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CLINICAL REVIEW

Hyperarousal and insomnia: State of the science

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SUMMARY

In the past few years it has become increasingly clear that insomnia is a chronic disease that interacts with many other medical conditions. As our ability to examine complex physiological activity during sleep has increased, additional evidence continues to suggest that insomnia is associated with inappropriate physiological arousal. It is now known that patients with primary insomnia have increased high-frequency EEG activation, abnormal hormone secretion, increased whole body and brain metabolic activation, and elevated heart rate and sympathetic nervous system activation during sleep. This activation can be measured throughout the day and night and is chronic. Other research suggests that insomnia, probably based upon the associated chronic physiologic arousal, is associated with increased risk for medical disorders such as depression, hypertension, or cardiac disease. An animal model that has used odor stress to produce poor sleep in rats has identified specific activated brain sites similar to those found in human brain metabolic studies to suggest that insomnia is a state in which sleep and arousal systems are both simultaneously active. The animal studies have also shown that the inappropriate arousal can be blocked by lesions in the limbic and arousal systems. It is hoped that these findings can be extended to identify new compounds that improve insomnia by acting at these sites of abnormal brain activation.

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In a Sleep Medicine Reviews report published in 1997,[1] the case was made that many patients given a diagnosis of primary or idiopathic insomnia suffered from a disorder of physiological hyperarousal that produced both poor sleep and their other commonly reported symptoms. This paper will revisit this hyperarousal hypothesis by re-examining the previous data and including significant new data that have accumulated in the intervening years.

Historically insomnia, like depression, has been viewed as a behavioral or emotional problem. One common view is that insomnia develops when an acute emotional stress produces poor sleep and becomes habitual when inappropriate behavioral responses to the poor sleep (i.e., staying in bed longer, using alcohol, worrying about poor sleep) are learned.[2] There is no question that acute emotional stress can produce insomnia in many individuals. However, experimental work has shown that stress exists primarily in the central nervous system of the patient – when many people were exposed to the same stressor, some had very poor sleep while others had little change from their baseline sleep.[3] Subjects who reacted to the stress of spending a night in the sleep laboratory by having poor sleep did not differ in mood, personality, or other demographic measures from those subjects who reacted to the same stress by having little change in their sleep. However, those subjects who had poor sleep in response to their first night in a sleep lab were found to have higher heart rates and decreased parasympathetic activity at baseline and greater sympathetic nervous system activation than the good sleepers after phase-advanced sleep. Instead of the traditional Spielman model, which posits a single pre-insomnia state with few predisposing factors,[2] even normal sleeping young adults were found to have a wide range of predispositions to poor sleep, and the most meaningful measure of predisposition was baseline level of central nervous system arousal as measured by cardiovascular activation. Those subjects with low levels of sympathetic activation maintained normal, efficient sleep despite the added stress that was sufficient to produce poor sleep in subjects with higher levels of sympathetic nervous system activation. On the second sleep laboratory night, the stress of the first sleep lab night was gone, and sleep normalized in the poor sleepers. Traditional psychological explanations would suggest a psychological response to a new environment, but, in fact, the same poor sleepers also were found to have significantly worse sleep (compared to the original stress insensitive subjects) when their bed time was advanced 3 or 6 hours (to produce a different

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type of physiological activation) and even when given caffeine (versus placebo) prior to a normal bed time. The point is that, given a predisposition to physiological activation, any number of physiological stressors will increase the likelihood of an insomnia response. In addition, sympathetic activation tends to increase with age, physical deconditioning, and numerous medical problems; and this increases the predisposition to chronic insomnia as individuals mature in our society. The implication is that there are numerous factors and widely variable amounts of physiological predisposition to poor sleep that interact with a range of state stressors (that may include both cognitive/emotional stress and state physiological activation) to produce insomnia on a given night.

The goal of this paper will be to 1) review the studies that have examined state and trait physiological responses in patients with insomnia and normals to better understand the significance of arousal level in insomnia and 2) to explore the medical and behavioral implications of insomnia as a chronic physiologic arousal disorder.

Evidence for physiological arousal in patients with primary insomnia

Extensive physiological differences between good and poor sleepers were first reported by Monroe,[4] who found increased rectal temperature, heart rate, basal skin resistance, and phasic vasoconstrictions 30 minutes prior to and during sleep in poor sleepers as compared to normal sleepers. In the 20 years that followed, several additional differences were reported when patients with insomnia were compared with normal sleepers. Poor sleepers had increased secretion of corticosteroids and adrenaline,[5,6] compared with good sleepers in most but not all studies.[7] Patients with sleep-onset insomnia had increased frontalis[8] and mentalis EMG[9,10]; increased heart rate[11]; increased finger temperature; and more beta and less alpha frequencies in the EEG.[9,10] Significantly elevated body temperature was reported in some but not all studies of poor sleepers.[4–6,12]

More recent experiments, often using carefully selected patient populations, have extended the range of physiological findings. These findings will be reviewed by category: cardiac measures, hormone measures, body temperature, metabolic measures, evoked and spectral EEG measures, and multiple sleep latency test measures.

Cardiac measures

A number of studies have replicated and refined the earlier experiments. In addition to the early study that showed a significantly higher heart rate in insomnia patients compared with normals,[11] two of three more recent studies have shown significantly higher heart rate during both sleep and wake periods in carefully selected insomnia patients.[13,14] Another more recent study that did not show a significant increase in heart rate[15] did document a 4-beat increase in the insomnia group (Effect Size [ES] = 1.04). When data were combined from these latter three studies, mean heart rate was 69.8 bpm in insomnia patients versus 64.1 bpm in controls ($t_{95} = 3.476$; $p < 0.001$ and ES = 2.80). Two studies have examined heart rate variability in insomnia patients versus controls. One found significantly decreased high/total frequency spectral power (parasympathetic activation) and increased low/high-frequency spectral power (sympathetic activation) in wake and all sleep stages in insomnia patients as compared with normal controls.[13] The other study did not find significant differences in Heart Rate Variability based upon a single 5-min recording from a waking afternoon session.[16] Vgontzas et al.[17] have shown a significantly increased risk for hypertension in insomnia patients with a polysomnographic sleep time of 6 hours or less. Risk was greatly reduced for patients without an insomnia complaint who slept for less than 6 hours and patients with an insomnia complaint who actually slept for more than 6 hours.

Hormone measures

Several measures including cortisol, ACTH, melatonin, norepinephrine, and Il-6 have been measured in matched groups of insomnia patients and controls. In addition to initial positive results,[5,6] at least seven newer studies,[18–24] have examined cortisol levels, and all except one[24] have found evidence for increased cortisol secretion in insomnia patients compared with controls. In the two studies with a large number of cortisol observations,[22,19] overall increases in cortisol were large (average ES = 2.32). One study with frequent sampling has found increased ACTH in patients with primary insomnia.[22] Studies have shown that patients with insomnia have decreased melatonin secretion at night.[25,26] One study has shown increased norepinephrine in insomnia patients compared with both controls and depressed patients.[27] Two studies have shown indication of increased Il-6 in insomnia patients, but the points of elevation varied from prior to bed time to 3–7 am.[28,29]

Body temperature

Body temperature was significantly elevated in insomnia patients compared with controls in 2 of 6 studies.[4,6,5,12,30,31] In a recent study that used a constant routine and careful subject selection to examine rectal temperature in older patients with insomnia,[32] a highly significant difference of only 0.29 °C (based upon careful measurement with very small error) was found during the night with patients awake in the constant routine. However, the difference, when measured during sleep, was not significant.

Metabolic measures

Two studies have measured whole-body metabolic rate across the night in insomnia patients and matched controls.[33,34] One showed significantly elevated VO_2 in insomnia patients compared with normals across the night, within matched sleep stages, and during daytime waking observation periods. The other study showed that VO_2 was also significantly elevated, although to a lesser degree, in patients with paradoxical insomnia (patients with sleep staging that did not differ from the controls). More recently, insomnia patients have been shown to also have elevated global brain metabolism both asleep and awake based upon functional neuroimaging.[35] In addition, insomnia patients had a smaller decline in metabolism during sleep in the reticular system, hypothalamus, thalamus, insular cortex, amygdala, and hippocampus compared with normal, and this suggested increased general arousal and increased activity in emotional arousal areas of the brain. In a following study, the same investigators reported positive correlations between wake time during sleep and brain metabolic rate in areas associated with emotion.[36]

Evoked and spectral EEG measures

Increased beta EEG activity has been noted during the night in 7 of 8 studies of patients with insomnia compared with normals.[10,37–43] One study has documented a significant decrease in beta activity in a group of patients with insomnia after 8 weeks of cognitive behavioral therapy.[44] After therapy, relative beta power was reduced to 82% of the pretherapy value (ES = 0.32). In comparison, another study reported that relative beta power in control subjects was 49% of the value found in insomnia patients (ES = 1.60).[37]