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Review Article

Early-life origin of adult insomnia: does prenatal–early-life stress play a role?

Laura Palagini [a,*], Christopher L. Drake [b], Philip Gehrman [c], Peter Meerlo [d], Dieter Riemann [e]

[a] Department of Clinical Experimental Medicine, Psychiatric Unit, University of Pisa, School of Medicine, Via Roma 67, 56100 Pisa, Italy
[b] Sleep Disorders and Research Center, Henry Ford Hospital, Detroit, MI, USA
[c] Department of Psychiatry Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA
[d] Center for Behavior and Neurosciences, University of Groningen, The Netherlands
[e] Department of Clinical Psychology and Psychophysiology/ Sleep Medicine, Center for Mental Disorders, Freiburg University Medical Centre, Freiburg im Breisgau, Germany

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ABSTRACT

Insomnia is very common in the adult population and it includes a wide spectrum of sequelae, that is, neuroendocrine and cardiovascular alterations as well as psychiatric and neurodegenerative disorders. According to the conceptualization of insomnia in the context of the 3-P model, the importance of predisposing, precipitating, and perpetuating factors has been stressed. Predisposing factors are present before insomnia is manifested and they are hypothesized to interact with precipitating factors, such as environmental stressful events, contributing to the onset of insomnia. Understanding the early-life origins of insomnia may be particularly useful in order to prevent and treat this costly phenomenon. Based on recent evidence, prenatal–early-life stress exposure results in a series of responses that involve the stress system in the child and could persist into adulthood. This may encompass an activation of the hypothalamic–pituitary–adrenal axis accompanied by long-lasting modifications in stress reactivity. Furthermore, early-life stress exposure might play an important role in predisposing to a vulnerability to hyperarousal reactions to negative life events in the adult contributing to the development of chronic insomnia. Epigenetic mechanisms may also be involved in the development of maladaptive stress responses in the newborn, ultimately predisposing to develop a variety of (psycho-) pathological states in adult life.

1. Introduction

Insomnia symptoms are very common, affecting one-third of the adult population; insomnia disorder is the most prevalent among the sleep disorders afflicting approximately 6–10% of adults [1].

Experimental and epidemiological studies conducted in adults show that poor sleep and insomnia have a wide spectrum of sequelae, including neuroendocrine and cardiovascular alterations as well as psychiatric and neurodegenerative disorders [2–9]. From a life-course perspective on health, understanding the early-life origins of insomnia may be particularly useful in order to prevent and treat this disturbance, which is of high economic relevance for health-care systems [10]. In addition, the association of insomnia with new-onset depressive disorder suggests the potential for downstream benefits of insomnia treatment with respect to prevention of psychiatric disorders [11,12]. The aim of this paper was to systematically review the evidence regarding the early-life origin of adult insomnia from prenatal to childhood origin.

2. Background of the hypothesis

2.1. Stress system and predisposition to insomnia: model of insomnia in adult and infant

A heuristic model of insomnia is the diathesis–stress model proposed by Spielman et al. [13] commonly known as the "3-P" model. The model describes predisposing, precipitating, and perpetuating factors relevant for the development and maintenance of insomnia. *Predisposing factors* include genetic, physiological, or psychological diatheses that confer differential susceptibility to individuals. These predisposing factors interact with *precipitating factors* such as physiological or environmental stressors, which lead an individual to cross a hypothetical insomnia threshold, eliciting the initial symptoms of insomnia. *Perpetuating factors* are proposed to play a role in the maintenance of insomnia.

* Corresponding author. Department of Clinical Experimental Medicine, Psychiatric Unit, University of Pisa, School of Medicine, Via Roma 67, 56100 Pisa, Italy. Tel.: +39 050 993165; fax: +39 050 992265.
E-mail address: lpalagini@tiscali.it, l.palagini@ao-pisa.toscana.it (L. Palagini).

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The neurocognitive model of insomnia [14] is founded on this diathesis–stress model, further integrating neurobiological and neurophysiologic observations, and it proposes that insomnia leads to conditioned cortical arousal. Hyperarousal on several levels (cognitive–emotional, autonomous, and central nervous system) as such is assumed to play a central role in the development and maintenance of adult insomnia [15,16]. Buysse et al. [17], in their neurobiological model of insomnia, hypothesized that the activation of cortico-limbic and brainstem hypothalamic centers may account for a relative increase in psychophysiological arousal observed in insomnia. The most face-valid animal model of insomnia presented by Cano et al. [18] using a cage-exchange paradigm also described insomnia as a consequence of the stressful experience of coactivation of sleep-inducing and arousing neuronal networks.

The relationships between response to a stressor and arousal deregulation have also been integrated in cognitive–psychological models of insomnia [19,20].

Roehrs et al. [21] reviewed evidence from nighttime and daytime electrophysiology, event-related brain potentials, neuroimaging, autonomic, and hypothalamic–pituitary–adrenal axis (HPA) studies that suggest insomnia is a 24-h disorder of hyperarousal. Numerous studies provide evidence for cognitive and physiological hyperarousal with an activation of the HPA in people with chronic insomnia (for an overview, see Refs. [15,16,21]). It has been hypothesized that hyperarousal may be a characteristic of individuals with elevated stress–sleep reactivity, that is, the degree of sleep disruption in response to stressful events [22–25], and that hyperarousal may constitute a premorbid characteristic of people with insomnia [22,26].

Sleep disturbances are common in infants and are a normal part of development that affects 20–33% of individuals; about half of these develop persistent sleep problems [27–29]. Infant sleep disorders, if not treated, may be quite persistent during childhood [28,29] and through adult life [30–32].

Sleep in the infant has been hypothesized to be influenced by a combination of processes including genetics and environmental factors [33]. A theoretical model of infant sleep regulation integrating multiple environmental systems was developed in 1993 [34] and revised in 2009 (for an overview, see Ref. [35]). This integrative model emphasizes the role of postnatal environmental stressors in developing infant insomnia [35].

Postnatal–childhood stressful experiences have been associated with lifelong consequences in response to stressful events later in life [36–39] leading to a variety of negative health outcomes into adulthood [38,40,41] including increased reactivity to stress [42] and insomnia [31].

Emerging data from both animals and humans indicate that environmental influences contributing to the development of insomnia may not be restricted to periods of postnatal development but may have origins in prenatal life: prenatal stress may contribute to a predisposition for insomnia in animals and humans [43–52].

2.2. Prenatal–early-life stress and stress system: implications for insomnia

Prenatal and postnatal periods are the most important and sensitive periods during the development of an individual [53,54]. Evidence from preclinical studies indicates that the brain is particularly sensitive to remodeling by environmental factors: adverse early-life experiences, such as stress exposure or suboptimal maternal care, can have long-lasting negative consequences leading to "early-life programming" of individual health and diseases [55].

Although knowledge on the possible mechanisms underlying relations between early-life programming and risk of disorders is limited, there is evidence for impaired glucocorticoid negative-feedback control of the HPA axis, altered glutamatergic neurotransmission, and reduced hippocampal neurogenesis in both prenatally and postnatally stressed rats (for an overview, see Ref. [54]).

The HPA axis appears to be particularly sensitive to the effects of early-life stress [37,54,56–59]. Preclinical and clinical studies show the most often proposed mechanism underlying the "early-life programming" of diseases is that involving the HPA axis and cortisol [54,60–62]. A general pattern, observed in rats and nonhuman primates, is that early-stressed offspring tend to show higher basal activity of the HPA axis, as well as potentiated and prolonged HPA responses to stressors with a consistent tendency towards hyperresponsivity (for an overview, see Refs. [54,62–64]). Decreased feedback inhibition of corticotropin-releasing hormone (CRH) and prolonged elevation of plasma glucocorticoids in response to stress have also been described. Prenatally stressed rats have higher levels of CRH in the amygdala and lower hippocampal levels of both glucocorticoid receptor (GR) and the mineralocorticoid receptor (MR) [57,63,65,66]. These findings have been integrated within the framework of the life history theory [67]. High stress responsivity can be adaptive in its nature, may be considered to be predictive for adaptations that serve to improve survival, and prepares the organism for a particular range of postnatal unpredictable environments [68]. Enhanced behavioral and neuroendocrine responses to stress may reflect greater vigilance to environmental threats, which may promote survival even if this has a long-term cost of adaptation [69,70]. Accordingly, some theorists have suggested that a hyperresponsive HPA axis may have been adaptive during evolution at the cost of vulnerability for various disorders, and it may no longer be adaptive – even becoming maladaptive or disadvantageous [69–71].

Although many individuals experiencing stressful events do not develop pathologies, chronic stress seems to be a triggering factor in those individuals who are particularly vulnerable. This vulnerability may in turn depend upon a permanent increase in the activation of the HPA axis. This can increase the susceptibility of the offspring to various stress-related diseases.

In fact, there is evidence to suggest that early-life stress has been associated with a wide range of health problems later in life such as increased reactivity to stress, and psychiatric and behavioral disorders [38,42,63,65,71–74].

Sleep is also one of many outcomes causally linked with early life in the animal literature, showing some changes in sleep architecture and more fragmented sleep related to early-life stress [43,46,47,75–78].

2.3. Epigenetic programming of the stress system: implications for insomnia

In the last decade, there has been increasing evidence that epigenetic mechanisms are likely to play a major role in the molecular mechanisms underlying the long-lasting effect of early-life stress on adult health. The early-life years represent a period of particular susceptibility to epigenetic alteration, as active changes in DNA methylation and histone marks occur as part of developmental programs and in response to environmental cues (for an overview, see Ref. [79]). Epigenetic mechanisms have been hypothesized to shape the responsiveness of the HPA axis to subsequent early-life stressors, thus substantially contributing to the development of stable individual differences in HPA hyperresponsivity to stressful stimuli [80–83]. The most investigated hypothesis on how early-life stress can alter the child's development in utero and postnatally is that this is mediated by long-term effects on the function/activity of genes involved in the regulation of the HPA axis.

A number of studies have shown that induction of early-life stress can lead to epigenetic changes in key regulators of the stress response. This impairs negative HPA axis feedback by, for example,