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The Pathophysiology of Insomnia

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Insomnia disorder is characterized by chronic dissatisfaction with sleep quantity or quality that is associated with difficulty falling asleep, frequent nighttime awakenings with difficulty returning to sleep, and/or awakening earlier in the morning than desired. Although progress has been made in our understanding of the nature, etiology, and pathophysiology of insomnia, there is still no universally accepted model. Greater understanding of the pathophysiology of insomnia may provide important information regarding how, and under what conditions, the disorder develops and is maintained as well as potential targets for prevention and treatment. The aims of this report are (1) to summarize current knowledge on the pathophysiology of insomnia and (2) to present a model of the pathophysiology of insomnia that considers evidence from various domains of research. Working within several models of insomnia, evidence for the pathophysiology of the disorder is presented across levels of analysis, from genetic to molecular and cellular mechanisms, neural circuitry, physiologic mechanisms, sleep behavior, and self-report. We discuss the role of hyperarousal as an overarching theme that guides our conceptualization of insomnia. Finally, we propose a model of the pathophysiology of insomnia that integrates the various types of evidence presented. CHEST 2015; 147(4):1179-1192

ABBREVIATIONS: GABA = γ-aminobutyric acid; MnPO = median preoptic area; NREM = non-rapid eye movement; PEP = pre-ejection period; PSG = polysomnography; REM = rapid eye movement; SNP = single-nucleotide polymorphism; TMN = tuberomammillary nucleus of the posterior hypothalamus; VLPO = ventrolateral preoptic area

Insomnia disorder is characterized by dissatisfaction with sleep quantity or quality, associated with difficulty falling asleep, frequent nighttime awakenings with difficulty returning to sleep, and/or awakening earlier in the morning than desired.[1,2] The disorder is also characterized by significant distress or impairment in functioning, and daytime symptoms including fatigue, daytime sleepiness, impairment in cognitive performance, and mood disturbances. Insomnia is differentiated from sleep deprivation by difficulty sleeping despite having adequate opportunity to sleep.[1] Prevalence estimates of insomnia vary, with 30% to 43% of individuals reporting at least one nighttime insomnia symptom.[3-6] Most reports suggest prevalence rates of insomnia disorder at 5% to 15%.[4,5,7,8] Insomnia is a chronic problem in 31% to 75% of patients,[1,6,7] with more than two-thirds of patients reporting symptoms for at least 1 year.[9]

Although progress has been made in recent years regarding our understanding of the nature, etiology, and pathophysiology of

Manuscript received July 3, 2014; revision accepted October 28, 2014.

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FUNDING/SUPPORT: Dr Buysse is supported by the National Institutes of Health [Grants MH024652, MH102412, AG020677, and HL125103]. Drs Levenson and Kay are supported by the National Institutes of Health [Grant HL082610, T32, PI Buysse].

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DOI: 10.1378/chest.14-1617

insomnia,[6,10-12] there is still no universally accepted model. This may be related to the heterogeneity of insomnia, its highly comorbid nature, or differences in what level of analysis the models use, from phenomenology to physiology. To be comprehensive, an etiologic or pathophysiologic model of insomnia should explain features such as the heterogeneity of symptoms and the risk insomnia confers for other comorbid conditions, such as depression and cardiometabolic syndrome. It should also explain the discrepancy between subjective (self-report) and objective (polysomnography [PSG]) measures of insomnia symptoms reported by some individuals with insomnia (see Reference 13 for a review). Greater understanding of the pathophysiology of insomnia may provide important information regarding how, and under what conditions, the disorder develops as well as potential targets for prevention and treatment. The aims of this review are (1) to summarize current breadth of knowledge on the pathophysiology of insomnia and (2) to present a model of the pathophysiology of insomnia that draws on evidence from various domains. Our article is intended to provide a brief overview of these topics for clinicians and researchers whose main focus is not insomnia. More extensive reviews of this topic can be found elsewhere.[12,14,15] Our article is primarily informed by perspectives drawn from psychology, psychiatry, and clinical neuroscience.

Levels of Analysis: An Approach to Understanding Insomnia

Although evidence-based assessments and treatments for mental disorders have been developed, diagnostic criteria for these conditions—including insomnia—are grounded in clinical consensus.[16] Further progress depends on better understanding the etiology and pathophysiology of mental health problems. One framework for doing this has been offered by the National Institute of Mental Health's "Research Domain Criteria" initiative. While recognizing the value of current diagnostic categories, the National Institute of Mental Health has begun to emphasize observable "domains" of brain function pertinent to mental health. These research domains, such as positive emotion, negative emotion, and arousal, often show similar patterns of dysregulation across traditional diagnostic categories and can be examined across levels of analysis from genes to symptoms. These points pertain to insomnia as well. The first two editions of the *International Classification of Sleep Disorders* introduced >25 diagnoses with "insomnia" as a cardinal symptom,[2,17] but evidence for the reliability, validity, and distinct pathophysiology of these insomnia phenotypes has proved elusive. Partially as a consequence of this, both the *International Classification of Sleep Disorders*, *Third Edition*[18] and *Diagnostic and Statistical Manual of Mental Health Disorders*, *Fifth Edition*,[1] now propose a single major category for Insomnia Disorder or Chronic Insomnia Disorder. Nevertheless, there remains an impetus for the field to develop an evidence-based model of insomnia that accounts for heterogeneity in cause, symptoms, course, comorbidities, and consequences. This review considers evidence across seven levels of analysis based on the Research Domain Criteria framework: genetic, molecular, cellular, neuroanatomic, physiologic, behavioral, and self-report.

Hyperarousal: An Overarching Theme

Insomnia is often considered to be a disorder of hyperarousal,[19] or increased somatic, cognitive, and cortical activation.[20,21] Individuals with insomnia may experience physiologic hyperarousal in both central (cortical) and peripheral (autonomic) nervous systems (see References 20, 22, 23 for full review). Hyperarousal in insomnia can also refer to cognitive and emotional processes, with several theories suggesting that cognitive and affective hyperarousal at bedtime may contribute to both acute and chronic insomnia.[24,25] Despite the frequent attention to hyperarousal in the literature, it is not frequently defined. In this report we conceptualize hyperarousal as heightened physiologic, affective, or cognitive activity, which interferes with the natural "disengagement from […] the environment"[26] and decreases the likelihood of sleep. Hyperarousal may be detected using such measures as increased cortisol, heart rate variability, EEG, or even self-report (eg, "I can't turn off my mind," "I feel so keyed up"). One of the challenges in identifying hyperarousal is that an individual always has some level of arousal, and the exact threshold for categorizing hyperarousal is not well defined. Thus, most studies have identified hyperarousal by noting differences between insomnia and control groups, rather than denoting a specific threshold.[27] We propose hyperarousal as an overarching theme that, along with other contributory factors, enriches our understanding of the pathophysiology of insomnia at each level of analysis and across levels in an integrated model.

Genetics of Sleep and Insomnia

Sleep-wake traits, such as sleep duration and timing, are heritable[28] and regulated by numerous genes.[29] Animal and human studies also implicate genetic mechanisms in the etiology of insomnia. Seugnet et al[30] isolated