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CLINICAL REVIEW

The hyperarousal model of insomnia: A review of the concept and its evidence

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SUMMARY

Primary insomnia is defined as difficulties in falling asleep, maintaining sleep or non-restorative sleep accompanied by significantly impaired daytime functioning in the absence of a specific physical, mental or substance-related cause. The current review provides substantial support for the concept that hyperarousal processes from the molecular to the higher system level play a key role in the pathophysiology of primary insomnia. Autonomous, neuroendocrine, neuroimmunological, electrophysiological and neuroimaging studies demonstrate increased levels of arousal in primary insomnia during both night and daytime. In the light of neurobiological theories of sleep–wake regulation, primary insomnia may be conceptualized as a final common pathway resulting from the interplay between a genetic vulnerability for an imbalance between arousing and sleep-inducing brain activity, psychosocial/medical stressors and perpetuating mechanisms including dysfunctional sleep-related behavior, learned sleep preventing associations and other cognitive factors like tendency to worry/ruminate.

Introduction

Insomnia as a diagnostic entity is defined as a complaint of prolonged sleep latency, difficulties in maintaining sleep, the experience of non-refreshing or poor sleep coupled with impairments of daytime functioning, including reduced alertness, fatigue, exhaustion, dysphoria and other symptoms. The complaints have to endure for at least 4 weeks to be diagnosed as insomnia. The Diagnostic and Statistical Manual of the American Psychiatric Association (DSM)[1] classifies insomnias into primary insomnia (PI), insomnia related to a medical or mental disease and insomnia related to the intake or abuse/dependency from substances. The International Classification of Sleep Disorders (ICSD)[2] goes beyond that approach and specifies 11 insomnia subtypes encompassing among others acute, psychophysiological, paradoxical, idiopathic and substance-induced insomnia.

Insomnia as a symptom is a highly prevalent health complaint afflicting up to 50% of the general population depending on criteria applied. Estimates for the prevalence of PI as a diagnostic entity in the general population range from 3 to 5%.[3] Research diagnostic criteria for insomnia[4] now provide operationalized and standardized criteria for the diagnosis of insomnia and its subtypes.

Polysomnographic research on insomnia revealed a remarkable discrepancy between the subjective experience of insomnia and polysomnographically rather undisrupted sleep in many patients with primary insomnia.[5,6] Thus, polysomnography (PSG), in contrast to other fields of clinical sleep medicine, has not become the via regia to the diagnosis of insomnia.[7] Insomnia diagnosis and assessment is based on subjective reports (sleep questionnaires) of sleep behavior and relies on sleep diaries filled out every evening and morning (for an overview of relevant instruments see[8,9]).

The effectiveness of cognitive-behavioral treatment for insomnia (CBT-I)[10–12] compared to the risks inherent with pharmacological insomnia treatment (e.g., benzodiazepines[13]) may have added to the conceptualization of PI as primarily a psychological disorder and negligence to study its biological aspects (compared to other sleep disorders or other disorders in the field of mental health).

The "hyperarousal" perspective of insomnia[14–16] has gained widespread attention as an integrative approach to the pathophysiology of insomnia (especially primary insomnia (PI) or psychophysiological

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Nomenclature

AASM	American Academy of Sleep Medicine
AIE	Attention–intention–effort model
APA	American Psychiatric association
BZ	Benzodiazepine
CAP	Cyclic alternating pattern
CNS	Central nervous system
CBT-I	Cognitive-behavioral therapy for insomnia
CREB	Cyclic AMP-response element binding protein
CRH	Corticotropin releasing hormone
DEX	Dexamethasone
DSM	Diagnostic and Statistical Manual of the American Psychiatric Association
ECG	Electrocardiogram
EEG	Electroencephalogram
ERP	Event-related potential
FFT	Fast Fourier Transformation
fMRI	functional Magnetic Resonance Imaging
GABA	Gamma-amino-butyric acid
GSC	Good sleeper control
GSR	Galvanic skin response
HPA	Hypothalamic–pituitary–adrenal axis
ICSD	International Classification of Sleep Disorders
Il	Interleukin
MRI	Magnetic Resonance Imaging
MSLT	Multiple sleep latency test
NREM	Non-REM sleep
PET	Positron emission tomography
PGO	Ponto-geniculo-occipital waves
PI	Primary insomnia
PSG	Polysomnography
REM	Rapid eye movement sleep
R&K	Rechtschaffen and Kales
SPECT	Single photon emission computed tomography
SWS	Slow wave sleep
TNF	Tumor necrosis factor
VLPO	Ventrolateral Preoptic Nucleus

insomnia), assuming an interplay between psychological and physiological factors in the etiology and perpetuation of chronic insomnia. Accordingly, acute episodes of insomnia are triggered by acute stressors ("threat", i.e., psychosocial, medical, drug factor). In many cases, with the cessation of the influence of the stressor, the sleep complaint resolves. Only a subpopulation of afflicted patients develops persistent, chronic insomnia which becomes independent of the initial stressors.[17]

The hyperarousal concept postulates that subjects who tend to focus cognitively on the insomnia and start to ruminate about their sleep complaint are prone to develop "learned sleep preventing associations" which explain the chronicity of the disorder. Maladaptive behaviors (i.e., prolongation of bedtime, daytime napping, increased alcohol consumption, etc.) are postulated to contribute additionally to the perpetuation of insomnia. The hyperarousal concept from early on encompassed physiological phenomena as it was demonstrated that chronic insomnia is accompanied by indices of increased autonomic activity.[14,18] The term "psychophysiological" insomnia as it was coined by Hauri[19] indicated that "psychophysiological insomnia… develops secondary to chronic, somatized tension and negative conditioning". Yet, 20 years later, when considering the description of psychophysiological insomnia in the ICSD-2,[2] not much knowledge seems to have been accumulated concerning the "physiological" (=somatized tension) aspect.

It is the aim of the present article to review the hyperarousal concept of primary insomnia and to discuss the underlying evidence with an emphasis on neurobiological studies. Furthermore we aim to integrate these findings with neuroscientific knowledge on sleep–wake regulation.

The hyperarousal concept of insomnia

Perlis and colleagues[16,20] provided a comprehensive review of the hyperarousal perspective including neurobiological variables which they termed "neurocognitive" theory of insomnia (modified version see Fig. 1).

The model is based on the behavioral perspective that insomnia occurs acutely in association with predisposing and precipitating factors (for example psychosocial stressors), and chronically in association with perpetuating factors[17] (for example extension of time in bed). The behavioral perspective is extended by explicitly allowing the possibility that conditioned arousal may act as a perpetuating factor. Arousal is expressed in terms of somatic, cognitive and cortical activation. Hence, the bed and the sleep environment and its circumstances become stimuli for arousal instead of "de-arousal". It is hypothesized that the cortical arousal (experienced subjectively as increased cognitive activity and measurable on an electroencephalographic level by increased fast frequencies of the sleep Electroencephalogram (EEG), (see section Electro- and neurophysiology of insomnia)) occurs as a result of classical conditioning and promotes abnormal levels of sensory and information processing, and of long-term memory formation. These phenomena are directly linked to sleep continuity disturbances and/or sleep state misperception (i.e., paradoxical insomnia). Specifically, enhanced sensory processing around sleep onset and during sleep is thought to render the insomniac individual especially vulnerable to perturbation by environmental (or other) stimuli, and these events may directly interfere with sleep initiation and/or maintenance. Enhanced information processing during sleep may distort the distinction between sleep and wakefulness and might thus account for the tendency of many insomniac patients to judge PSG measured sleep as wakefulness. Enhanced memory formation for the events around sleep onset and arousals during sleep may interfere with the subjective experience of sound and uninterrupted sleep. An increased ability to encode and retrieve information in insomnia would be expected to correlate with altered assessments about sleep latency, wakefulness after sleep onset and sleep duration.

The model assumes that the experience of chronic insomnia may have a decisive impact on the development of relevant psychopathology, i.e., depression, addiction and anxiety disorders. From a psychological point of view depressed mood as a consequence of chronic insomnia might be explained with the model of "learned helplessness". Not unsurprising, dependence on alcohol, hypnotic and sedating drugs is more common in patients with insomnia compared to subjects not afflicted with chronic sleep complaints. The relationship to anxiety disorders on a psychological level is less clear: yet, there is considerable anxiety about sleep, insomnia and its consequences in many afflicted patients which might lead to a generalization of increased levels of anxiety.

Espie and colleagues[21] provided a cognitive model for the development and maintenance of chronic insomnia which they called the AIE (attention–intention-effort) pathway. The focus of this model lies on cognitive mechanisms that accompany or underly the assumed hyperarousal in insomnia patients. By taking a perspective of sleep normalcy as its starting point the model