HOSTED BY

ELSEVIER

Available online at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/ssci

Sleep Science named series: Pedunculopontine nucleus physiology – Review Article

Pedunculopontine arousal system physiology – Implications for insomnia

Edgar Garcia-Rill[a,*], *Brennon Luster*[a], *Susan Mahaffey*[a], *Veronica Bisagno*[b], *Francisco J. Urbano*[b]

[a]*Center for Translational Neuroscience, University of Arkansas for Medical Sciences, Little Rock, AR, USA*
[b]*IFIBYNE-CONICET and ININFA-CONICET, University of Buenos Aires, Argentina*

ARTICLE INFO

Article history:
Received 22 May 2015
Received in revised form
8 June 2015
Accepted 12 June 2015
Available online 10 July 2015

Keywords:
Calcium channels
Gamma band activity
Neuronal calcium sensor protein
N-type calcium channel
P/Q-type calcium channel

ABSTRACT

We consider insomnia a disorder of waking rather than a disorder of sleep. This review examines the role of the reticular activating system, especially the pedunculopontine nucleus, in the symptoms of insomnia, mainly representing an overactive waking drive. We determined that high frequency activity during waking and REM sleep is controlled by two different intracellular pathways and channel types in PPN cells. We found three different PPN cell types that have one or both channels and may be active during waking only, REM sleep only, or both. These discoveries point to a specific mechanism and novel therapeutic avenues for insomnia.

1. Insomnia – symptoms, etiology, and manifestations

We consider that although insomnia is called a "sleep disorder", it is actually a "waking disorder", in which the waking system is overactive, intruding excessively into sleep time. Perhaps in treating insomnia, we should not be trying to increase sleep but rather to decrease arousal. Insomnia is termed "primary" if it is not related to some other medical or psychiatric condition [1]. The American Academy of Sleep Medicine defines insomnia as a persistent difficulty with sleep initiation, duration, consolidation, or quality that occurs despite adequate opportunity and circumstances for sleep, and results in some form of daytime impairment [1].

Abbreviations: CaMKII, calcium/calmodulin-dependent protein kinase; cAMP, cyclic adenosine monophosphate; EEG, electroencephalogram; KA, kainic acid; NCS-1, neuronal calcium sensor protein 1; NMDA, n methyl d aspartic acid; ω-Aga, ω-agatoxin-IVA; ω-CgTx, ω-conotoxin-GVIA; PGO, ponto-geniculo-occipital; PPN, pedunculopontine nucleus; RAS, reticular activating system; REM, rapid eye movement; SWS, slow wave sleep

*Correspondence to: Director, Center for Translational Neuroscience, Department of Neurobiology and Developmental Sciences, University of Arkansas for Medical Sciences, Slot 847, 4301 West Markham St., Little Rock, AR 72205 USA. Tel.: +1 501 686 5167; fax: +1 501 526 7928.
E-mail address: GarciaRillEdgar@uams.edu (E. Garcia-Rill).

Peer review under responsibility of Brazilian Association of Sleep.

http://dx.doi.org/10.1016/j.slsci.2015.06.002

However, insomnia is a hallmark of a number of psychiatric disorders such as schizophrenia, bipolar disorder, and major depression, in which insomnia is termed "secondary". Insomnia is also present in a number of neurological diseases such as Alzheimer's disease and Parkinson's disease [1,2]. Insomnia includes difficulty falling asleep (prolonged sleep latency), frequent awakenings (difficulty maintaining sleep), and shortened sleep duration (resulting in daytime sleepiness, irritability and fatigue), all of which leads to impairments in daytime functioning [1]. Almost any condition that affects arousal and vigilance can induce insomnia [2].

Aside from comorbid neurological and psychiatric disorders, risk factors generally include exposure to continued stress. About half of the population experiences insomnia at least half the nights, and about 5% meet clinical criteria. This makes insomnia fairly common in modern society, and, unfortunately, sleeping less than 4 h per night does increase mortality [3]. There may be a genetic component since over one half of patients diagnosed with primary insomnia reported familial insomnia [4]. A number of imaging studies suggest decreased frontal lobe function and/or hypofrontality are present in insomnia [5,6].

The electroencephalographic (EEG) characteristics of patients with insomnia do not show major differences compared to good sleepers, with some studies reporting an increase in low beta and decrease in high beta frequency power [7], as well as decreases in REM sleep [8]. In general, the differences in the EEG are subtle but do suggest intrusion of higher frequency activity during low frequency states, such as the incidence of higher beta activity during slow wave sleep [9–11]. Experts in the field agree that primary insomnia patients not only show hyperarousal at night, but also during the day, manifesting in part as the inability to nap despite sleep deprivation symptoms [4,5]. This particular spectrum suggests that there is high frequency activity during slow wave sleep as well as decreased REM sleep, and the hyperarousal persists during waking. This is why we consider insomnia a "waking disorder", one in which the mechanisms specifically driving waking are exaggerated [2].

Treatments for insomnia are palliative and include benzodiazepines and non-benzodiazepine hypnotics to increase sleep, but the risk of physical dependence is high when used chronically [1]. However, from the foregoing discussion, it appears that insomnia does tend to manifest specifically with symptoms of excessive waking drive, rather than changes in REM sleep drive.

2. Hyperarousal and the reticular activating system (RAS)

Given the information outlined above, what aspects of RAS function will be involved in insomnia? There are five major factors that apply to disorders involving the RAS. (1) We know that the RAS participates in fight-*vs*-flight responses; therefore, we would expect that responses to sudden alerting stimuli will be abnormal. For disorders in which the RAS is overactive, this would mean that such stimuli will produce exaggerated responses that would be manifested as exaggerated startle responses or hyperactive reflexes, such as the blink reflex. Few such studies have been performed in patients with insomnia, so we lack critical information about the condition. (2) Another property of the RAS is its rapid habituation to repetitive stimuli. This is reflected in its lack of responsiveness to rapidly repeating stimuli, that is, its rapid habituation. This endows the RAS with its capacity for sensory gating, the property of decreasing responsiveness of repetitive events in favor of novel or different stimuli. For disorders in which this property is affected, we expect a decrease in habituation or a sensory gating deficit. Again, little information on this mechanism is available for insomnia. (3) The RAS controls waking and sleep, so that sleep patterns would be dysregulated. If the RAS is down regulated by a disorder, we expect an inability to remain awake, the presence of excessive daytime sleepiness, and an excess of total sleep time, especially a decrease in slow wave sleep. If, on the other hand, the RAS is up regulated, we expect difficulty in getting to sleep and maintaining sleep. This would be reflected in insomnia or disrupted sleep during the night, and perhaps increased REM sleep drive, which is characterized by vivid nightmares and frequent awakenings. Such a condition would lead to increased REM sleep drive during sleep (resulting in intense dreaming), but perhaps also during waking. That is, resulting in dreaming while awake or hallucinations, along with hypervigilance. Patients with insomnia do not appear to suffer from increased REM sleep drive or hallucinations. Therefore, we assume that the dysregulation in insomnia represents increased waking drive, instead. (4) The RAS also modulates the maintenance of waking, a property ignored by many investigators but one that affects a host of functions. The inability to maintain a steady waking state, in the form of maintained gamma band activity, will interfere with attention, learning, and memory, to name a few processes. The EEG studies mentioned above do suggest excessive high frequency activity in insomnia, further emphasizing that the disorder is one more related to the waking state.

(5) Another factor in all of these disorders is the level of frontal lobe blood flow. Decreased frontal lobe blood flow, or hypofrontality, is present in a number of disorders, *e.g.* insomnia, schizophrenia, bipolar disorder, to some extent. Such a state during waking would lead to reflexive reactions with lack of consideration of consequences. This condition is probably involved in a lack of habituation to repetitive stimuli, or a sensory gating deficit. Under the condition of decreased cortical modulation, fight-*vs*-flight responses and reflexes would be exaggerated. Whether hypofrontality is a cause of RAS dysregulation or RAS dysregulation leads to hypofrontality remains to be determined. Decreased frontal lobe function does appear to be present in insomnia, as described above [5,6]. Moreover, successful treatment of the condition should be marked by normalization of frontal lobe blood flow.

3. Pedunculopontine nucleus (PPN) physiology and high frequency activity

The two most important advances on the physiology of the RAS in the last 10 years were, (a) the discovery of electrical coupling in some cells of certain RAS nuclei [12], and (b) the finding that every cell in the same RAS nuclei manifests intrinsic membrane beta/gamma oscillations [13]. These are