have been mainly performed in patients with narcolepsy type 1 (NT1), a sleep disorder featured by the loss of orexin-producing neurons, and characterized by excessive daytime sleepiness and pathological hyper-expression of REM sleep, featuring symptoms such as cataplexy, hypnagogic/hypnopompic hallucinations, and sleep paralysis (Scammell, 2015). Fewer studies are present in literature investigating the orexin system and not focused on narcolepsy. Notably, it has been documented that partial sleep deprivation is associated with an increase in CSF orexin levels in healthy subjects (Olsson et al., 2018). Moreover, fluctuations in CSF orexin levels can occur depending on day length and light exposure, with higher levels in summer and lower levels in winter (Boddum et al., 2016). Therefore, the dynamics of orexin concentrations in the CSF can reflect a modulating system changing its expression in response to external stimuli. In particular, increased vigilance and sleep deprivation have been associated with higher CSF orexin levels, as a possible effect of the increased output and function of the orexinergic system.

Orexin and epilepsy: literature analysis

What is known in animal models

The experimental orexinergic agonism, that mirrors physiologic phasic orexin bursts during state transitions when seizure propensity is high, has a proconvulsant effect; on the other hand, the experimental orexinergic antagonism, which mirrors physiologic orexin neuronal silence in REM sleep when seizure propensity is low, has an anticonvulsant effect. A preliminary experiment was performed in adult male Wistar Albino rats showing epileptic seizures due to the induction of cortical penicillin, which can enhance epileptic activity. In this animal model, the intra-cortical administration of OX-A and OX-B (100 pmol, respectively) produced a significant increase in spike number, amplitude and spectral power values in the EEG and an escalation in the epileptic contractions compared to a negative control (Kortunay et al., 2012). Intracortical injections of OX-A and OX-B (100 pmol, respectively) in the primary motor area, without using any epileptogenic drug also cause

epileptic seizures in rats, an increase in the EEG power spectrum and tonic–clonic contractions on the whole extremities, tail and body (Erken et al., 2012).

Furthermore, at the molecular and cellular levels, orexins are found to increase the excitability of hippocampal neurons and the excitatory neurotransmitter levels (Chen et al., 2017). This evidence is also supported by the fact that pilocarpine, pentylenetetrazol (PTZ) and maximum electroshock-induced seizure activities increase the expression of orexin in the rat hippocampus (Morales et al., 2006; Socała et al., 2016).

Orexinergic antagonists were found to be preventive against epilepsy. Consistently, intrahippocampal and intracerebroventricular (ICV) injections of orexin receptor antagonists reduce seizure severity and duration in animal PTZ models (Goudarzi et al., 2015; Kordi Jaz et al., 2017; Ni et al., 2014). Administration in the bilateral hippocampus of orexin 1 receptor (OX1R) antagonist (SB-334867) and OX-B receptor (OX2R) antagonist (TCS OX2 29), coupled with intravenous PTZ injection to provoke behavioural convulsions, reduced convulsive intensity. This effect is partially mediated by the modification of hippocampal glutamate and γ-Aminobutyric acid (GABA) contents (Goudarzi et al., 2015). In this study convulsions were scored as follows: 0, no response; 1, ear and facial twitching; 2, convulsive waves through the body; 3, myoclonic jerks; 4, tonic-clonic convulsions, rearing; 5, generalized tonic-clonic seizures, turnover into side position, and loss of postural control (modified from Racine et al. (Corda et al., 1990; Racine, 1972)). Consistently, SB-334867 (50 nmol or 200 nmol) infusion reduced seizure stage and duration, decreased hippocampal glutamate levels and increased GABA content only at the lower dose. TCS OX2 29 (20 nmol) infusion also reduced seizure stage and duration without a concomitant change in glutamate and GABA contents, while a higher dose (40 nmol) did not affect the seizure nor the GABA level but decreased glutamate content, measured using a fluorimetric assay, in the hippocampus tissue. Co-administration of SB-334867 (50 nmol or 200 nmol) with TCS OX2 29 (40 nmol) lowered seizure stage and duration, and reduced glutamate but increased GABA content (Goudarzi et al., 2015). ICV injections of SB-334867 (10 μg/rat) before PTZ injections in male Wistar rats decreased seizure-related behaviours of kindled rats

and reversed the PTZ-induced anxiety-like behaviours (Kordi Jaz et al., 2017). Also, ICV injection of TCS OX2 29 in PTZ-kindled rats reduced seizure-related behaviours without any significant effect on PTZ-induced anxiety (Asadi et al., 2018). As a further proof of the beneficial effect of orexin antagonists on seizures, suvorexant (100 and 200 mg/kg), a dual orexin receptor antagonist (DORA) approved for treating insomnia disorder by the Food and Drug Administration, decreased the total duration of seizure compared to a control group in PTZ mice. In addition to this inhibitory effect on orexin receptors, Suvorexant interacts partly with $GABA_A$ and glutamate receptors (Razavi et al., 2020). Thus, considering all the mentioned studies, orexin antagonism seems to facilitate the inhibitory instead of the excitatory neurotransmission.

As reported in the paper of Ni and coauthors, sleep deprivation may increase the risk for seizures, and OX-A was speculated to be involved in this activation through OX1R and OX2R. Sleep-deprived Wistar rats treated with SB-334867 or TCS OX2 29 (30 nM/kg for both compounds), followed by PTZ administration (50 mg/kg) significantly prolonged the latency and reduced the duration of seizures, also lowering the mortality rate. OX1R and OX2R antagonists may alleviate the damage of PTZ-induced seizures that are exacerbated by sleep deprivation (Ni et al., 2014). The protective effect of SB-334867 against convulsive seizures, obtained using 4-aminopyridine (4-AP) and urethane anaesthesia in male rats, was also demonstrated by low-dose (50 and 100 nmol) of this compound injected into the ventral hippocampal commissure (Hayatdavoudi et al., 2017). Moreover, another DORA, almorexant (100 mg/kg, intraperitoneally), reduced seizure activity in a genetic model of multiple epilepsy syndromes, Kcna1-null mice (Roundtree et al., 2016). A Kcna1-null mouse is used to examine symptoms of sleep impairment associated with epilepsy (Simeone et al., 2013) due to the following characteristics: high variable diurnal rest-activity pattern, peak activity and diurnal period (Fenoglio-Simeone et al., 2009a; Fenoglio-Simeone et al., 2009b), increased latency to rest onset and rest fragmentation, and reduced NREM and REM sleep during periods of rest (Roundtree et al., 2016). Almorexant significantly increased the number and duration of NREM sleep epochs and reduced the

latency to REM sleep onset and reduced also the incidence of severe seizures and overall seizure burden (Roundtree et al., 2016).

Interestingly, SB-334867 (30 mg/kg) was also found to elevate the threshold for the PTZ-induced clonic seizures, and for tonic hindlimb extension in the PTZ and maximum electroshock threshold tests, respectively, in male Albino Swiss mice (Razavi et al., 2020; Socała et al., 2016). Both unilateral hypothalamic neuron inactivation with lidocaine injected stereotaxically and the CSF administration of SB-334867 were found to prevent PTZ kindling development in young rats (Akbari et al., 2014).

The Kv1.1 knockout mouse models the loss of Kv1.1 protein function, associated with the human sudden unexpected death in epilepsy (SUDEP) (Bagnall et al., 2017; Klassen et al., 2014), and displays severe spontaneous recurrent seizures (Glasscock et al., 2010; Moore et al., 2014; Simeone et al., 2016; Smart et al., 1998). Similarly to humans, this model exhibits the risk factors for SUDEP, such as multiple generalized tonic-clonic seizures (GTCS), cognitive impairment, and cardiac arrhythmias (Glasscock, 2014; Glasscock et al., 2010; Moore et al., 2014; Simeone et al., 2016). A concurrent increase of the number of orexin neurons in high-risk Kv1.1 knockout mice is supposed in the literature, and the antagonism to the orexin receptors with the intraperitoneal (IP) administration of DORA ACT-078573 can attenuate cardiorespiratory abnormalities and increase longevity (Iyer et al., 2020).

What is known in human studies

The investigation of orexin activity in clinical studies can be exclusively performed by measuring CSF levels of orexin, as the expression of orexinergic system activity; moreover, post-mortem autoptic studies can quantify the orexinergic neurons in the brain of PWE. Consistently, the measurement of intraventricular levels of orexin has been previously performed during surgery in patients with Parkinson's disease (PD) (Bridoux et al., 2013) and can display a more realistic picture as it can better reflect the activity of the orexinergic neurons considering the proximity of these neurons to the ventricular system; conversely, the quantification of CSF levels of orexin obtained by a lumbar puncture can be affected by the CSF cranio-caudal dynamics.

Great part of the studies investigating orexin in neurological disorders has been set by measuring CSF orexin levels. It is well known that reduction in CSF orexin levels are one of the diagnostic criteria for NT1. Although significantly low (less than one-third of the control levels) CSF orexin levels is a hallmark of NT1, there is no consensus about the significance of intermediate or high CSF orexin levels. As previously described, the modification of CSF orexin concentrations can occur following sleep deprivation or external stimuli (day length or light exposure) (Boddum et al., 2016; Olsson et al., 2018), but the literature suggests the correlation between CSF orexin concentrations and sleep and wake parameters to better understand the clinical significance of these changes. A large case-control study (Ripley et al., 2001) highlighted that the majority of patients with chronic neurologic conditions had CSF orexin levels in a normal range (e.g. Alzheimer's disease – AD- and PD), although a subset of patients with acute or subacute disorders can show decreased CSF orexin levels (e.g. intracranial tumours, brain trauma, CNS infections, encephalitis and Guillain-Barrè syndrome). To explain the reduction of CSF orexin levels in these neurological conditions, it was hypothesized that the sleep disturbances and the impairment of consciousness presented by the patients can influence the CSF orexin levels (Friedman et al., 2007; Liguori et al., 2014). On the other hand, the increase of CSF orexin levels has been associated with reduced sleep efficiency, increased sleep fragmentation, REM sleep impairment, dysregulation of the sleep-wake cycle, and the presence of neurobehavioral symptoms in patients with mild cognitive impairment and dementia due to AD. High CSF orexin levels have been also documented in patients with obstructive sleep apnea (Gabelle et al., 2017; Liguori et al., 2019, 2018, 2016). The pathophysiological mechanisms at the basis of these findings are still unknown, and it has been only potentially hypothesized the effect of hypothalamic dysfunction and orexinergic neurons activity impairment in these neurological diseases, considering the association found between the increased nocturnal wakefulness and sleep fragmentation with the high CSF orexin levels (Liguori et al., 2017).

Although neurons expressing OX-A and OX-B are situated in a small part of the lateral hypothalamus, they play a central role in several cerebral functions considering their widely expressed cortical

projections. There is growing evidence that the orexinergic system may have a key role in the onset of seizures (Ng, 2017). Although experimental studies highlight intriguing results, clinical studies are still few. One of the main relevant data emerging from the literature is shown in a large case-control study, primarily designed to detect CSF orexin levels in patients with NT1, and reporting in the secondary outcomes a moderate decrease of CSF OX-A levels in three of seven PWE after generalized tonic-clonic seizures, although with no significant difference compared to controls (Ripley et al., 2001). To support this data, CSF OX-A concentrations from 21 patients with single and repetitive GTCS were found to be significantly lower compared to the levels detected in 19 controls. The lowest levels were showed by a subgroup of patients with repetitive GTCSs. The lumbar puncture was performed within 48h after GTCS but no significant correlations with the time frame emerged (Rejdak et al., 2009). These results concord to the preclinical findings documenting the reduction of OX-A levels following a seizure, possibly due to a lower synthesis in the hypothalamus of the neuropeptide or to an increase in blood-brain barrier (BBB) permeability permitting the leakage of orexin from the CNS. Among the hypothesis suggested by the Authors about the reduction of CSF orexin levels, the more reasonable were the typical post-ictal somnolence observed after GTCS and the propagation of epileptic activity to the deep brain structures. The same group of authors (Rejdak et al., 2009) confirmed these results with a second study that included 20 patients with generalized convulsive status epilepticus (GCSE), 24 patients with epilepsy in remission and 25 controls. CSF samples did not reveal pathological levels of orexin. Lumbar puncture was performed within 48h after the GCSE cessation. Data highlight a significant overall difference in median CSF OX-A concentrations between controls (314.1 pg/mL [234.4–379.1]), patients with epilepsy in remission (305.6 pg/mL [203.4–450.5]), and GCSE patients (194.3 pg/mL [105.8–248.1]). GCSE patients showed lower CSF levels of orexin as compared with PWE in remission and controls. Another interesting result is that CSF OX-A levels in patients with GCSE inversely correlated with the clinical outcome, as assessed by the modified Rankin Scale (mRS) measured at 1 month follow-up (Samzadeh

et al., 2020). This result suggested the potential role of orexin as a useful biomarker for clinical outcome, in terms of disability, after status epilepticus (SE).

Although more results have been provided by blood-based studies, it is currently not recommended the measurement of orexin levels in blood considering the lack of correlation between CSF and blood orexin levels. Accordingly, literature discourages the quantification of orexin in blood since it cannot correspond to the brain levels and can reflect a systemic secretion of a similar neuropeptide released by the gut (Arihara et al., 2001; Mäkelä et al., 2018; Tang et al., 2017) Although these premises, studies demonstrating changes in blood orexin levels have been included in this review. Çikriklar and collaborators investigated the diagnostic efficiency of OX-A as a biomarker for the differential diagnosis of epileptic and non-epileptic seizures. Blood OX-A levels of 80 individuals (39 with first unprovoked generalized seizure, 20 psychogenic non-epileptic seizures and 21 healthy volunteers). were collected, within 4h after seizure onset in PWE and non-epileptic subjects, and the morning after a "healthy night's sleep" for controls. The study showed that OX-A levels were higher in patients with epileptic seizures compared to non-epileptic seizures and controls. No correlation was found between duration (time interval between seizure and blood sample) and OX-A levels (Çikriklar et al., 2020a). In the same context, to identify peripheral biomarkers of paroxysmal sleep disorders in children, Kaciński and collaborators compared serum OX-A levels in paediatric patients affected by sleep disturbances and epilepsy. The study enrolled 56 patients, but orexin level measurement was performed in 49 children, including 14 with parasomnias, 25 with epilepsy and 10 with epilepsy and recorded seizures during sleep. OX-A levels were significantly lower in children with epilepsy in remission compared to patients with parasomnia only, unlike patients in which seizures were recorded (with epilepsy, not in remission) had higher orexin levels (Kaciński et al., 2012).

Discrepancies and contradictory results

The orexin system has been evaluated particularly in the preclinical models of epilepsy. Most of the data were obtained considering the injection of orexin or orexin antagonists to evaluate changes in the orexinergic system functioning. Clinical studies present fewer data and are based on the

measurement of orexin levels in CSF or blood; CSF studies were mainly performed in PWE following GTCS.

Preclinical data

All the evidence collected in animal model studies mainly suggests that orexins play a detrimental role in the pathogenesis of epilepsy and thus the antagonism to orexin receptors, reducing orexin neurotransmission activity, can be a potential antiseizure therapy for PWE. However, the contrary was also reported in few animal studies. Doreulee and collaborators investigated the electrophysiological effects of OX-A in an in vitro study and found that it inhibits epileptiform discharges induced by bicuculline methiodide in CA1 (Doreulee et al., 2010). Moreover, OX-A showed a protective effect on the impairment of spatial learning and memory in PTZ-kindled rats by promoting neurogenesis in the dentate gyrus. This protective effect of OX-A was abolished by treatment with SB-334867 (Zhao et al., 2014).

All in all, the evidence regarding the role of the orexinergic system on the pathophysiology of epilepsy is contentious. The amplitude of data shows the pro-convulsant effect of orexin but un-ignorable data, although limited, shows the opposite. These discrepancies may arise from the differences in the epilepsy models used, in the study design not aimed at measuring the anti-convulsant effect of orexin receptor antagonism (Zhao et al., 2014), and in the planning of experiments not reproducible in further confirmatory studies since outdated (Doreulee et al., 2010). Therefore, future studies should focus on digging out the sources of the discrepancies of orexin effects in epilepsy.

Clinical data

Clinical data presented mixed results due to heterogeneous study designs and the assessment of orexin levels either in the CSF or blood. Consistently, CSF-based studies showed reduced levels of orexin in PWE, in particular following GTCS; conversely, blood-based studies showed higher levels of orexin in PWE following seizures, and possibly related to the BBB damage induced by seizures.

Synthesis of what is known

Preclinical data

Intracortical injection of OX-A and B causes epileptic seizure or increases spike numbers and spike amplitude sizes during convulsion induced by cortical penicillin (Erken et al., 2012; Kortunay et al., 2012). On the contrary, antagonisms to OX receptors reduce convulsive intensity in rats (Goudarzi et al., 2015) with or without any significant effect on PTZ-induced anxiety (Asadi et al., 2018; Kordi Jaz et al., 2017), decrease the duration of spike trains and prevent kindling development in rats (Akbari et al., 2014; Hayatdavoudi et al., 2017), prolong the latency and reduce the duration of seizures in sleep deprived rats (Ni et al., 2014). In mice, dual orexin receptor antagonist or OX1R antagonist injection prior to PTZ decreases total duration of seizure or elevates threshold for the PTZ-induced clonic seizures (Razavi et al., 2020; Socała et al., 2016), and this reduction is also confirmed in Kcna1-null mice (Roundtree et al., 2016).

Clinical data

Few clinical studies have analysed OX-A levels either in blood or in CSF, alternatively. The data has shown that blood OX-A levels are increased in PWE with active seizures when detected within 4 h after seizures (Çikriklar et al., 2020b; Kaciński et al., 2012). Authors have speculated about the fact that the higher concentration of OX-A levels in PWE following seizures might be related to an increase in BBB permeability thus observing a leakage of orexins from the CNS to the systemic circulation. Other studies highlighted that CSF OX-A levels in patients after repetitive GTCS or after SE were decreased and proposed that this might be related to the post-ictal sleepiness frequently reported by patients following a GTCS or a SE (Rejdak et al., 2009; Samzadeh et al., 2020; Ripley et al., 2001). Further clinical studies are needed to evaluate the effect of DORAs on epilepsy, possibly monitoring a sleep-mediated effect allowing the reduction of seizures.

Discussion

Orexin neurons are located in the lateral hypothalamus and perifornical region and when activated, promote wakefulness, attention, and arousal (Sakurai, 2007). Orexin neurons funnel different afferent signals and send projections to the ascending reticular activating system to increase activation of

wake-promoting norepinephrine, acetylcholine, serotonin, histamine, and dopamine neuronal populations (Peyron et al., 1998; Sakurai, 2007; Sakurai et al., 2010; Szymusiak and McGinty, 2008). Notably, the orexin system has been receiving increasing attention in the last decades considering its critical role mainly in regulating the sleep-wake cycle, although its implications also in the autonomic system regulation, cardiovascular control, feeding behaviour, reward, and body temperature regulation (Berteotti et al., 2021). Apart from NT1 where the absence of orexin neurotransmission produces several clinical implications, the importance of this system is continuously increasing also considering the possibility to counteract orexin activity by using a novel class of drugs called DORAs.

Potential role of DORAs and SORAs beyond insomnia

DORAs have been approved for the treatment of insomnia disorder since the administration of the drug before going to bed can facilitate sleep by the antagonisms to both orexin receptors. The drug acts on deactivating orexin neurotransmission, thus reducing latency to sleep and night-time awakenings. The mechanism of action of DORAs is indeed based on hampering the effects of orexins during the night to facilitate sleep and in particular REM sleep. Moreover, recent animal model studies and clinical trials are testing the effect of DORAs and selective orexin (1 or 2) receptor antagonists (SORAs) on other medical conditions (Berteotti et al., 2021; Hoffmann et al., 2015; Kaufmann et al., 2021). Specifically, orexin receptor antagonism has been studied for the treatment of anxiety and depression. Clinical trials have reported that Suvorexant (DORA), administrated in psychiatric patients with insomnia, improves anxiety and depression; moreover, a SORA (Seltorexant) seems to reduce subjective symptoms of depression in patients treated for major depression and symptoms of insomnia (Brooks et al., 2019; Nakamura and Nagamine, 2017). Recent preclinical studies suggest that SORAs, in particular SORA directed to OXR1, may reduce the effect of drug addiction thus highlighting the important role that the orexin system plays in reward system (Dhaher et al., 2010; Gentile et al., 2018; Quarta et al., 2010). Another interesting field of research is the use of DORAs and SORAs in systemic disorders such as hypertension and obesity. The antihypertensive effects and the regulation of food intake of these drugs have been demonstrated in

preclinical models, underlying the role of orexin in the neurogenic control of metabolic functions (Imperatore et al., 2017).

Orexin receptor antagonism in PWE: not just a sleep issue.

The importance of targeting the orexin system to manage and treat metabolic, psychiatric, and neurologic disorders includes also the recent evidence supporting the hypothesis of a critical role of orexin on seizures and epilepsy, not only by considering the bidirectional link between epilepsy and sleep but also by considering a direct effect of orexin on seizures and epilepsy.

The indirect effect of orexin on seizures and epilepsy is indeed mediated by sleep (see Figure 2). As already mentioned, orexin promotes wakefulness and the antagonism to orexinergic neurotransmission can promote NREM and REM sleep, as shown in animal model studies (Mahoney et al., 2020). However, the importance of the orexinergic neurotransmission lies in the evidence that a physiologic switch-on and switch-off of the orexin neurons can maintain the circadian regulation of the sleep-wake rhythm, which can be altered in PWE (Liguori et al., 2022; Saper, 2006). Therefore, also the ultradian cycling of sleep can be regulated by the orexin and then the importance of this network is also related to the interconnections of the projections of the orexin neurons to the other brain regions controlling sleep. It has been documented that only 1% or less of seizures occurred in REM sleep, whereas wakefulness displays eight times more seizures than REM sleep (Ng and Pavlova, 2013). During NREM sleep inter-ictal phenomena resulted increased, and both IEDs and HFOs are boosted by NREM sleep, and particularly in N2. Conversely, IEDs are less present in the last third of the night, when REM sleep is more present (Anderson et al., 2015). Moreover, seizure tendency is high during periods of transition from REM sleep to wakefulness (Ng, 2017; Shouse, 1986). Indexed to duration, REM sleep is the most protective stage of sleep against focal seizures, generalized seizures, focal IEDs or HFOs, and two particular epilepsy syndromes (e.g. self-limited epilepsy of childhood with centro-temporal spikes, Landau-Kleffner) (Ng and Pavlova, 2013). Accordingly, the kindling of animals is most difficult during REM sleep (Calvo and Fernandez-Mas, 1991; Shouse, 1986; Tanaka and Naquet, 1975) and REM sleep deprivation facilitates kindling

(Cohen et al., 1970). Therefore, the propensity of seizure is higher during the transition from sleep to wakefulness and less during REM sleep. Accordingly, the promotion of REM sleep can represent a treatment strategy against IEDs, seizures and epilepsy. Orexin receptor antagonisms can permit sleep stability and REM sleep increment, other than wakefulness after sleep onset and arousal reduction (Xue et al., 2022). Consistently, PWE frequently experience insomnia, sleep fragmentation, increased sleep latency, arousals, and sleep-wake cycle dysregulation (Kotagal and Yardi, 2008; Malow, 2005; Malow et al., 1997). Recent data also include the increased frequency of sleep stage shifts in PWE, coupled with more frequent wake bouts, producing sleep instability, lack of sleep continuity and REM sleep impairment (Calvello et al., 2022). Sleep fragmentation has been previously associated with changes in orexin neurotransmission in animal models and human studies (Brisbare-Roch et al., 2007; Horvath and Gao, 2005; Olsson et al., 2018; Prober et al., 2006; Vgontzas and Chrousos, 2002) and, although in a pure hypothetical model, it is conceivable that sleep impairment in PWE may be associated with increased orexin expression and function and that this neurotransmission over-activity can, in turn, impair sleep and possibly trigger IEDs and seizures (Figure 3). Therefore, antagonisms to orexin receptors may represent a strategy for improving sleep and thus seizures in PWE.

There is a further hypothesis directly linking orexin system activity to epilepsy. According to the need of studying the sleep-regulating pathways in epilepsy, among all the neurotransmitting systems controlling the sleep-wake rhythmicity in PWE, recent literature highlights the involvement of the orexin system in the pathogenesis of epilepsy. In keeping with the literature proposed by this review, it has been hypothesized a novel role of orexin in brain excitability and seizure occurrence and propagation. Accordingly, animal model studies documented a direct role of orexin in seizure pathogenesis (Kortunay et al., 2012; Erken et al., 2012). Orexin neurotransmission is state dependent: high in wakefulness, mild in slow wave sleep and completely absent in REM sleep (Schwartz and Kilduff, 2015; Tsujino and Sakurai, 2009). In case of sleep deprivation (partial or complete), orexin levels significantly increase in the CSF (Olsson et al., 2018; Schwartz and Kilduff, 2015; Tsujino and

Sakurai, 2009). Fitting all the pieces together, the propensity of seizure is higher in periods of high orexin level and less in periods when orexin is absent. Therefore, it is conceivable to speculate that the over-activity of orexinergic transmission is associated with seizure and thus the antagonism to orexin receptors may reduce the seizure risk.

Conclusion

In conclusion, translating previous data about sleep fragmentation and increased orexinergic neurotransmission to the evidence of sleep macro and microstructure impairment in PWE, it can be hypothesized that orexin neuron function and output can be altered in epilepsy, and can represent a target for therapeutic strategies for improving both sleep and epilepsy. Orexin neurons are indeed directly and indirectly connected to the seizure-generating hippocampal network via monosynaptic and polysynaptic efferent and afferent projections (Dubé et al., 2001; Kukkonen et al., 2002; Wang et al., 2008; Yoshida et al., 2006). Also considering the implication of orexin neurotransmission modulation on SUDEP and behavioral symptoms, this review further supports the need for studies investigating the role of orexin in epilepsy to take the opportunity to use SORA and DORA in clinical practice for improving sleep, treating epilepsy, reducing seizure frequency, ameliorate neuropsychiatric comorbidities and cognitive deficits, and even lowering the risk of SUDEP.

Key bullet points:

- The orexin system is involved in the regulation of the sleep-wake cycle that in turn is bi-directionally linked to epilepsy.
- Animal model studies showed the pro-convulsive effect of orexin and the reduction of neuronal spiking following antagonism to orexin receptors.
- Few data are present in human studies, with controversial results on CSF orexin levels measured following seizures or status epilepticus.
- Antagonizing the orexin system for promoting sleep and reducing seizures may be hypothesized in the management of epilepsy.
- Sleep enhancement and improvement by DORAs may be evaluated in the management of patients with epilepsy for improving seizure control and epilepsy-related comorbidities.

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Table 1: Animal model studies investigating the role of orexin in epilepsy.

Animal model	Experiment	Effect	Reference
Adult male Wistar Albino rats	Cortical injection of penicillin to produce penicillin-induced epilepsy followed by intracortical administration of OX-A and OX-B (100 pmol, respectively).	OX-A and OX-B significantly increase spike numbers, spike amplitude sizes and total EEG power spectrum during convulsions induced by cortical penicillin.	Kortunay et al., 2012
Adult male Wistar Albino rats	Intracortical injections of OX-A and OX-B (100 pmol, respectively).	OX-A and OX-B cause epileptic seizure, increase total EEG power spectrum, induce tonic–clonic contractions on the whole extremities, tail and body.	Erken et al., 2012
Male Wistar rats (2.5 months old)	Intrahippocampal injections of SB-334867 and TCS OX2 29) (different doses) before intravenous PTZ injections.	OX1R and/or OX2R antagonist reduces convulsive intensity, partially through alteration of hippocampal	Goudarzi et al., 2015

		glutamate and GABA contents.	
Male Wistar rats	ICV injections of SB-334867 (10 µg/rat) before PTZ injection.	OX1R antagonist decreased the median of seizure stages, prolonged the latency and reduced the duration of different seizure stages, and reversed the PTZ-induced anxiety-like behaviours.	Kordi Jaz et al., 2017
Adult male Wistar rats	ICV injections of TCS OX2 29, followed by a convulsive dose of PTZ (IP injection).	Blockade of OX2R reduced seizure-related behaviours without any significant effect on PTZ-induced anxiety.	Asadi et al., 2018
Male Albino mice	Suvorexant (100 and 200 mg/kg) administrated by gavage 60 min prior to PTZ (80 mg/Kg, IP).	Suvorexant decreased total duration of seizure.	Razavi et al., 2020
Sleep deprived adult male Wistar rats	ICV injections of SB-334867 or TCS OX2	OX1R or OX2R antagonist	Ni et al., 2014

	29 (30 nM/kg for both compounds), followed by PTZ (50 mg/kg, IP).	significantly prolonged the latency and reduced the duration of seizures.	
Male Wistar rats	Vental hippocampal commissure injection of SB-334867 (50 nmol) after 4-AP (IP injection).	OX1R antagonist decreased the duration of spike trains and of convulsive seizures; increased seizure onset.	Hayatdavoudi et al., 2017
Adult Kcna1-null mice	Almorexant (100 mg/kg, IP)	Dual orexin receptor antagonist reduced the incidence of severe seizures and overall seizure burden	Roundtree et al., 2016
Male Albino Swiss mice	SB-334867 (30 mg/kg, IP) in the PTZ seizure threshold and maximal electroshock seizure tests respectively.	OX1R antagonist elevated threshold for the PTZ-induced clonic seizures, and for tonic hindlimb extension.	Socała et al., 2016
Male Sprague Dawley rats (2 months old)	Unilateral hypothalamic neurons inactivation with lidocaine injected	SB-334867 prevented PTZ kindling development.	Akbari et al., 2017

	stereotaxically plus SB-334867 and PTZ (40 mg/kg, IP).		

Table 2: Orexin levels measurement in patients with epilepsy.

Population	Methods	Result	Reference
Blood-based studies			
80 individuals: - 21 healthy controls - 39 generalized seizure - 20 non-epileptic seizures	OX-A levels were detected in a venous blood sample of 80 individuals. The measurement was done within 4 hours from seizures/non-epileptic seizures in 59 patients. The same data were obtained from a sample of 21 healthy control, detected in the morning after a healthy night's sleep.	Mean blood OX-A levels are higher in patients with epileptic seizures compared to patients with non-epileptic seizures	Halil Ibrahim Çikriklar et al., 2020
49 children with paroxysmal sleep disorders - 14 parasomnias - 25 epilepsy in remission 10 epileptic seizures recorded	Two blood samples for OX-A analysis were taken from 49 children (1 month to 18 years): - before recording - after 2.5 h of sleep or 0.5 h after clinical seizures.	Blood OX-A levels were decreased in epileptic children without seizures compared to parasomnic patients but were elevated in epileptic patients with seizures.	Marek Kaciński et al., 2012

		Significant results were found only in the second blood samples.	
CSF-based studies			
40 individuals: - 19 healthy controls - 11 single GTCS - 10 repetitive GTCS	All patients underwent lumbar puncture within 48 h after GTCS to detect CSF OX-A levels. Both patients and controls underwent lumbar puncture between 7 am and 5 pm. The control group included 19 patients with aspecific symptoms that did not lead to a neurological diagnosis.	CSF OX-A concentrations are lower in patients with GTCS compared to controls	Konrad Rejdak et al., 2009

69 individuals: - 25 healthy controls - 24 epilepsy in remission - 20 GCSE	Lumbar puncture was performed in GCSE patients within 3–10 days from the last seizures. Patients with epilepsy in remission, GCSE patients, and controls underwent lumbar puncture between 7 am and 5 pm.	CSF OX-A levels are lower in patients with GCSE compared to patients with epilepsy in remission and controls	Mojdeh Samzadeh et al., 2020
325 individuals: - 42 narcolepsy type 1 - 48 healthy controls - 235 neurological disorders (7 epilepsy)	CSF from all neurologic patients and controls was collected by a lumbar puncture for diagnostic and research purposes and was kept at -80 °C prior to measurement. Lumbar punctures in all patients were carried out between 7 am and 5 pm.	CSF OX-A levels were decreased in 3/7 epileptic patients.	Ripley et al.,2001

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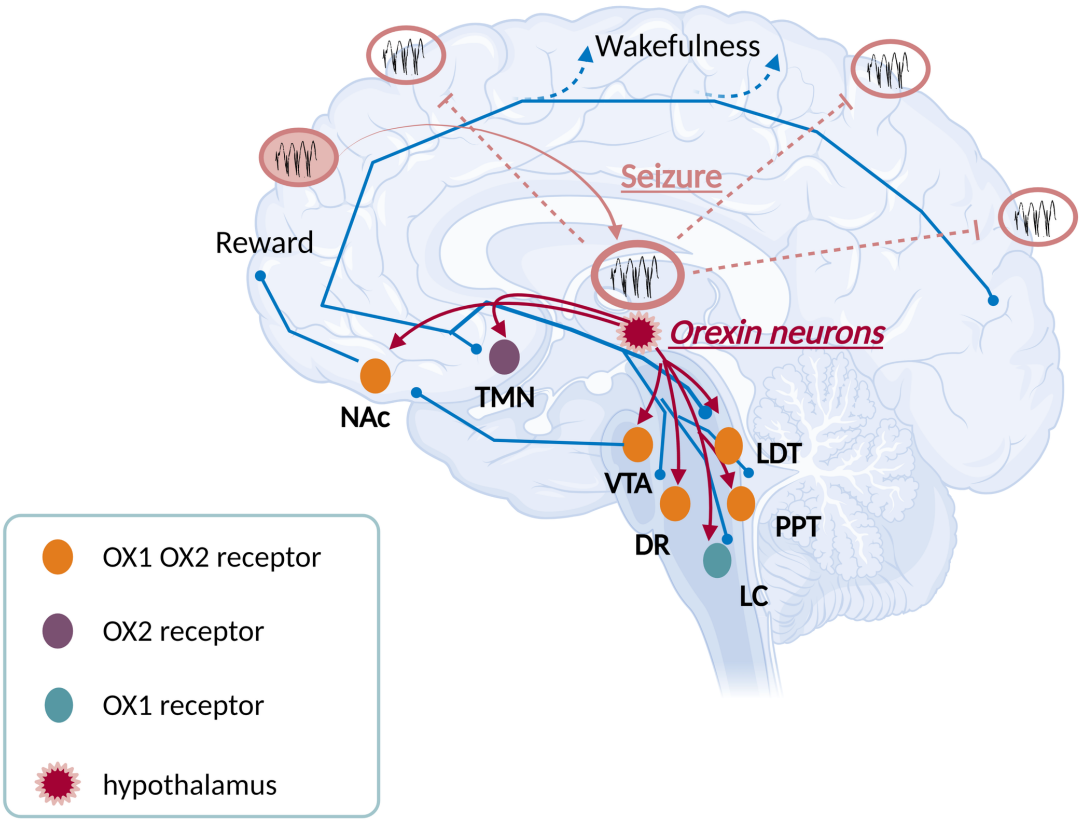
Figure legends (all figures are created with BioRender.com).

Figure 1. This figure shows orexinergic projections to the human brain: orexin neurons from hypothalamus control the sleep-wake rhythm. Excitatory projections range from hypothalamus to the most of central nervous system: monoaminergic and cholinergic nuclei including laterodorsal tegmental nuclei (LDT) and pedunclopontine tegmental nuclei (PPT), locus coeruleus (LC), dorsal raphe nucleus (DR) and tuberomammillary nucleus (TMN). Moreover, the reward system is characterized by connection between orexin neurons, ventral tegmental area (VTA) and nucleus accumbens (NAc). The figure also shows a schematic seizure network: propagation of seizure activity from cortical to midline subcortical structures determines an aberrant connectivity that led to reduced cortical activation.

Figure 2. This figure highlights the critical role of the orexin system on seizures and epilepsy. In particular, orexin can modulate epileptic activity and seizures via a direct pro-convulsant effect, and via an indirect effect, mediated by sleep deprivation and fragmentation, which can induce epileptic interictal and ictal activity, more evident in the transition from wakefulness to sleep (central panel) or in the Non-REM sleep stages.

Figure 3. This figure explicates the hypothesis linking orexin, sleep and epilepsy. Considering the ictal and interictal activity present during sleep in patients with epilepsy and causing the sleep fragmentation, it is conceivable that this loss of sleep stability and continuity can be associated with a higher orexinergic tone, which in turn can support the proconvulsant effect related to this upregulated neurotransmission.



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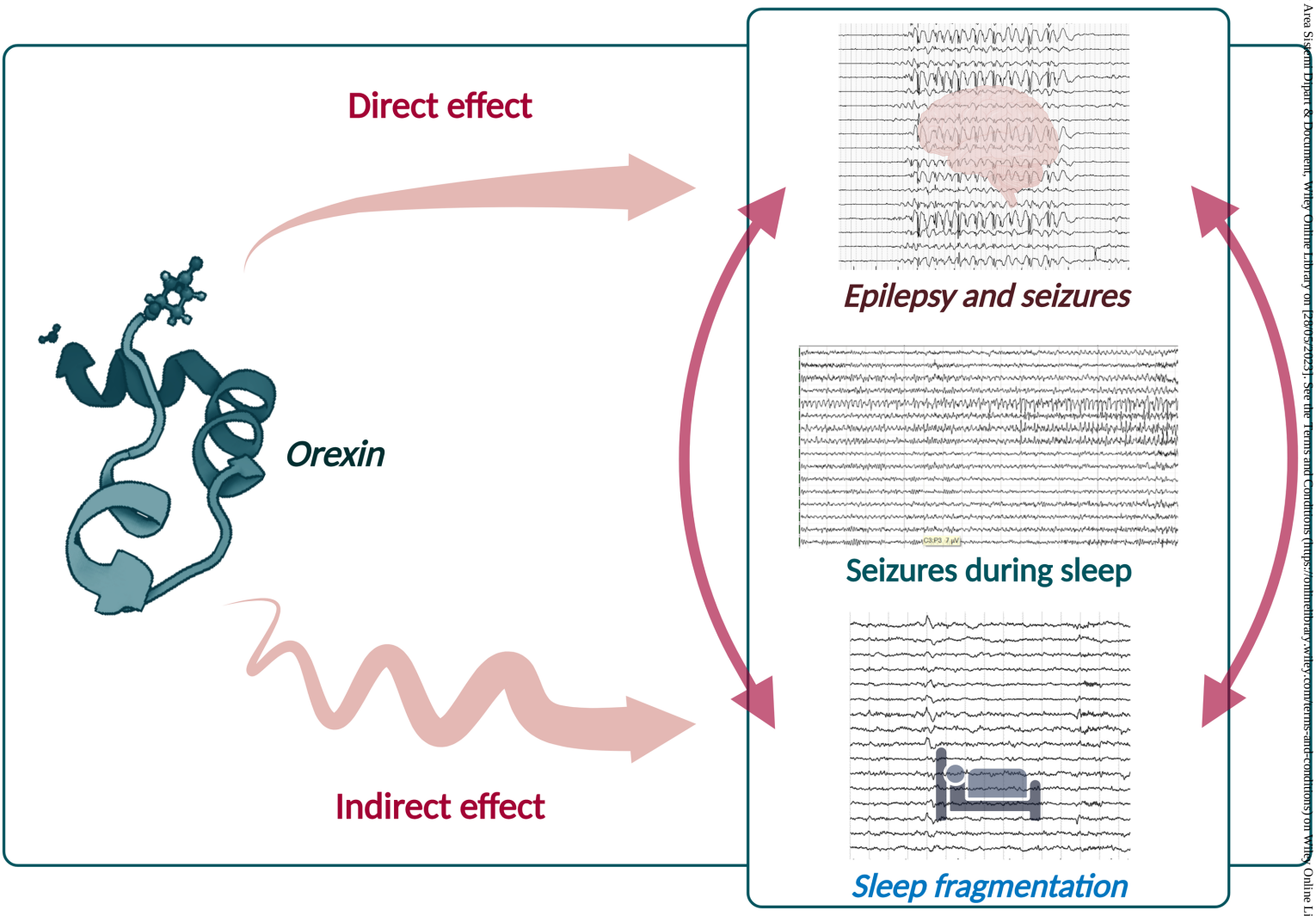

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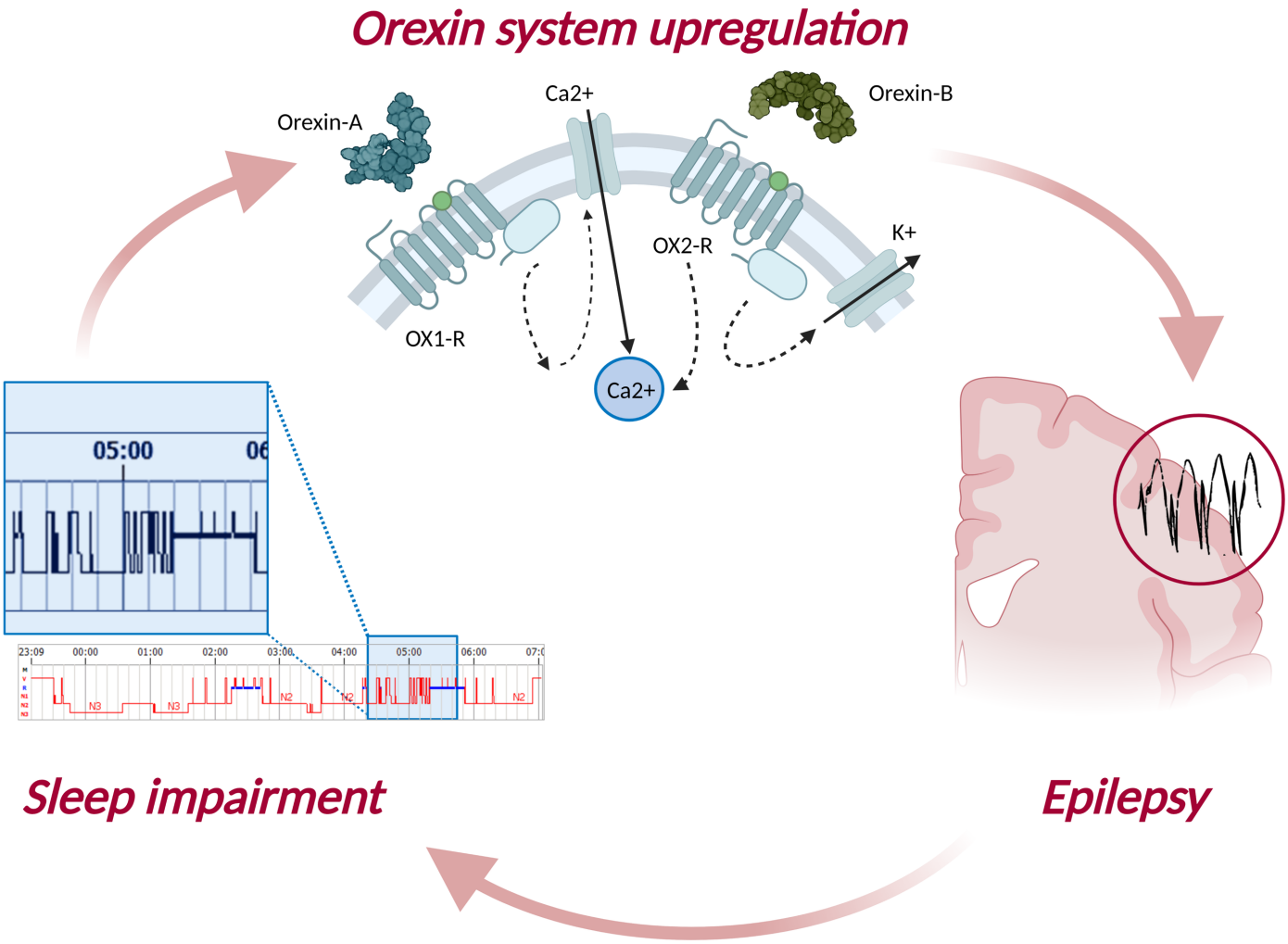

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