

An Epigenetic Model of Insomnia?

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Sleep is a complex physiological process and remain one of the great mysteries of science. Hypotheses for sleep include somatic, metabolic, cellular theories, as well as brain-specific functions such as synaptic plasticity, or synaptic downscaling. Over the past 10 years, genetics provides a new way to address the regulation and function of sleep. Major findings include the identification of loci that make quantitative contributions to sleep characteristics and variability. From *Drosophila*, zebrafish, and worms to mammalian model organisms, some genes implicated in sleep homeostatic regulation have been identified [1]. Circadian genes (Clock, PER1, 2, 3 Bmal1, Timeless), neurotransmitters (serotonin, dopamine, norepinephrine, histamine, acetylcholine, orexin/hypocretin (Orexin/Hcrtrt2), adenosine, GABA receptor), cytokines/immune or stress response genes (Nfkb1, Nfkb, TNF- α , BiP, IL-1b, IL-6, IL-10), synaptic transmission genes (Homer, c-Fos, Gria3), ion channels (K⁺ channels, Ca⁺⁺ channels) and signal metabolic/cellular growth genes (Ghrelin Rho, Leptin EGF, Dwarf, GHRH) have been identified in mammalian. Moreover genetic determinants underlying variability in sleep phenotypes have begun to be revealed and reasearch of the past 10 years focussed on understanding factors contributing to sleep disturbances [2]. Well-documented familial and twin sleep disorder studies suggest an important influence of genetic factors. However only few sleep disorders have an established genetic basis including rare diseases that may result from a single gene mutation: fatal familial insomnia (mutation of prion protein gene PRNP), familial advanced sleep-phase syndrome (mutations in hPER2), delayed sleep phase syndrome (polymorphism in Per3) and narcolepsy with cataplexy (orexin/hypocretin genes) [1,2]. Indeed, most sleep disorders are complex in terms of their genetic susceptibility together with the variable expressivity of the phenotype and contribution of genes. Moreover environment and epigenetic gene-environment interactions have been recently hypothesized to control sleep and its disorders. In *Drosophila*, several histone modifications have been identified to contribute to chromatin remodeling and thereby to the epigenetic control of circadian gene expression [3]. Recently sleep regulation have been linked to activity-dependent epigenetic brain plasticity [4]. An alteration in both the histone Elp3, essential for the epigenetic control of neurogenesis [5] and the histone Tip60 which epigenetically regulates genes enriched for neuronal functions resulted involved in the sleep-wake regulation encompassing neural network in *Drosophila* [6]. This latter has been hypothesized to provide insight into epigenetic based regulation of sleep disturbances observed in neurodegenerative diseases like Alzheimer's disease [6].

Little is known about the genetic and epigenetic background of insomnia, one of the most common sleep disorders, which affects 10-15% of the adult population. Fatigue, cognitive impairments and poor motivation are commonly reported with a negative impact on personal, professional and social functioning. One of the most influential heuristic models of the evolution of insomnia is the 3P model developed by Spielman et al. [7]. This model provides a useful framework includes predisposing, precipitating, and perpetuating factors that are proposed to play important roles in the initiation and maintenance of the disorder. It has been proposed that stress could be a common precipitant of an insomnia disorder on a predisposing substrate: a

sleep reactivity to stress with a substantial genetic component have been hypothesized. A number of family studies have provided evidence for a possible genetic basis for insomnia: the majority of twin studies have shown substantial heritability of insomnia [8]. Specific genotypes that account for some phenotypic variance has been identified and suggest that genetic underpinnings might be identified. Recently a 44-base-pair insertion/deletion polymorphism in the promoter region of the serotonin transporter gene (5-HTTLPR) has been found to be associated with primary insomnia [9]. A higher recurrence of initial, middle, and terminal insomnia has been found in patients homozygous for the Clock genotype [10]. In a genome-wide study insomnia-associated genotypic differences were highly concentrated within genes involved in neural function, neurite growth and synapse formation i.e. ROR1 and ROR2 genes [11]. In the case of insomnia, even if a genetic basis for a sleep reactivity has yet to be demonstrated, it has been hypothesized a strong contribution of both genes and environment. Sleep disorder might arise by an interaction between the environment and the genetic makeup of the individual [10]. Moreover we might hypothesize an epigenetic gene-environment interaction. It has been recently demonstrated that insomnia endangers adult neurogenesis and inhibit hippocampal brain plasticity [12,13]. Brain plasticity has been hypothesized to be also under an epigenetic control [4] and we might consider that also circadian rythms have been suggested to be epigenetically regulated [5]. Probably we might hypothesize that, in insomniacs, something might happen from the gene-environment epigenetic interaction in response to stress.

Although phenotype of individuals with high sleep reactivity in response to stress should be studied further, epigenetic of both circadian rythm gene and brain plasticity should be another target of further reasearch in insomnia. We need to consider the genetic and environmental overlap between sleep and numerous phenotype and processes of gene-environment interplay and epigenetics. These identified susceptibility genetic determinants will provide clues to better understand pathogenesis of sleep disorders, to assess the risk for diseases and also to find new drug targets to treat and to prevent the underlying conditions.

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