

Orexin and Epilepsy: Potential Role of REM Sleep

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Abstract

Interest in orexin receptor antagonism as a novel mechanism of action against seizures and epilepsy has increased in recent years. Loss of orexinergic activity is associated with REM sleep onset, and REM sleep is generally protective against seizures. This paper discusses the dynamic modulation of seizure threshold by orexin through a postulated “orexi-cortical” axis in which the specific type of orexinergic activity exquisitely regulates sleep-wake states to modify ascending subcortical influences on cortical synchronization with profound subsequent consequences on seizure threshold. This paper also explores the current state of research into experimental orexinergic modulation of seizure threshold, and suggests possible future research directions to fully understand the promise and peril of orexinergic manipulation in seizures and epilepsy.

1. Introduction

In recent years, there has been growing interest on the use of orexin receptor antagonism as a novel mechanism of action against seizures. Discovered at the turn of the century, orexin has become widely established as a key modulator of sleep, and sleep has been known for millennia to exert a profound impact on seizures and epilepsy. Loss of orexinergic activity has been associated with REM sleep onset, and REM sleep is generally protective against seizures. The purpose of this paper is to discuss orexinergic modulation of seizure threshold through a postulated “orexi-cortical” axis in which subcortical orexinergic activity exquisitely regulates sleep-wake states to modify ascending subcortical influences on cortical synchronization with profound subsequent consequences on seizure threshold. This paper begins by reviewing orexinergic physiology from hypothalamic origin to downstream synchronization effects at the cerebral cortex, then the current state of research into orexinergic modulation of seizure threshold, and finally possible future research directions to fully understand the promise and peril of experimental orexinergic manipulation.

2. From Hypothalamus to Cortex

Because orexin is a subcortical neuropeptide and seizures are cortical phenomena, these two processes intersect where ascending subcortical orexinergic projections meet a hyperexcitable and hypersynchronized cerebral cortex. Starting from a mere 50,000 to 80,000 neurons in the human posterolateral hypothalamus, the excitatory hypothalamic peptide orexin, also known as hypocretin, is exclusively manufactured from these neurons as the precursor preproorexin.¹ This

precursor then becomes the 33 amino acid residue peptide orexin A, and 28 amino acid residue peptide orexin B.² Orexin A binds to two types of orexin receptors, OX1R and OX2R, with equal affinity.² Orexin B preferentially binds to OX2R.² OX1R preferentially promotes arousal (defined as onset of wakefulness) and OX2R preferentially promotes wakefulness.² Through excitatory mediators such as glutamate, dynorphin, and galanin, active orexinergic neurons exhibit oscillatory, phasic, and tonic firing characteristics (Fig. 1).^{1,3} Oscillatory activity is circadian regulated and associated with a myriad of non-sleep related functions.³ Phasic activity modulates arousals as bursts of orexinergic neuronal firing, which last 1 to 10 seconds at a frequency greater than 5 Hz, to precede sleep-wake transitions.²⁻³ Tonic activity maintains a particular state of consciousness with interruptions in tone resulting in a sudden lapse into sleep.⁴

Orexinergic tone is highest in wakefulness, mild in slow wave sleep (SWS), and completely absent in REM sleep (Fig. 1).^{1,5} Orexinergic neuronal silence in REM sleep is only interrupted during the transition to wakefulness when phasic burst activity ensues.⁶⁻⁹ In wakefulness, orexinergic tone is further increased by emotional limbic input.^{1,5} Orexinergic neurons sustain wakefulness by projecting to wake-promoting areas with effects on the histaminergic system via the tuberomammillary nucleus; the cholinergic system via the laterodorsal tegmentum, pedunculopontine tegmentum, and basal forebrain; the serotonergic system via the dorsal raphe nuclei; the noradrenergic system via the locus coeruleus; and the dopaminergic system.^{1,4} These regions express both OX1R and OX2R with the locus coeruleus and tuberomammillary nucleus being particularly rich in OX1R and OX2R respectively.² GABA, noradrenaline, dopamine, and serotonin from these regions provide negative feedback.¹ In contrast to active wakefulness promotion, orexinergic neurons tonically suppress REM sleep.⁴ For example, directly injecting

orexin A into the laterodorsal tegmentum increases wakefulness but suppresses REM sleep.¹⁰

Similarly, selective orexinergic activation of the ventral periaqueductal grey circuit suppresses REM but spares non-REM (NREM) sleep.¹¹

When orexinergic tone is lost, strong wakefulness promotion is lost, mild SWS promotion is lost, active REM sleep suppression is lost, and the net result tends toward REM sleep onset. These onsets form the clinical basis of type I narcolepsy, which is characterized by marked orexinergic neuronal loss.⁴ In orexin receptor knockout mice, levels of choline acetyltransferase, vesicular acetylcholine transporter, and the high-affinity choline transporter are elevated in the laterodorsal pontine tegmentum, which is the location of a main cluster of REM-on neurons responsible for the initiation of REM sleep.¹²⁻¹³ Ascending cholinergic inputs from REM-on neurons reach the cerebral cortex in a diffuse generalized manner *en masse* via the thalamus or a subthalamic basal forebrain pathway in order to activate muscarinic metabotropic cholinergic receptors.¹⁴

Activated metabotropic G-protein coupled muscarinic receptors inhibit potassium channels to shift cortical neuronal excitability from a synchronized rhythmic bursting mode of activity to a desynchronized single spike mode of action potential generation.¹⁴ The resultant sum of excitatory and inhibitory postsynaptic potentials from apical dendrites of pyramidal cells in the outer layer of the cerebral cortex is captured as voltage fields on the electroencephalogram (EEG).¹⁵ Like wakefulness, another state characterized by the presence of acetylcholine, the EEG of REM sleep is also diffusely desynchronized but to a greater degree.¹² Unlike wakefulness in which other neurotransmitters are active, REM sleep is an acetylcholine-exclusive state.¹⁴

3. The Cortex and Synchrony

Absence of orexinergic activity leads to REM sleep onset and diffuse cortical desynchronization, which reduces the opportunity for spatial and temporal summation of aberrant neuronal activity into interictal epileptiform discharges (IEDs) and seizures.¹⁶⁻¹⁷ In feline kindling models of epileptogenesis, REM sleep is the most difficult state in which to kindle the cat.^{16,18-20} In contrast, selective REM sleep deprivation accelerates kindling and kindling decreases REM sleep.^{18,21} REM sleep deprivation also increases hypocretin-1 (orexin-A) levels in cerebrospinal fluid.²² Moreover, cortical cholinergic denervation accelerates murine amygdalar kindling and septal cholinergic denervation accelerates murine hippocampal kindling.²³⁻²⁴ In humans, only 1% of nearly 2000 seizures in a systematic review occurred in REM sleep, including severe pediatric epileptic encephalopathies.²⁵ When adjusted for state duration, the rate of seizures, focal and generalized IEDs, and focal high frequency oscillations (HFOs) were all lowest in REM sleep.²⁵⁻²⁶ These findings were validated in years of implanted ambulatory electrocorticography as part of responsive neurostimulation, which found a reproducible IED nadir in the latter third of the night when REM sleep is most likely; however, the extent of intracranial implantation was limited and may not have surveyed all pertinent cerebral areas.²⁷ Cortical desynchronization in REM sleep also suppresses seizure, IED, and HFO distribution to enhance epileptogenic zone localization.²⁸⁻³⁰ Better localization has successfully guided otherwise non-localizable epilepsy surgeries.²⁸⁻³⁰ , REM sleep has also been shown to selectively and persistently rebound after successful surgery.³¹ These findings suggest that absence of orexinergic activity in REM sleep, which is characterized by diffuse cortical desynchronization, is overall protective against IEDs and seizures (Fig. 1).

In contrast to orexinergic quiescence, strong orexin tone promotes wakefulness with only mild cortical desynchronization, weak orexin tone promotes SWS with strong thalamocortical synchronization, and orexin phasic bursts promote hypersynchronized state transitions. In wakefulness, a human systematic review found 8 times more seizures, 1.11 times more focal IEDs, and 3 times more generalized IEDs than REM sleep (Fig. 2).²⁵ The greater impact of desynchronization on seizures than IEDs confirms that organization of aberrant epileptiform activity is affected more than generation of aberrant activity in the first place; in other words, cortical desynchronization makes it harder for spontaneously occurring aberrant activity to organize into an IED and then harder still for IEDs to organize into seizures. In SWS, there were 60 times more seizures, 2 times more focal IEDs, and 7 times more generalized IEDs than REM sleep (Fig. 2).^{25,32} Aberrant activity in primary generalized epilepsy (PGE) often “hijacks” synchronization mechanisms in SWS to organize into an IED which is physically embedded within normal NREM sleep architecture that depends on thalamocortical synchrony in a phenomenon termed “dyshormia”.³³ Regarding state transitions, there is often cortical synchronization, such as in hypnagogic and hypnopompic hypersynchrony.³⁴ In the cat, kindling is easiest in the transition from REM sleep to wakefulness.¹⁶ In murine temporal lobe epilepsy (TLE), seizures are increased in transitions from SWS to REM sleep in a tetanus toxin model which reduced inhibitory neurotransmitter release, and from REM sleep to SWS in a kainate model using repeated low-dose intraperitoneal injections to generate TLE.³⁵⁻³⁶ In humans, there is a specific PGE subtype named “generalized tonic-clonic seizures upon awakening”.³⁷ The classic and best known PGE, juvenile myoclonic epilepsy, is characterized by morning myoclonus and generalized tonic-clonic seizures after awakening.³⁸ These findings overall

suggest that the presence of orexinergic activity in wakefulness, SWS, and state transitions, which are characterized by a relatively greater degree of cortical synchronization than REM sleep, is overall less protective against IEDs and seizures (Fig. 1). However, even though wakefulness is relatively more synchronized than REM sleep, it remains the second most protective state against seizures because the cortex is still mildly desynchronized during this state.

While diffuse cortical desynchronization in REM sleep usually prevents epileptiform activity from organizing due to destructive interference, random constructive interference may lead to paradoxical synchronization. For example, there is a unique synchronized focal theta rhythm in the hippocampus that is associated with focal seizures during REM sleep onset in a murine TLE model.³⁵ In contrast, infusing carbachol (a synthetic long-acting muscarinic cholinergic receptor full agonist) into the pontine reticular formation forces REM sleep onset and hippocampal theta rhythm, which abruptly aborts seizures in a pentylenetetrazol model of generalized epilepsy in the rat.³⁹⁻⁴⁰ In humans, IED firing rates are overall lowest in REM sleep but these rates are subject to individual variability. In a systematic review, 11% of patients with focal epilepsy experienced the highest rate of IED firing in REM sleep (Fig. 2).²⁵ However, no patients in a systematic review of generalized epilepsy experienced the highest rate of IED firing in REM sleep (Fig. 2).²⁵ These findings suggest that paradoxical focal cortical synchronization in REM sleep activates appropriately situated focal epileptiform activity in both animals and humans but generalized epileptiform activity remains resistant to the effects of paradoxical focal synchronization.

4. Orexinergic Manipulation

The effects of experimental orexinergic modulation generally mirror physiologic state-dependent orexinergic effects on seizure threshold via effects on cortical synchronization. Direct orexinergic agonism mirrors phasic orexin bursts during state transitions when seizure propensity is high. In a murine penicillin epilepsy model, direct application of orexin to cerebral cortex exacerbates seizures.⁴¹ On the cellular level, intraventricular orexin lead to excitatory changes in hippocampal CA1 pyramidal neurons.⁴²⁻⁴³ In contrast, orexinergic antagonism mirrors orexin neuronal silence in REM sleep when seizure propensity is low. In humans, supraphysiologic doses of a clinical dual orexin receptor antagonist (suvorexant) increased REM sleep duration in addition to increasing total sleep time, NREM sleep duration, and sleep efficiency.⁴⁴ In murine pentylenetetrazol models, intrahippocampal and intraventricular injections of a single orexin receptor antagonist reduce seizure severity and duration.⁴⁵⁻⁴⁶ On the cellular level, injection of intrahippocampal orexin receptor antagonist in mice decrease regional glutamate.⁴⁵ In *Kcna1* knockout mice, the dual orexin receptor antagonist almorexant shortens REM sleep latency, which correlates with decreased seizures.⁴⁷ These studies are overall consistent with a proconvulsant effect of experimental orexinergic agonism which mirrors physiologic phasic orexin bursts during state transitions when seizure propensity is high, and an anticonvulsant effect of experimental orexinergic antagonism which mirrors physiologic orexin neuronal silence in REM sleep when seizure propensity is low (Fig. 1).

However, many studies on orexin and epilepsy do not measure sleep and it is possible that REM sleep-independent influences, such as sleep fragmentation and sleep deprivation, may account

for study findings instead. For example, injections of a ventricular orexin receptor antagonist in mice partially reverse dentate gyrus cellular proliferation and hippocampal CA3 neuronal injury secondary to sleep deprivation.⁴⁶ While consistent with the presumed orexi-cortical axis, one is unfortunately forced to assume that the quantity and quality of sleep is the same through the entire study in order for these data to be valid. Another example is almorexant, which increased NREM sleep quantity in *Kcna1* knockout mice (a generalized epilepsy model), but this finding did not correlate with seizure burden even though strong diffuse thalamocortical synchronization in SWS lowers seizure threshold.⁴⁷ One possible explanation is that stages N1 and N2 sleep were promoted more than, or instead of, SWS (stage N3 sleep), which is a much more synchronized state; however, data directly correlating seizures with state and cortical synchrony were not available to confirm or refute this possibility. Similarly, a recent human case series of type I narcolepsy, marked by orexinergic neuronal loss and frequent lapses into REM sleep, found a greater than chance association with juvenile myoclonic epilepsy (a PGE syndrome).⁴⁸ Although this observation agrees with frequent state transitions marked by diffuse cortical hypersynchrony exacerbating seizures, one may have also expected seizure reduction due to more REM sleep bouts with cortical desynchronization impairing seizure formation. Although paradoxical REM sleep synchronization may have activated seizures, generalized epileptiform activity should remain resistant to the effects of paradoxical focal synchronization. Without data correlating seizures with state and cortical synchrony, clarifying these findings to yield potentially novel insights into the orexinergic influence on seizures and epilepsy is not possible.

5. Future Directions

To refine our understanding of orexinergic effects on seizures and epilepsy, future studies should routinely incorporate EEG and hypnography to measure sleep. As it stands, there is already a need for more studies in animals and humans to rigorously assess the relationship between seizures and orexin receptor antagonists, some of which are already in clinical use. Further animal and human studies are also needed to verify the clinical association between narcolepsy, PGE, and other epilepsy types. There is also a need for orexinergic studies in a variety of epilepsy types as different epilepsies likely have different vulnerabilities to orexinergic influence. More basic science is needed to examine the impact of single and double orexin receptor agonists and antagonists on fundamental mechanisms of epileptogenesis at the cellular and network levels, including further basic science into the extent to which fundamental metabotropic cholinergic mechanisms in REM sleep may be altered in epilepsy. These studies can clarify whether observed effects on seizure threshold are reproducible and transcend the species barrier. Incorporating EEG and hypnography into future research can immediately translate these purely observational studies into mechanistic studies by simultaneously correlating seizures with data on cortical synchrony and the states from which seizures emerge. These data can repeatedly test the orexi-cortical axis hypothesis that orexinergic antagonism induces REM sleep to usually yield diffuse cortical desynchronization and increase seizure threshold (Fig. 1). These data can also clarify the theoretical proconvulsant risks of orexinergic antagonism, which include inadvertent NREM sleep promotion through partial incomplete antagonism, increased sleep instability through non-sustained antagonism, and paradoxical constructive interference in REM sleep. Lastly, these data may also potentially demonstrate

novel orexinergic effects on seizure propensity independent of the orexi-cortical axis through mechanisms of action yet to be discovered; for example, the role of REM sleep-independent influences, such as sleep fragmentation and sleep deprivation.

Even if EEG and hypnography are fully incorporated into all future research, however, state transitions still deserve further attention. Most studies are insensitive to transitions by summing all bouts of a sleep-wake state, irrespective of proximity to onset or offset, to yield an overall propensity for that state over the course of a night.²⁵ These studies score sleep by visual inspection (clinical gold standard) to assign a single stage to a 10 or 30 second EEG epoch (depending on whether the laboratory has a respective epilepsy or sleep emphasis). However, more recent murine studies use spectrography and power ratios to score at a finer resolution of 1 second which, while sensitive to ambiguous intermediate states, are not in official American Academy of Sleep Medicine guidelines.³⁴⁻³⁵ Nevertheless, guidelines are dynamic; for example, previously NREM sleep stages 3 and 4 are now merged into the single state N3. Future guideline revisions may want to focus on state transitions, epoch duration, spectrography, and applicability to commonly shared animal models in sleep and epilepsy research. While more studies are needed on seizure propensity during state transitions, the ultimate success of these studies depends on crisper scoring guidelines that are universally adopted among the clinical and basic science sleep and epilepsy communities.

6. Conclusions

Through unique firing characteristics, the subcortical peptide orexin exerts exquisite control over wakefulness, NREM sleep, REM sleep, and state transitions with profound consequences on cortical synchrony and the subsequent ability of aberrant epileptiform activity to organize into seizures. This orexi-cortical axis has recently been manipulated to therapeutic advantage through orexin receptor antagonism by presumably inducing REM sleep and diffuse cortical desynchronization. However, theoretical proconvulsant risks include inadvertent NREM sleep promotion, increased sleep instability, and paradoxical constructive interference in REM sleep. Future research should routinely incorporate EEG and hypnography to focus on cortical synchrony and the state from which seizures emerge is needed, as REM sleep is likely not the whole story behind the interaction between orexin and epilepsy. Increased understanding of the orexinergic effects on seizures and epilepsy holds the exciting promise of a novel antiepileptic mechanism of action that may one day be translated into clinical practice.

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Figure 1

Hypothesized mechanisms of the “orexi-cortical” axis. Originating in the hypothalamus, orexinergic neuronal firing characteristics determine sleep-wake state to modulate the degree of cortical synchronization with resultant effects on seizure threshold.

Figure 2

Sleep-wake state-dependent effects on human epilepsy. (A) IED (interictal epileptiform discharge) firing and seizure rates in wakefulness and SWS (slow wave sleep) relative to REM (rapid eye movement sleep). (B) Percentage of patients by sleep-wake state in which they experience the highest rate of IED firing (“peak discharge state”).

Figure 1

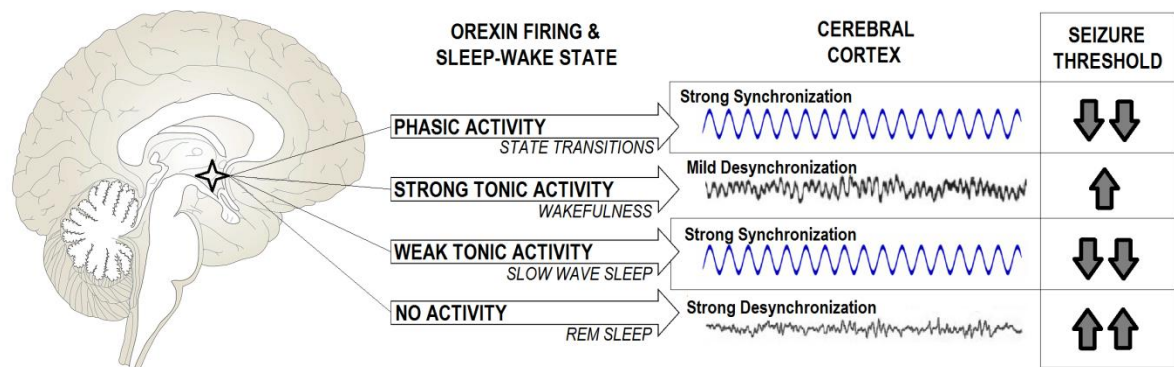


Figure 2

