REVIEW ARTICLE

Insight into the pathophysiology of insomnia

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Abstract

Insomnia is a major public health hazard. Complexity of insomnia patho-physiology is intriguing and is an exciting subject of inquiry. The current article summarizes the recent developments in our understanding of insomnia. Although the early models of insomnia were unidirectional, they provided foundation for development of more integrative models. Sleep- wake regulation and more specifically conceptual understanding of sleep homeostasis, circadian influence, and hyperarousal further added new dimensions to our understanding of insomnia. However, there is more appreciation than ever of the fact that a lot more work must be done before even thinking about finding a conclusive evidence of what causes insomnia and what maintains it. Some of the legendary work is cited in the reference section to develop an understanding of intricate interplay of multiple systems within the body that cause sleep and lack of it.

Introduction

Insomnia as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition, is a predominant complaint of dissatisfaction with sleep in terms of its quality or quantity that is associated with one or more symptoms, including difficulty initiating sleep and difficulty maintaining sleep, where a person experiences problems associated with an inability to return to sleep. Insomnia is a common disorder that has significant impairment of daytime function. It presents in many ways including delayed sleep onset, sleep maintenance, or early sleep offset. Although insomnia is an emerging disorder in children and adolescents, the risk is greatest in patients with mental and physical illnesses. In addition, there is a significant overlay of socioeconomic adverse situations that increase the risk of insomnia. Over the recent years, a simple unidirectional model has evolved into a bidirectional construct of multiple psychological, neurophysiologic, and genetic correlates.

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Conventional/early models for pathogenesis of insomnia

The early pathophysiologic models of insomnia included the classic behavior model of Spielman[1]. According to this model, insomnia may occur in predisposed individuals due to precipitating stressors and perpetuating factors such as maladaptive behaviors and cognitions. The predisposing, precipitating, and perpetuating factors can combine to trigger and maintain insomnia.

The *stimulus control model* of insomnia is based on the theory of conditioning. In this model, sleep is the response to the stimulus such as bed, bedroom, and sleep environment. The response may be sleep onset or other

activities such as watching television, eating, or doing office chores in bed. The stimulus–response strength weakens if there is more than one response. Non-sleep responses can be removed by stimulus control therapy, thereby improving insomnia[2].

The *cognitive model* of insomnia is related with negative thoughts and dysfunctional cognitions such as worry over sleep loss, rumination over consequences of lost sleep, and other unrealistic expectations[3]. Such activities provoke arousal and eventually lead to maladaptive sleep behaviors such as spending excessive time in bed, irregular sleep schedule, and daytime napping to compensate for their sleep loss.

These models of insomnia have served as the foundation for newer integrative models. Recent advances and conceptualization of neuroscience of sleep–wake regulation have significant impact on understanding the pathophysiology of insomnia. Recent studies were designed to apply multiple independent and combined interventions to patients with primary insomnia[4]. A Veterans Affairs medical center study compared the effects of single-component and multicomponent behavioral treatments for insomnia in 179 older adults with chronic primary insomnia. Participants were assigned stimulus control therapy, sleep restriction therapy, and a combination of both therapies. The results indicated that all three interventions were equally efficacious and produced sustained treatment gains. However, combined treatment showed higher remission rate. These studies have documented improvement in many sleep parameters but were unable to discriminate if any interventions were targeting underlying mechanisms of insomnia. Another similar study applied intensive sleep retraining and conditioning in patients with insomnia and documented improvement in sleep parameters supporting the role of conditioning in the maintenance of chronic insomnia[5]. This study compared effectiveness of intensive sleep retraining in comparison and combination with traditional behavioral interventions for chronic primary insomnia. Although all interventions significantly improved sleep, the 25-h intensive conditioning treatment for chronic insomnia produced rapid improvements in sleep.

Alternative/newer models for pathogenesis of insomnia

The development of insomnia seems to involve dysregulation of the sleep homeostasis, circadian processes, and hyperarousal. Chronobiologic abnormalities such as phase shifts cause clinical symptoms of insomnia. Various mechanisms including genetic predisposition, maladaptive behaviors, or altered core body temperature rhythms have been contemplated to be potential contributing factors.

The *hyperarousal theory* has been the focus of attention, and there is evidence of both physiologic and cognitive arousal[6–8]. Many studies in patients with insomnia have documented increased heart rate, hyperactivation of the hypothalamic–pituitary axis, and evidence of markers of sympathetic response. In addition, increased worrying, selective attention to sleep, and preoccupation with adverse consequences of poor sleep suggest cognitive arousal. There is electroencephalographic (EEG) evidence of increase in high-frequency EEG, cyclic alternating patterns, and unstable sleep in patients with insomnia. In insomnia, hyperarousal state has been documented throughout the 24-h period. Objective sleep measures, EEG activity, physiologic findings, hypothalamic–pituitary axis, and markers of inflammation suggest that insomnia is a disorder of hyperarousal and not a state of sleep loss. Many confounding factors such as anxious/ruminative traits, stressful events, age-related sleep changes, and biologic/genetic diathesis of central nervous system may be present. Interleukin-6 (IL-6) and tumor necrosis factor (TNF) are considered fatigue-inducing cytokines. These are negatively affected by the poor quality nighttime sleep. The daytime secretion of IL-6 and TNF-a in combination with high 24-h hypersecretion of cortisol explained the daytime fatigue and difficulty falling asleep. In another study, although nighttime cortisol levels were not different in patients with insomnia versus controls, the levels of nighttime melatonin were reduced in the patients with insomnia.

The *neurocognitive model* is an integrative model that suggests classical conditioning responsible for the cortical arousal. Once the cortical arousal is established, it loses its original association and becomes self-reinforcing. In keeping with the behavioral model, the acute insomnia is caused by acute stress, followed by persistent insomnia due to maladaptive coping strategies and finally, proceeds to chronic insomnia as a result of the conditioned arousal. According to this theory, the cortical arousal an analog of cognitive arousal is involved as part of the somatic arousal. The cortical arousal is a useful concept as it can be measured by the specific EEG frequencies. Elevated beta- and gamma-range EEG activity has been well documented in the patients with insomnia.

The *psychobiological inhibition model* is based on the notion of insomnia as an adaptive response to stress. The idea of perceived threat even in the absence of the stress counteracts and inhibits sleep onset. This leads to perpetual cognitive and behavioral changes[9]. The proposed attention–intention pathway is based on the notion of sleep normalcy as an automatic process. Sleep may be inhibited by the focused attention and by direct attempts to control its expression[10]. Both these models do not specify any neural substrate, but do take into account the recent findings from the sleep neuroscience discoveries.

The *sleep–wake regulation* has been an area of investigative interest for a long time. The ventrolateral preoptic area is proposed as a flip–flop switch that regulates the sleep–wake cycle[11]. The opposing neurotransmitter systems dictate the tendency to sleep by a balance of the sleep- and wakefulness-promoting systems. Greater activity of sleep-promoting system increases sleep propensity and lesser activity of wakefulness-promoting systems enhance sleep. This model postulates the manifestations of insomnia as a result of defective neurobiological switch. The orexin–hypocretin system promotes wakefulness and maintains it. Neurons containing orexin are implicated in sleep regulation. Orexin can upregulate the monoaminergic neurons. Although further research is needed to explore increased wake-promoting inputs causing hyperarousal or a downregulation that decreases inhibitory input to flip the switch to sleep.

The *local sleep model* proposes that sleep is an emergent cumulative outcome of many neural networks that have their own independent sleep–wake transitions[12]. In such local networks, the sleep might be initiated by metabolically driven cellular changes in the production of sleep-regulatory substances (SRSs). Many SRSs increase the delta-wave power of the EEG spectrum including IL-1, TNF-a, and adenosine. Sleep can be manipulated in predictable manner by interventions such as ambient temperature that increases sleep duration and TNF levels. Infection increases the sleep duration and concentration of many SRSs. Excessive food intake increases IL-1, TNF, and adenosine levels.

The *Drosophila model* has evolved after genetic manipulation and breeding of a fly with typical findings of insomnia such as lower sleep onset latency, total sleep time, and less consolidated sleep. This model shows many negative daytime consequences of insomnia[13].

The *cage exchange model* created a stressful situation for rats by changing their cage. Over time, the rats developed acute insomnia. The researchers identified simultaneous activation of the cortical arousal and opposing ventrolateral preoptic neural circuit. This model supports the environmental stress as a precipitant of insomnia[14].

The *PER2* and *PER3* genes are members of the Period family of genes. These are expressed in a circadian pattern in the suprachiasmatic nucleus. The *PER3* gene is known to be responsible for sleep regulation, which implicates genetic vulnerability as a predisposing factor for insomnia. A mutated *PER2* gene is associated with advanced sleep phase syndrome, and a functional polymorphism in *PER3* gene is associated with delayed sleep phase syndrome[15]. Twin studies estimated 30–50% heritability of insomnia symptoms[16]; another twin study supported an association between stress reactivity that disrupts sleep, its heritability, and insomnia[17].

Neuroscientific work has documented higher frontal beta power in the electroencephalogram of patients with insomnia[18]. The rapid eye movement (REM) instability hypothesis suggests that patients with primary insomnia have less amount of REM sleep and more REM arousals. This theory proposes that instability of the REM sleep contributes to the disrupted and non-restorative sleep in patients with insomnia[19]. (See Box 1. Below)

The role of cytokines is being gradually established in the development and maintenance of insomnia. IL-1 and TNF-á are directly implicated in the non-REM sleep regulation. Early evidence is building to favor improvement in cytokine levels in patients with insomnia after the cognitive behavior therapy[20].

Well-recognized cognitive and neurobiological processes have now been related to stress and its counterproductive effects on sleep. The conditioning effects continue to maintain insomnia in susceptible individuals. Maladaptive beliefs and behaviors along with dysregulation of the homeostatic and circadian systems form the basis of conceptual frame of integrative models of insomnia[21]. Increasing knowledge of the pathophysiology of arousal and sleep is facilitating development of targeted treatments of insomnia and guides future research directions.

Box 1: Models for the pathogenesis of insomnia

Conventional or early models for pathogenesis of insomnia

- Speilman's 3P model
- Stimulus control model
- Cognitive model

Alternative/newer models for pathogenesis of insomnia

- Hyperarousal theory
- Neurocognitive model
- Psychobiological inhibition model
- Sleep–wake regulation model
- Local sleep model
- *Drosophila* model
- Cage exchange model

(Box content complied by Deepak Shrivastava, MD)

Conclusion

In conclusion, per available evidence in the pathogenesis of insomnia, none of the proposed models is conclusive. Thus, it may be surmised that though more than one of the models mentioned earlier could contribute to the pathogenesis of insomnia, a conclusive unified model still eludes us.

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