Neurobiological Mechanisms in Chronic Insomnia

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KEYWORDS

• Insomnia • Neurobiology • VLPO • ARAS • Homeostasis • Inhibition of wakefulness

KEY POINTS

- This article states that insomnia can or should be defined in physiologic terms; insomnia is better understood from a neurobiological perspective.
- A review of the neurobiology of sleep and wakefulness is provided with a special emphasis on the implications for insomnia.
- A complete understanding of insomnia requires the neurobiological characterization of insomnia be informed by modern cognitive concepts and methods.

INTRODUCTION

Insomnia has long been conceptualized in psychologic and physiologic terms[1]; hence, the primary diagnostic classification of "psychophysiologic" insomnia. This diagnostic category[2] was adopted to indicate that this form of sleep disturbance was primary (a disorder vs. a symptom) and determined by both psychologic and physiologic factors. Psychological factors were thought to be related to cognitive phenomena, such as worry and rumination, and behavioral processes, such as instrumental and classical conditioning. Physiologic factors were thought to be related to elevated heart rate, respiration rate, muscle tone, and so on (ie, elevated end organ tone and/or increased metabolic rate). The term psychophysiologic insomnia (as opposed to the alternative construction physiopsychological insomnia) implies that this form of insomnia occurs primarily as a physiologic phenomenon. This conceptualization not only questions the primacy of cognition[3] in insomnia but also leads one to wonder whether somatic hyperarousal (or elevated metabolic rate) is appropriately identified as the primary cause. The emphasis on physiology seems to be a historical precedent than the likely possibility that somatic arousal is sufficiently elevated in patients with chronic insomnia to directly interfere with sleep initiation and maintenance.

The alternative perspective is, if "sleep is of the brain, by the brain, and for the brain,"[4] that insomnia is better conceptualized in terms of abnormal neurobiology. This perspective is supported by the information provided regarding (1) the brain structures that are implicated in sleep-wake regulation and how abnormal function within these areas may lead to specific insomnia complaints and (2) the neurophysiologic control of sleep and wakefulness and how dysregulation at the system level may contribute to the incidence and severity of insomnia. Following this review, information is provided regarding insomnia in terms of neurobiological abnormalities as assessed with

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neurophysiological, neuroendocrine, and neuroimaging measures. This overview concludes with a comment on the dual nature of psychophysiologic insomnia.

STRUCTURES IMPLICATED IN SLEEP-WAKE REGULATION AND DYSREGULATION

Although this article does not review every brain structure that is thought to play a role in sleep-wake regulation, a short review illustrates the role of functional neurobiology in understanding the clinical entity of insomnia. Information regarding the role of the following brain regions is provided: the pons, the thalamus, the frontal cortex, and the basal ganglia.

Pons

The pons is located in the brain stem and contains nuclei that are related to the coordination of eye and facial movements, facial sensation, hearing, balance, respiration, and the genesis of REM sleep. Because pons is mostly dedicated to the performance of nonautonomic functions, the behavioral quiescence of NREM sleep is paralleled by the global deactivation within this region. An equally important consideration is the extent to which the aminergic and cholinergic components of the ascending reticular activating system (ARAS) (see below) reside within, or traverse through, the pons. The most straightforward consequence of hyperarousal in the pons on NREM sleep would be a direct link to the inability to initiate and maintain sleep. At the level of patient report, this condition would translate as the complaint of feeling alert while desiring to fall asleep.

Thalamus

The thalamus contains a variety of nuclei that are believed to process and relay sensory information to various parts of the cerebral cortex. For example, visual information from the eyes travels to the thalamus on the way to the occipital cortex. The thalamus also contains structures (the reticular nuclei) that actively inhibit sensory flow from the thalamus to the cortex. Increased thalamic activation in the nuclei related to sensory processing and/or decreased activity within the reticular nuclei during sleep could lead to more sensory information reaching the cortex and thus greater sensory processing perisleep onset or during sleep. Presumably, this mechanism would be related to the tendency of patients with insomnia to be hyper-responsive to environmental stimuli, which may account for patients' difficulties falling and staying asleep and/or the perception of shallow sleep. This mechanism might be the neurobiological basis of patients' reports of being light sleepers.

Frontal Cortex

The frontal lobes contain many subregions involved in cognitive processes related to, among other things, working memory, problem solving, the planning of goal-directed activity, and evaluative judgment.[5] Thus, abnormal activity in the frontal cortex will depend on the specific subregion involved and whether the area or circuit is inhibitory or excitatory. An example of excitatory subregions would be the dorsolateral prefrontal and left limbic areas. Activation within these areas is associated with anticipatory anxiety.[6] In insomnia, increased activation within this region is associated with the worry and rumination that may interfere with sleep initiation and possibly sleep maintenance. An example of inhibitory subregions would be the orbital frontal cortex and the cortical-striatal-thalamic-cortical loops.[7] Reduced activation in this region/circuit is associated with behavioral, and likely, cognitive disinhibition of subcortical structures. In this instance, hypoactivation may be associated with the tendency of patients with insomnia to be highly ruminative and their complaint of being unable to turn their minds off.[8–10]

Basal Ganglia

The primary structures of the basal ganglia (caudate, putamen, globus pallidus, substantia nigra, and subthalamic nucleus) and the striatum have major projections from the motor cortex and are known to play a well-defined role in the execution of voluntary movement. In addition, the basal ganglia has been (1) implicated in neurobiological models of obsessive compulsive disorder[11] and (2) found to play a role in the homeostatic regulation of sleep.

Regarding sleep homeostasis, Braun and colleagues[12] have hypothesized that the basal ganglia may be actively involved in the regulation of slow wave sleep because of their ability to modulate cortical arousal.[13] Structures within the basal ganglia may, in feed forward fashion, modulate the activity of the reticular nucleus of the thalamus and contribute to the homeostatic regulation of sleep.[14] The basal ganglia may not only be involved in the homeostatic regulation of sleep but also be the sleep homeostat itself because they are responsible for the execution of voluntary movement and potentially the modulation of cortical arousal. Thus, it is uniquely situated to modulate cortical arousal based on diurnal activity levels.

At the level of symptom complaint, abnormal metabolism within the basal ganglia during sleep may be associated with a variety of clinical phenomena. To the extent that the circuits are related to inhibition and disinhibition, abnormal activity within these regions may be associated with a patient's tendency to ruminate and worry. Alternatively, abnormal activity in the basal ganglia may be related to the homeostatic dysregulation that seems to occur with insomnia. To the extent that the basal ganglia are related to sleep homeostasis, it may account for the occurrence of sleep initiation and maintenance problems on a given night and for the cyclic pattern of symptoms across time.

NEUROPHYSIOLOGIC CONTROL OF SLEEP AND WAKEFULNESS

Based on the early work of Von Economo[15] and Moruzzi,[16–18] cortical arousal is regulated by the ARAS). This system originates in the brain stem with 2 major branches. One branch originates from cholinergic cell groups in the upper pons (including the pedunculopontine and the laterodorsal tegmental nuclei), inputs into the thalamus, and activates the thalamic relays that densely innervate the cortex. This system and its source neurons fire maximally during wakefulness and REM sleep and lowest during NREM sleep.[6,19–21] The other branch originates in the lower pons from a series of neurons, including the locus coeruleus (norepinephrine), dorsal and medial raphe (serotonin), and tuberomammillary cells (histamine) to innervate neurons in the lateral hypothalamic area, the basal forebrain, and throughout the cortex. The ascending aspect of this system is monoaminergic and the end target neurons are cholinergic or γ-aminobutyric acid (GABA) -mediated. Neurons within this system fire maximally during wakefulness, more slowly during NREM sleep, and are relatively silent during REM sleep. This description of cortical arousal as it is modulated by the cholinergic and monoaminergic systems was, in 2000, significantly amended with the discovery of orexin (also called hypocretin).[22–25] This neurotransmitter seems to augment activity within the monoaminergic branch of the ARAS (particularly the output from the lateral hypothalamus) and is thought to act in concert with the circadian system to promote the consolidation of wakefulness during the diurnal phase of the 24-hour day. **Fig. 1** provides a schematic representation of the aforementioned arousal systems.

Although the above description serves to delineate the pathways within the ARAS and their relative degree of activation across the wake, NREM, and REM states, the characterization does not suggest how sleep is initiated, maintained, and terminated in favor of new episodes of wakefulness. To comprehend this mechanism, it is necessary to posit that there is either a gating system or

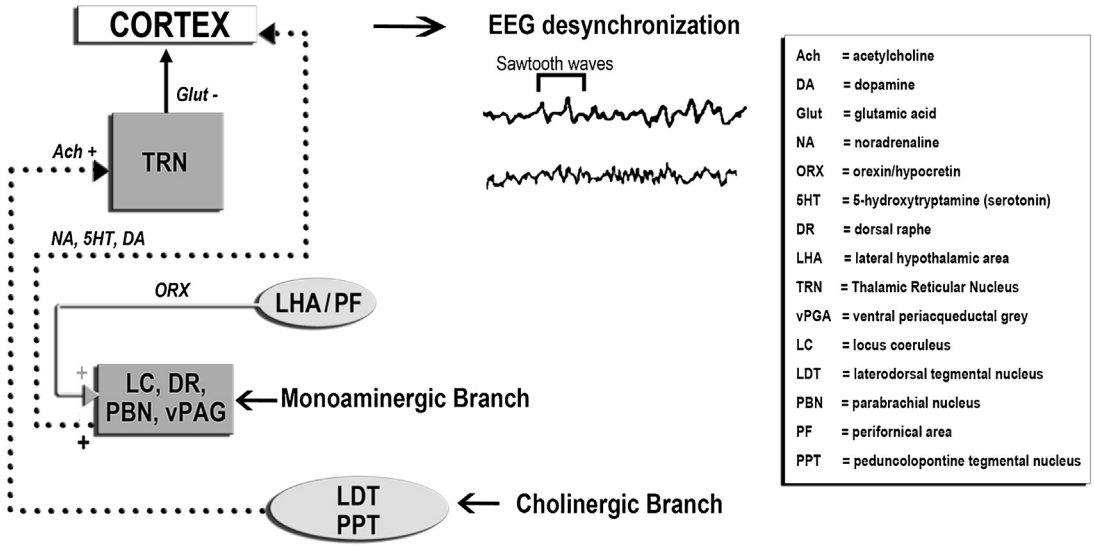

Fig. 1. Ascending pathways that lead to cortical desynchronization (activation). Although the cholinergic and monoaminergic branches of this system have been well characterized, orexinergic component (and its contribution to the consolidation of wakefulness) is relatively new. One of the many important aspects of this system is that this arousal system is not the same as the ARAS (the Ascending Reticular Activation System [the fight or flight system]) anatomically of functionally. With respect to the latter, the orexin system appears to be under the control of, or intimately related to, the circadian system.

a related descending system that influences the structures that initiate cortical arousal. In the cholinergic branch of the ARAS, there is substantial evidence to suggest that the reticular nucleus of the thalamus serves to block ascending inputs and thereby permit cortical synchronization (ie, sleep). In the monoaminergic branch of the ARAS, investigators during the 1980s and 1990s found a mechanism that might serve as the switch for a descending de-arousal system; the switch being the ventrolateral preoptic area (VLPO).[6,21] The VLPO is maximally active during sleep; has major *outputs* to most, if not all, the hypothalamic and brain stem components of the monoaminergic branch of the ARAS; and contains inhibitory neurotransmitters (ie, galanin and GABA). Thus, the VLPO seems to be uniquely positioned to function as an "off switch" (to inhibit arousal). This putative function was confirmed by Saper and colleagues,[6,21] who have shown that lesions within this region reduce NREM and REM sleep by more than 50%.

Saper and colleagues[6,21] have also demonstrated that the VLPO also has major *inputs* from the hypothalamic and brain stem components of the monoaminergic branch of the ARAS and that the VLPO is strongly inhibited by noradrenaline and serotonin. The existence of such inputs and neurotransmitter effects suggests that the VLPO not only inhibits wakefulness but also inhibited by wakefulness. Saper and colleagues[6,21] compared this reciprocal relationship between the VLPO and the ARAS with the functioning of a "flip flop circuit." This analogy is taken from electrical engineering and provides a framework for conceptualizing how the wake-promoting and sleep-promoting halves of the circuit are mutually influential. Each half of the circuit strongly inhibits the other and creates a bistable feedback loop. When the brain is in a state of wakefulness, sleep is inhibited so that there is a consolidated period of wakefulness. When the switch moves in the sleep direction, wake is inhibited, producing a consolidated period of sleep. This pattern prevents frequent transitions between sleep and wake and the presence of intermediate states characterized by features of both wakefulness and sleep. **Fig. 2** represents the VLPO's inhibitory influence on the cortex and its "bi-stable" configuration.

Although elegant, this conceptualization also does not explain how sleep is initiated and terminated (ie, it only serves to explain how sleep and wakefulness tend to occur in a consolidated fashion). To initiate and terminate sleep, there must also be a system that impinges on the circuit and allows for homeostasis and allostasis.

In the case of sleep/wake homeostasis, there must be a process that represents the accumulation of wakefulness and/or sleep that can act to "trip the switch." The concept of sleep/wake homeostasis

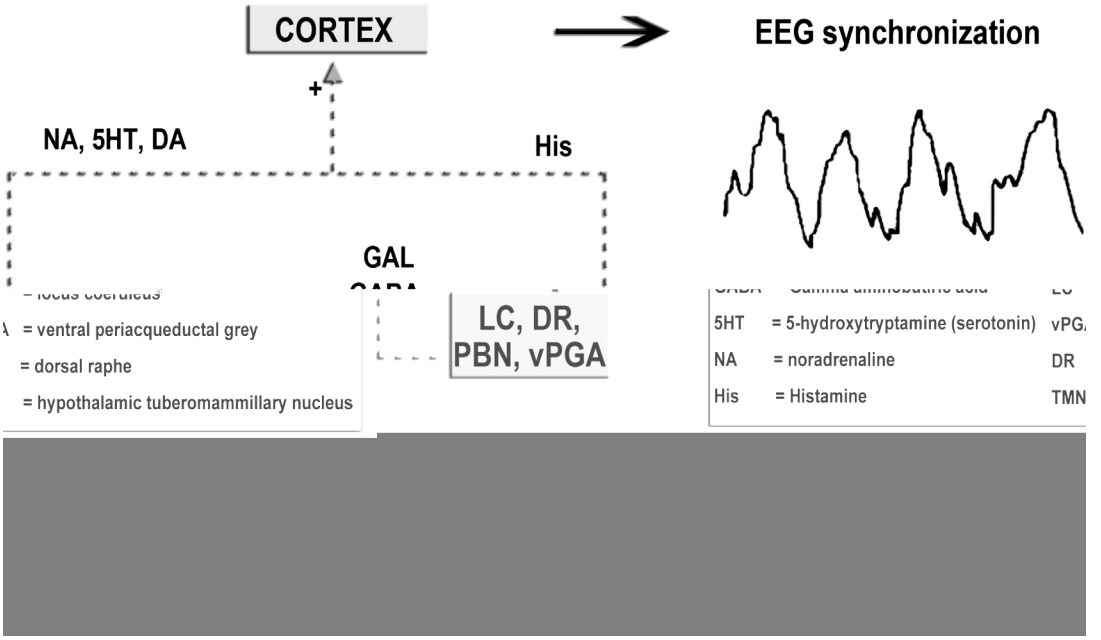

Fig. 2. This figure provides a simplified representation of the "Sleep Switch," ie, the circuit and ascending pathways that lead to cortical synchronization (deactivation). One of the many important aspects of this system is the mutually inhibitory functioning between the VLPA and the TMN. For a thorough review of this system the reader is referred to Saper and colleagues.[21]

(and its interaction with the circadian system) has been described theoretically and tested empirically by Borbely and colleagues.[26–29] In this model, the accumulation of wakefulness is represented by "Process S" and is measured in terms of the relationship between the duration of wakefulness and the discharge of slow wave activity during NREM sleep. To date, the neurobiological structures that comprise the sleep homeostat are unknown. The accumulation of adenosine within the basal forebrain may represent the duration of wakefulness. Experimental work with this hypothesis has shown that (1) adenosine levels increase in proportion to the duration of wakefulness and (2) when injected into the basal forebrain, adenosine induces sleep and promotes activity within the VLPO.

In the case of sleep/wake allostasis, it has been proposed that orexin neurons within the posterior half of lateral hypothalamus serve to reinforce wakefulness (promote sustained wakefulness) and thereby act as a "finger" on the flip-flop switch that prevents unwanted transitions into sleep[1].

NEUROBIOLOGICAL IMPLICATIONS FOR INSOMNIA

The above description of the normal regulation of sleep and wakefulness suggests that insomnia may occur in association with one of several neurobiological abnormalities. First, the switch itself may be malfunctioning. Saper and colleagues[6] describe this as follows

> *…mathematical models show that when either side of a flip-flop neural circuit is weakened, homeostatic forces cause the switch to ride closer to its transition point during both states. As a result, there is an increase in transitions, both during the wake and the sleep periods, regardless of which side is weakened. This is certainly seen in animals with VLPO lesions, which fall asleep about twice as often as normal animals, wake up much more often during their sleep cycle and, on the whole, only sleep for about one-quarter as long per bout - in other words, they wake up and are unable to fall back asleep during the sleep cycle, but also are chronically tired, falling asleep briefly and fitfully during the wake cycle….*[6]

This description seems to characterize, not so much psychophysiologic insomnia, sleep as it occurs in neonates/infants and insomnia as it occurs in the elderly (ie, polyphasic sleep with middle and/or late insomnia), and/or in patients with narcolepsy. A malfunctioning switch could also produce an intermediate state characterized by aspects of both sleep and wakefulness. This malfunctioning can be seen in several studies of individuals with insomnia who, compared with good sleepers, show evidence of wakefulness in terms of increased beta electroencephalogram (EEG) activity while otherwise appearing to be asleep.

Chronic activation of the monoaminergic branch of the ARAS might lead to some form of desensitization and/or a compensatory down-regulation, which results in insufficient "force" to trip the switch and a switch that tends to favor the "wake on" position (ie, there is a failure to inhibit wakefulness and/or substantially more wakefulness is required to flip the switch to the sleep position.) In this instance, a decreased activation within the nuclei that input to the VLPO (eg, locus coeruleus, the dorsal and/or medial raphe, and/or the tuberomammillary cells) is expected. From a neuroendocrine point of view, however, continued evidence of hyperarousal in parallel with the neurobiological down-regulation is expected, that is, patients with chronic insomnia would exhibit hypercortisolemia, and/or excessive secretion of the monoamines and/or even hypocretin/orexin, despite diminished activity of the central nervous system . Evidence for some of these possibilities, which are presaged by the Psychobiological Inhibition Model,[30] are reviewed in the sections entitled Neuroendocrine Measures of Insomnia and Neuroimaging Measures of Insomnia.

The neurobiological abnormalities that occur with insomnia may occur within the cholinergic branch of the ARAS and appear as altered functioning within the thalamus, basal forebrain, and cortex. For example, one might expect

1. A reduction in activity during wakefulness within the adenosinergic regions of the basal forebrain
2. An overall decrease in cortical arousal during wakefulness
3. An increase in activity during the sleep period within the thalamic nuclei related to sensory processing and reduced activity within the sensory gating nuclei (ie, the reticular nucleus)
4. An overall increase in cortical arousal during sleep.

Alterations within this system may be relevant to sleep, not only for continued disturbance but also

[1] A second possible, albeit highly speculative, candidate mechanism for sleep wake homeostasis is noted in the above discussion regarding the Basal Ganglia.

the phenomenon of sleep state misperception as it is known to occur in psychophysiologic insomnia and paradoxical insomnia, and perhaps in all forms of primary insomnia (PI). The evidence for these possibilities, which are presaged by the Neurocognitive Model,[31] are also reviewed in the sections entitled Neurophysiologic Measures of Insomnia, neuroendocrine Measures of Insomnia, and Neuroimaging Measures of Insomnia.

EVIDENCE FOR NEUROBIOLOGICAL ABNORMALITIES IN INSOMNIA

Neurophysiologic Measures of Insomnia

To date, several studies have shown that patients with PI exhibit more cortical arousal than either good sleepers or patients with insomnia comorbid with major depression.[32–38] These studies show that patients with PI exhibit more high-frequency EEG activity (beta and gamma frequencies) at sleep onset and during NREM sleep. These EEG frequencies are associated with the active processing of mental information during wakefulness, suggesting that patients with insomnia have a failure to terminate mental processing while otherwise asleep. There is also evidence that (1) patients with sleep state misperception (ie, paradoxical insomnia) exhibit more beta EEG activity than good sleepers or patients with PI[38] and (2) beta EEG activity is negatively associated with the perception of sleep quality[39,40] and positively associated with the degree of subjective-objective discrepancy.[37] These data suggest that cortical arousal may occur uniquely in association with PI (ie, one or more of the types of PI, including psychophysiologic insomnia, paradoxical insomnia, idiopathic insomnia, etc.) and may be associated with the tendency toward sleep state misperception.

Comment

Although the data acquired from this measurement strategy strongly support cortical arousal as a biomarker for insomnia (and this is theoretically appealing to the extent that the increased occurrence of beta and gamma activity is thought to be permissive of increased sensory and information processing), the lack of replication across larger scale contemporary investigations[41] and unpublished studies (Buysse D, personal communication, 2005; Perlis M, unpublished work, 2005) suggests that this approach has some limitations. According to the authors, the occurrence of beta and gamma activity varies not only with trait considerations (diagnostic category) but also appears to be mediated/moderated by a variety of factors including first night effects,[42] prior sleep debt, degree of circadian dysrhythmia, type of insomnia, technical considerations, and the extent of environmental noise. There is also recent evidence that beta and gamma activity varies by sex.[43]

Neuroendocrine Measures of Insomnia

Several studies have begun to examine the activation of stress response system in patients with insomnia, focusing on the hypothalamic-pituitary-adrenal (HPA) axis. These studies provide evidence that insomnia involves, or results from, chronic activation of the stress response system. Other neuroendocrine measures, including norepinephrine, melatonin, and, most recently, GABA have also been examined as potential correlates of insomnia.

Urinary measures

An early study of urinary free 11-hydroxycorticosteriods (11-OHCS), which are metabolites of HPA axis activity, in young adult good and poor sleepers found that the mean 24-hour rate of 11-OHCS excretion over 3 days was significantly higher in the poor sleepers.[44] A subsequent study of urinary cortisol and epinephrine in middle-aged good and poor sleepers found no significant differences although poor sleepers showed higher urinary cortisol and epinephrine secretion.[45,46] More recently, Vgontzas and colleagues[45,46] collected 24-hour urine specimens for urinary free cortisol (UFC), catecholamine metabolites (3,4-dihydroxyphenylglycol [DHPG] and 3,4-dihydroxyphenylacetic acid [DOPAC]), and growth hormone and correlated these measures with polysomnographic measures of sleep continuity and sleep architecture in subjects with PI. UFC levels were positively correlated with total wake time, and DHPG and DOPAC measures were positively correlated with percent stage 1 sleep and wake after sleep onset time. Although not statistically significant, norepinephrine levels tended to correlate positively with Stage 1 and wake after sleep onset, and negatively with percentage of slow wave sleep. These data suggest that HPA axis and sympathetic nervous system activity are associated with objective sleep disturbance.

Plasma measures

Plasma measures of corticotropin (ACTH) and cortisol have also been compared among patients with PI and matched with good sleepers. In one study, patients with insomnia had significantly higher mean levels of ACTH and cortisol over the course of the 24-hour day, with the largest group differences observed in the evening and first half of the night.[45,46] Patients with a high degree of sleep disturbance (sleep efficiency <70%)

secreted higher amounts of cortisol than patients with less sleep disturbance. In contrast to these findings, a recent study of patients with PI and age and gender matched good sleepers found no differences in the mean amplitude or area under the curve for cortisol secretion over a 16-hour period (19:00 to 09:00 hours).[47]

Comment

Some of the variability of neuroendocrine findings in insomnia may be explained by the intrusion of wakefulness into the measured sleep period. This intrusion is a particular concern for studies using urinary measures, which integrate biological activity over a long period. This possibility is important when considering causality, that is, whether increased HPA activity leads to insomnia or whether insomnia leads to increased HPA activity. However, there is a certain degree of face validity in the association between insomnia and HPA axis activity given the presumed relationship between stress and insomnia. A recent study investigating a possible animal model of acute insomnia demonstrated that activity in the amygdala, a key brain region for activation of the stress response, is critically necessary for stress-induced insomnia to occur.[48,49] There is evidence that the VLPO contains receptors for the stress hormone ACTH-releasing factor, suggesting that stress may have direct effects on the sleep switch.[6] Although the findings from various studies are not entirely consistent, the elevations in ACTH and cortisol levels before and during sleep in insomnia patients may help to shed light on the intimate association between insomnia and major depression, which is also associated with HPA axis activation. Specifically, insomnia is a risk factor for,[11,50–57] a prodromal symptom of,[58] and a ubiquitous[59,60] and persistent symptom of major depression.[60] The common link may be that acute stress leads to both an activation of the HPA axis and insomnia, and that chronic insomnia in turn leads to a persistent activation of the HPA axis.

Neuroimaging Measures of Insomnia

To date 2 studies on brain activity, which evaluate sleep in patients with insomnia have been undertaken: 1 using technetium hexamethylpropyleneamine oxime single-photon emission computed tomography (Tc 99 HMPAO SPECT) and the other using positron emission tomography (PET) with fludeoxyglucose F 18. In the Tc 99 HMPAO SPECT study, imaging was conducted around the sleep onset interval in patients with PI and good sleepers. Contrary to expectation, patients with insomnia exhibited a consistent pattern of reduced activity across 8 preselected regions of interest, with the most prominent effect observed in the basal ganglia.[61] The frontal medial, occipital, and parietal cortices also showed significant decreases in blood flow compared with good sleepers. In the PET study, imaging data were acquired from patients with chronic insomnia and participants in the control group for an interval during wakefulness and during consolidated NREM sleep. Patients with insomnia exhibited increased global cerebral glucose metabolism during wakefulness and NREM sleep.[62] In addition, patients with insomnia exhibited smaller declines in relative glucose metabolism from wakefulness to sleep in wake-promoting regions, including the ARAS, hypothalamus, and thalamus. A smaller decrease was also observed in areas associated with cognition and emotion including the amygdala, hippocampus, insular cortex, and in the anterior cingulate and medial prefrontal cortices.

In addition to the brain activity studies, Winkelman and colleagues[63] used proton magnetic resonance spectroscopy to assess brain GABA levels in 16 patients with PI andcompared it with 16 good sleepers. GABA was measured in terms of global activity within the basal ganglia, thalamus, and the temporal, parietal, and occipital cortical areas. Average brain GABA levels were nearly 30% lower in patients with PI. Given that GABA is the primary inhibitor neurotransmitter in the brain, this finding suggests that there was less inhibition (ie, more activation) in the insomnia group. Further, GABA levels were negatively correlated with wake after sleep onset measures. This data suggest that (1) GABA deficiency may be a neurobiological characteristic of insomnia and (2) the efficacy of benzodiazepine hypnotics may reside in their potential to increase GABA secretion/activity within the brain.

Comment

Although results from the 2 studies on brain activity seem to be inconsistent, numerous methodological differences may help to explain differences in the findings. For example, the SPECT study with its short time resolution may have captured a more transient phenomenon that occurs when subjects with chronic and severe insomnia first achieve persistent sleep. The PET study with its longer time resolution may have captured a more stable phenomenon that occurs throughout NREM sleep in subjects with moderately chronic and severe insomnia. In addition to the temporal resolution issues, the PET study used a sample of insomnia patients who did not show objective sleep continuity disturbances in the laboratory, whereas the SPECT study included patients with objective sleep continuity

disturbances. Thus, the samples may have differed with respect to the type of insomnia, the degree of partial sleep deprivation, and the degree of sleep state misperception. Although further studies are needed, these preliminary investigations clearly demonstrate the feasibility of using functional neuroimaging methods in the study of insomnia, and suggest that insomnia complaints may indeed have a basis in altered brain activity. For additional information on how imaging may be informative regarding the neurobiology of insomnia, the reader is referred to an article by Drummond and colleagues.[64]

SUMMARY

Although it is provocative and intellectually challenging to claim, in essence, that insomnia is "of the brain and by the brain…",[4] the causes and consequences of insomnia are not likely to be so narrowly circumscribed.

First, if chronic insomnia occurs because of the abnormal functioning of specific brain regions or the sleep-wake systems, it is still likely that the changes in brain function are permissive of cognitive processes that independently contribute to problems with initiating and maintaining sleep (and/or perceiving sleep as sleep). For example, if the insomnia occurs in relation to altered thalamic activation, the consequent increase in sensory processing (via either increased sensory flow or reduced sensory inhibition) likely independently contributes to insomnia because the individual experiences an increased sensitivity to external stimuli.

Second, if it is demonstrated that insomnia is neurobiological condition, it is still likely to be true that insomnia frequency, severity, and/or chronicity are mediated/moderated by cognitive and behavioral factors. For example, one may not be awake during the preferred sleep phase because of, for example, worry or attention bias, but these factors are nevertheless likely to exacerbate the condition in ways that make it more serve, more frequent, and more chronic.

Third, irrespective of the mechanisms that cause insomnia, it is likely that the condition interferes with many, if not, all the putative functions of sleep. Thus, in the end, the causes of insomnia may be primarily related to the brain, but the effects of insomnia may span many domains including both the psychological (eg, mood, daytime fatigue and/or sleepiness, cognitive capacity from executive function to long term memory) and the physiologic domains (eg, immunity, the capacity to recover from traumatic injury, and even longevity in the absence of illness).

In the final analysis, insomnia may be precisely, as it has been classically defined: a psychophysiologic condition. Perhaps the only difference between the original concept and the current one is a matter of scope. Originally, it may have been the case that (1) psychological factors were construed only in terms of mental phenomena like worry and rumination and behavioral phenomena, such as sleep extension and poor stimulus control, and (2) physiologic factors were construed only in terms of metabolic rate. At present, psychological factors include sensory and information processing abnormalities and attentional bias, and physiologic factors include not only end organ function and tone but also the brain abnormalities that may directly cause the insomnia condition. Expanding existing frames of reference in this manner may allow us to abandon the mind-brain dichotomies and long-standing discipline-specific research agendas (eg, psychology vs neuroscience) that have long plagued mind-brain research and specifically insomnia research. Further, expanding existing frames of reference in this manner may lead us to a new approach to the problem of insomnia, one that is more integrative and synthetic.

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