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REM Rebound Effect

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REM Rebound Effect

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Continuing Education Activity

REM rebound behavior refers to the increased frequency, depth, and intensity of rapid-eye-movement (REM) sleep following sleep deprivation or significant stressors. This activity describes the neurophysiology and hormonal processes that contribute to the phenomenon of REM rebound. The article reviews the role of interprofessional teams in improving care for patients who may be experiencing REM rebound due to medical conditions or psychosocial/physical stressors.

Objectives:

- Describe REM rebound behavior.
- Outline the basic pathophysiology of REM rebound.
- Review the common clinical implications of REM rebound in the context of disorders and stressors that affect sleep.
- Identify the importance of enhancing the understanding of sleep deprivation to improve outcomes for patients.

Earn continuing education credits (CME/CE) on this topic.

Introduction

Sleep is a state consisting of several different stages of reversible disconnection from the environment with accompanying reduced consciousness, atonia, and metabolic changes.[1] These stages are primarily divided into rapid-eye-movement (REM) sleep, which is characterized by classic ocular saccadic movement and fast-wave EEG patterns reminiscent of wakefulness, and non-rapid-eye movement (NREM) which can be subdivided further into three stages each distinguished by distinct EEG wave patterns. Normally an individual will progress through a predictable cycle of stages beginning with wakefulness, then through each stage of NREM sleep before quickly reversing through the stages to enter REM sleep.[2]

The maintenance of appropriate sleep architecture appears to play an important role in promoting physiological and mental health.[3][4][5][6] Such health benefits may include modulating memory, emotion, and cognitive integration of stressors and mechanisms are in place to restore sleep homeostasis if sleep is disrupted. One of these mechanisms is REM rebound, which refers to the compensatory increase of the frequency, depth, and intensity of rapid-eye-movement (REM) sleep following sleep deprivation or significant stressors. Several experimental studies utilizing EEG and hormonal measurements have illustrated that human and animal participants who experience sleep deprivation or significant stressors will experience increased frequency and intensity of REM sleep to compensate for said deprivation.[4]

Etiology

As described earlier, researchers have hypothesized many potential benefits of engaging in REM sleep and that, consequently, REM sleep rebound is an evolutionarily advantageous adaptive strategy with the inability to engage in it having potentially disastrous consequences.[5]

Researchers have hypothesized that REM sleep may be an ideal period of reframing negative experiences and regulating emotional reactivity during a period when stress responses are normally quiescent. This hypothesis has been supported by studies such as one in which human participants expressed diminished negative reactions to images of fearful faces, and positive reactions to happy faces were augmented following a 90-minute nap.[7]

With that in mind, REM sleep deprivation and stress have been shown to induce changes in hormone release via the hypothalamic-pituitary-adrenal (HPA) axis as well as alterations in levels of neurotransmitters.[3] These signal alterations lead to a reduction in the length and quality of sleep and maintenance of wakefulness, leading to insomnia.[5]

Studies utilizing rat models exposed to multiple types of stress, including footshock, immobilization demonstrated dysregulation of the HPA axis and sympathetic response systems such as those found in the locus coeruleus and adrenal medulla. While rat models have been useful in elucidating the effects of physical stress, the most potent stressors to humans appear to be of a social nature, such as issues in the family, work, and interpersonal relationships.[5]

Epidemiology

Due to the high prevalence of sleep deprivation and stress, REM sleep rebound appears to be a common phenomenon both in the U.S. and worldwide. According to the CDC, more than a third of the U.S. population experiences sleep deprivation, which has been defined as greater than 7 hours of nightly sleep.[8]

Adequate sleep has been recommended to adults aged 18-60 to promote physical health and well-being, though the true extent of chronic sleep debt in the population remains to be measured accurately.[9] One recent study estimated that the average length of sleep has diminished, on average, 1 hour globally over the last 100 years with the greatest changes corresponding to Europe, North America, and Asia.[10]

Sleep deprivation is associated with the development of a multitude of comorbid conditions, including obesity, metabolic disorders, high blood pressure, vascular pathologies including coronary disease and stroke, and psychiatric morbidity.[5] Such comorbidities combined with motor vehicle accidents, workplace accidents, medical errors, and diminished work productivity contributes to national and global concern over the effects of poor sleep.[8]

Pathophysiology

Sleep is regulated by an interplay of neurotransmitters and neuropeptide systems located primarily in the hypothalamus and brain stem via two main mechanisms: homeostatic and circadian.[3] Homeostatic (“S process”) refers to the physiological drive to sleep, also referred to as “sleep pressure.” Circadian (“C process”) refers to sleep induction as a function of the day/night cycle and acts as the timing mechanism for the waxing and waning of alertness. Both mechanisms interact to induce sleep when sufficient pressure has accumulated, and the light/dark cycle favors sleep, while wakefulness is promoted in the waning of their interaction.

While normal sleep architecture depends heavily on the interaction of the homeostatic and circadian systems, sleep homeostasis appears to depend on the preceding waking period, especially its length and quality.[3] Sleep deprivation is associated with the development of a multitude of comorbid conditions, including obesity, metabolic disorders, high blood pressure, vascular pathologies including coronary disease and stroke, and psychiatric morbidity.[5] Such comorbidities combined with motor vehicle accidents, workplace accidents, medical errors, and diminished work productivity contributes to national and global concern over the effects of poor sleep. For example, short periods of sleep deprivation of up to 6 hours are associated with increased non-REM sleep. Those who experience greater sleep deprivation of 12 to 24 hours have a demonstrable increase in both non-REM sleep and REM sleep. Compare both these groups to those who experience approximately 96 hours of sleep deprivation and show nearly exclusive

increases in REM sleep.[3] These findings suggest that the severity of sleep deprivation and stress is correlated with increasingly greater compensatory architecture changes.

- **Corticotropin-releasing Hormone (CRH)**

Several studies have illustrated the powerful role that CRH plays in sleep regulation and REM sleep rebound.[11][5][6][5] CRH increases during stressful situations simulated in experimental studies utilizing electric footshock, immobilization, restriction of food, and sleep deprivation.[3] CRH has also been shown to reduce REM sleep rebound,[5] REM sleep, and non-REM sleep as well as increase wakefulness when injected intravenously.[3][11] Compare this to findings that CRH hypersecretion in the forebrain is linked with increased REM sleep; this finding provides a possible avenue for utilizing REM sleep as a biomarker for a variety of clinical conditions.[6]

- **Adrenocorticotrophic Hormone (ACTH)**

Adrenocorticotrophic hormone has been identified as a promoter of wakefulness in both light and dark periods of the circadian rhythm.[5]

- **Plasma Corticosterone**

Cortisol and other steroid hormones analogs appear to play a role in the regulation of sleep, and multiple studies have shown an association between aberrations in plasma cortisol and sleep architecture. For example, Addison disease patients experience more non-REM sleep and less REM sleep, which is corrected with corticoid replacement therapy, whereas patients with excess cortisol in conditions such as Cushing syndrome display less NREM sleep and more awakening associated with excess cortisol secretion.[3][5] Restoring basal levels of cortisol in such conditions restores normal sleep architecture.[5] This suggests that glucocorticoids play an integral role in establishing appropriate sleep patterns in humans, and the full expression of REM sleep rebound following stress.

- **Corticotropin-Like Intermediate Peptide (CLIP)**

CLIP is derived from proopiomelanocortin (POMC) and is associated with inducing long REM sleep episodes.[3]

- **Prolactin (PRL)**

Prolactin is an important neurotrophic hormone that prevents stress-induced reduction of neurogenesis and constitutes an important mechanism for stress coping and resilience via REM sleep rebound.[3][4] Several studies testing micro-infusions of PRL into the dorsal raphe nucleus (DRN) and the association of anti-PRL antibodies with suppressed REM sleep in rats demonstrated that PRL induces REMS and appears to play a role in regulating the stress-induced REM sleep rebound phenomenon.

- **Serotonin (5-HT)**

Studies of serotonin suggest that it may have a bidirectional relationship with prolactin as studies have correlated the length of REM sleep rebound with increased plasma prolactin and hypothalamic serotonin levels.[4][5]

History and Physical

A thorough clinical evaluation would reveal sleep disruptions and associated pathology that may lead to REM rebound behavior. Gathering a detailed sleep history will likely reveal important information regarding the number of hours slept, the onset of sleep, difficulty in waking, disruptions in sleep maintenance, and quality of sleep. Other pertinent information would include prior medical history and medical comorbidities (e.g., obstructive sleep apnea) and social history, which may influence sleep patterns (e.g., night shift work).

Such information will prove useful in establishing differential causes for disruptions in sleep and the necessity for further work-up of possible medical comorbidities. A comprehensive physical exam will further hone differential

diagnoses or conditions and the appropriateness of polysomnography for further work-up.

Evaluation

Under normal clinical conditions, there is no need to evaluate specifically for REM rebound behavior using EEG or other diagnostic modality.

Treatment / Management

Management of REM rebound is typically consistent with treatment for an identified sleep disorder a patient may be experiencing. The resolution of sleep aberrations has been shown to improve REM sleep once REM pressure has been sufficiently alleviated with quality sleep. Implementing sleep hygiene techniques may improve sleep quality, but research suggests that empirical data regarding their utility is lacking.[12]

Differential Diagnosis

REM rebound behavior itself is not a clinical diagnosis but a phenomenon that accompanies many sleep disorders. Such sleep disorders include a wide range of clinical conditions such as insomnia, psychosocial stress, psychiatric or neuropsychiatric disorders, parasomnias, narcolepsy, obstructive sleep apnea (OSA), or behavioral issues such as poor sleep hygiene or shift work.

Toxicity and Side Effect Management

Many medications can influence normal REM sleep, most notably antidepressants and antipsychotics. For example, research suggests that benzodiazepines normally suppress REM sleep when taken and will increase REM rebound once discontinued or in withdrawal.[13] The same effects are seen in barbiturates and ethanol. This is in contrast to new benzodiazepine-like hypnotic sleep aids such as zolpidem that have no associated REM rebound when discontinued. In the case of antidepressants, many patients tend to experience prolonged and more intense dreams associated with REM rebound following the abrupt withdrawal of antidepressant medications.[14]

A meta-analysis of multiple substances of abuse showed that withdrawal, recovery, or treatment with a placebo of marijuana, tetrahydrocannabinol (THC), cocaine, heroin, and stimulants result in increased REM sleep rebound, indicating a compensatory return to sleep homeostasis.[15]

Prognosis

The prognosis for resolution of REM rebound is generally favorable but dependent on the resolution of underlying sleep pathology and restoration of normal sleep architecture.

Complications

Several studies have shown that poor sleep can have significant detrimental effects on human health. Such effects include poor mood regulation, diminished memory consolidation, and correlative increased risk of developing psychiatric illnesses such as major depressive disorder, anxiety, and posttraumatic stress disorder (PTSD).[5]

Deterrence and Patient Education

Patient education regarding the consequences of poor sleep and avenues for improving sleep quality is an important part of providing quality care to patients. Poor sleep has been shown to increase the risk of comorbid conditions and diminished well-being illustrated by the following research findings:

- One recent study showed a negative correlation between the length of REM sleep episodes and the development of PTSD following a traumatic event.[16] Increased REMS, in general, appears to be protective against the effects of stress in a similar fashion.

- Stress and sleep deprivation have both been shown to cause significant changes in hormonal and neurotransmitter regulation. One study showed women who suffered from chronic burnout with associated anxiety and poor sleep exhibited reduced prolactin levels, a neurohormone that has neuroprotective properties. [5]
- Several epidemiological studies suggest that insomnia and disruptions in normal sleep during stressful periods significantly increase the risk of developing depression.[5]
- Nearly all antidepressants are known to reduce REM sleep by approximately 30%, while some antipsychotics such as phenelzine suppress nearly all REM sleep.[17] This has raised questions about the interplay of psychiatric symptoms, REM sleep deprivation, and medications of weight gain in this population.
- According to some studies, normal REM sleep appears to lower the risk of developing obesity. Moreover, the loss of the final REM period (fREMP) likely enhances appetite, which can lead to excessive caloric intake and associated weight gain in those with chronic sleep deprivation.[17]

Pearls and Other Issues

- REM rebound refers to the compensatory increase of the frequency, depth, and intensity of rapid-eye-movement (REM) sleep following sleep deprivation or significant stressors.
- REMS deprivation and stress have been shown to induce changes in hormone release via the hypothalamic-pituitary-adrenal (HPA) axis as well as alterations in levels of neurotransmitters.
- The most potent stressors to humans appear to be social such as issues in the family, work, and interpersonal relationships.
- According to the CDC, more than a third of the U.S. population experiences sleep deprivation, which has been defined as less than 7 hours of nightly sleep.
- Sleep deprivation is associated with the development of a multitude of comorbid conditions including obesity, metabolic disorders, high blood pressure, vascular pathologies including coronary disease and stroke, psychiatric morbidity, motor vehicle accidents, workplace accidents, medical errors, and diminished work productivity. Sleep deprivation represents a national and global concern.
- Management of REM rebound is typically consistent with treatment for an identified sleep disorder a patient may be experiencing. For example, correctly diagnosing and treating obstructive sleep apnea (OSA) will result in REM rebound and promotion of normal sleep homeostasis.
- Many medications suppress REM sleep and result in REM rebound when discontinued and include benzodiazepines, ethanol, barbiturates, antidepressants, some antipsychotics, marijuana, heroin, cocaine, and other stimulants.

Enhancing Healthcare Team Outcomes

Obstructive sleep apnea (OSA) is a common medical condition that significantly impairs the quality of sleep experienced by patients. OSA is diagnosed using overnight polysomnography, which is considered the diagnostic gold standard, while treatment consists of using overnight continuous positive airway pressure (CPAP) is the most effective treatment.[18][19] [Level 1] A meta-analysis of OSA treatments reveals that there is no significant difference in outcomes between CPAP and bilevel positive airway pressure (BiPAP) and that compliance remains one of the greatest limiting factors of any OSA treatment excluding surgical intervention.[19] Interestingly, Koo et al. showed that REM sleep rebound following the initial treatment of patients with OSA was correlated with improved sleep quality and mood elevation.[20]

Sleep hygiene is a well-known concept that advocates for behavioral modifications to promote sleep quality, including reducing alcohol and caffeine use prior to bedtime, reducing smoking, consistently exercising, and reducing stress,

noise, and light at bedtime. Although these recommendations appear logical at their face, a meta-analysis performed by Irish et al. suggests that there is a paucity of empirical data to support these practices.^[12] This issue highlights the need for continued research in sleep and evidence-based interventions to address the growing prevalence of sleep deprivation.

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