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Dopaminergic Neurogenetics of Sleep Disorders in Reward Deficiency Syndrome (RDS)

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Abstract

It is well known that sleep has a vital function for prevention of substance-related disorders as discussed in the DSM-V. We are cognizant that certain dopaminergic gene polymorphisms have been associated with various sleep disorders. The importance of "normal dopamine homeostasis" is tantamount for health status and quality of life for the recovering addict. Since it is now know that sleep per se has been linked with metabolic clearance of neurotoxins in the brain, it is essential to encourage continued research in sleep science, which should ultimately result in attenuation of sleep deprivation especially associated with substance related disorders.

Keywords: Sleep; Dopaminergic system; Neurogenetics; Metabolic clearance of neurotoxins; Reward Deficiency Syndrome (RDS)

Introduction

A sleep disorder, or somnipathy, is a medical disorder of sleep patterns. Accordingly, some sleep disorders are serious enough to interfere with normal physical, mental, and emotional functioning. Disruptions in sleep can be caused by a variety of issues, from teeth grinding bruxism to night terrors. Dyssomnia refers to a group of sleeping disorders that involve difficulties in falling asleep or maintaining sleep. These disorders might cause an elevated sense of sleepiness during the day. Importantly, when a person suffers from difficulty falling asleep and staying asleep with no obvious cause, it is referred to as insomnia [1]. Furthermore, insomnia is characterized by an extended period of symptoms including trouble with retaining sleep, fatigue, decreased attentiveness, and dysphoria.

Clinicians agree that a diagnosis of insomnia involves patients' symptoms persisting for a minimum of four weeks. The DSM-V categorizes insomnias into primary insomnia, insomnia associated with medical or mental diseases, and insomnia associated with the consumption or abuse of substances. Insomnia also is linked to negative health consequences such as anxiety and depression [2].

It is well established that virtually all substance related disorders (SRD) and psychiatric disturbances are associated with sleep disruption, and psychiatric disorders are the most common cause of insomnia [3]. Alcohol dependence leads to sleep disturbances that persist in many cases for months even after abstinence and recovery [4]. In fact, it has be noted that insomnia is a risk factor for depression, anxiety and SRD [5].

There is significant evidence that sleep disorders such as Sleep Disordered Breathing (SDR), Restless Leg Syndrome (RLS) and sleep-movement disorders are unrecognized in adults and in children with psychiatric disorders including SRD and even alcohol spectrum disorder [6]. Moreover, insomnia and certain types of electroencephalography (EEG) sleep patterns, such as reduced REM latency or increased REM sleep, have been associated with relapse or recurrence of depression and alcoholism [7,8]. Across the number of Reward Deficiency Syndrome (RDS) subsets, for example, Posttraumatic Stress Disorder (PTSD), have been associated with nightmares (e.g., REM and NREM dream disturbances, movement disorders) and insomnia [9].

In terms of psychoactive drug abuse, specific effects on sleep have been observed and reported in the literature. For example, heroin addicts often report sleep disturbances, notably insomnia, as precipitating causes of relapse [10]. Methadone maintenance has resulted in sleep disorder breathing [11], and chronic cocaine addicts have lower sleep efficiency and significant sleep onset delay [12], followed by hypersomnia upon withdrawal or abstinence [13]. Users of GHB (gamma-hydroxybutyrate) experience constant waking and must take more to reinstate sleep [14]. It is noteworthy that cytokines regulate sleep, and a number of CNS functions including opioid systems and even food consumption [15].

Interestingly, neuroimaging studies have revealed neuro-anatomic correlates of sleep disturbance in depression and schizophrenia, showing that schizophrenics present slow wave deficits and frontal cortical volume loss [16], and depressed patients show higher absolute cerebral glucose metabolic rate than healthy subjects, and blunted activation of limbic structures (amygdala, anterior cingulate) during rapid-eye-movement (REM) sleep compared to wakefulness [17]. Certainly, we must be cognizant that many drugs can damage brain areas and neural pathways important in sleep maintenance. One example is MDMA ("ecstasy"), which has been shown to induce a reduction in serotonin axons and axon terminals [18]. Another example of drug induced brain damage is that cocaine causes severe depletion of dopaminergic neural pathways especially in low serotonin function [19].

Importantly, young adults diagnosed with attention-deficit-hyperactivity disorder (ADHD, a known subset of RDS), show evidence for sleep-disorders [20], and these patients should be monitored for delayed sleep phase disorder [21]. Understanding the neural correlates of sleep function, especially trait based neurogenetic dopaminergic polymorphic antecedents and state epigenetic induced dysfunction of sleep, is tantamount to providing informative treatment strategies.

Dopaminergic Neurogenetics and Sleep Disorders

In this editorial we briefly describe the potential neurogenetic and epigenetic effects on sleep. It is well-known that healthy homozygous 10-repeat (10R/10R) allele carriers of this genetic variant have reduced striatal dopamine transporter (DAT) protein expression when compared with 9-repeat (9R) allele carriers. Holst et al. [22] found that slow wave sleep, electroencephalographic slow-wave activity (0.5-4.5 Hz), and number of low-frequency (0.5-2.0 Hz) oscillations in non-rapid-eye-movement sleep, was significantly larger in the 10R/10R genotype than in the 9R allele carriers of DAT1. The results would suggest that dopamine transporter plays a role in regulating neurophysiological markers of sleep-homoeostasis in humans. Moreover, Landolt et al. [23] pointed out that the contribution of slow brain oscillations including delta, theta, alpha, and sigma frequencies (0.5-16 Hz) to the sleep EEG is regulated by circadian and homeostatic influences, and reflects functional aspects of wakefulness and sleep. Accumulating evidence demonstrates that individual sleep EEG patterns in non-REM sleep and REM sleep are heritable traits. More specifically, multiple recordings in the same individuals, as well as studies in monozygotic and dizygotic twins, suggest that a very high percentage of the robust inter-individual variation and the high intra individual stability of sleep EEG profiles can be explained by genetic factors (>90% in distinct frequency bands). However, there has been no association found within intron 8 of the DAT1 gene and sleep architecture measured by SPECT [24].

It is well known that a functional polymorphism in the gene encoding catechol-O-methyltransferase (COMT), an enzyme involved in cortical dopamine metabolism, causes a common substitution of methionine (Met) for valine (Val) at codon 158 of COMT protein. Resultant Val allele homozygotes exhibit higher COMT activity and lower dopaminergic function in prefrontal cortex than Met/Met homozygotes. Specifically, catechol-O-methyltransferase (COMT) inactivates nor epinephrine and dopamine via methyl conjugation, and a G-A transition in the COMT gene (rs4680) influences the enzyme activity. Bodenmann et al. [25] reported that the Val158Met polymorphism predicts stable and frequency-specific, inter-individual variation in brain alpha oscillations. Alpha peak frequency in wakefulness was 1.4 Hz slower in Val/Val genotype than in Met/Met genotype. In addition, Val/Val allele carriers exhibited less 11-13 Hz activity than Met/Met homozygotes in wakefulness, REM sleep, and non-REM sleep. Polymorphisms of the COMT gene have also been shown to influence the anti-depressant effects of certain drugs when utilized for bipolar depression and associated sleep problems [26].

Other work related to the relationships among the variable number of tandem repeats in the monoamine oxidase-A linked polymorphic region allelic variation (MAOA-uVNTR) and the symptoms of depression and sleep quality has been executed by Brummett et al. [27]. The MAOA gene, plays a role in degradation of neurotransmitters such as serotonin, norepinephrine, and dopamine, and contains a polymorphism in its promoter region (MAOA-uVNTR) that affects transcriptional efficiency. Interesting, Brummett et al. [27] found that MAOA-uVNTR alleles associated with less transcriptional activity presented with significantly increased symptoms of depression and poorer sleep quality. Therefore, these results suggest that patients with less active MAOA-uVNTR alleles may be at increased risk for depressive symptoms and poor sleep. Along these lines studies continue on evaluating reward gene polymorphisms and long- and short-sleep animal models [28]; circadian rhythm [29] as well as innate physical activity [30].

Future Perspectives and Encouraged Research

The role of sleep in complex disorders like RDS is extremely important especially in terms of relapse prevention. Most recently, evidence is accumulating showing that sleep has an important function in ensuring metabolic homeostasis. In mice, natural sleep is associated with a 60% increase in interstitial space, and as such, there is an increase in convective exchange of cerebrospinal fluid with interstitial fluid. This process results in an increased rate of β-amyloid clearance during sleep. According to Xie et al. [31] sleep drives metabolic brain clearance of potentially neurotoxic waste products. We are proposing that sleep may also clear foreign drug-like compounds such as opioids as an example.

Understanding the long-term problem of sleep even in abstinent opiate abusers, based on this new knowledge we encourage our scientific peers to continue their research in developing tools that will enhance sleep in these patients-a vital part of recovery.

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Conflict of Interest

Kenneth Blum holds US and foreign patents on a nutraceutical complex and nutrigenomics. He is the owner of IGENE LLC. There are no other conflicts.

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