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Stress and insomnia – a vicious circle.

Estrés e insomnio: un círculo vicioso

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ABSTRACT

Insomnia refers to the complaint of experiencing unsatisfactory sleep, typically characterized by difficulties in initiating or maintaining sleep. Individuals with insomnia are dissatisfied with their sleep quality and perceive it as hindering their ability to perform well in work, school, and social settings. Common symptoms of insomnia include fatigue, decreased mood, irritability, general discomfort, and cognitive difficulties. Stress, on the other hand, is the result of emotional or physical tension triggered by various events that can lead a person to feel frustrated, angry, or anxious. Stress is the body's response to a challenge or demand, and it is accompanied by the release of hormones. The specific physiological response to stress depends on factors such as the type of stress, the individual's characteristics, their neuroendocrine system, and the combination of these elements, which collectively determine how the brain and body react to a particular stressor. The activation of the Hypothalamic-pituitary-adrenal (HPA) axis is a response mechanism triggered by stress. Disturbed sleep, particularly insomnia, is a common side effect of stress, varying in intensity. Sleep plays a crucial role in maintaining both physical and mental well-being, making the physiological connections between sleep and stress vital in understanding the development of stress-induced pathophysiology. Current treatments for insomnia include Cognitive Behavioral Therapy, improving sleep hygiene, and employing psychological and pharmacological interventions. However, these approaches primarily aim to improve insomnia symptoms rather than addressing its underlying cause. In the context of Homoeopathy, the concept of constitution refers to an individual's unique structure, composition, nature, and physical makeup, influenced by both inherited qualities and environmental factors. Therefore, it is essential to individualize each case and administer a similimum remedy to achieve complete healing according to Homoeopathic principles. This review aims to explore the physiological and neuroendocrine changes that occur as a result of the interplay between stress and the development of insomnia.

Key words - Stress, Insomnia, Physiological and Molecular alterations, Homoeopathy

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RESUMEN

El insomnio se refiere a la queja de experimentar un sueño insatisfactorio, típicamente caracterizado por dificultades para iniciar o mantener el sueño. Las personas con insomnio no están satisfechas con la calidad de su sueño y perciben que esto obstaculiza su capacidad para desempeñarse bien en el trabajo, la escuela y los entornos sociales. Los síntomas comunes del insomnio incluyen fatiga, disminución del estado de ánimo, irritabilidad, malestar general y dificultades cognitivas. El estrés, por otro lado, es el resultado de la tensión emocional o física desencadenada por diversos acontecimientos que pueden llevar a una persona a sentirse frustrada, enojada o ansiosa. El estrés es la respuesta del cuerpo a un desafío o demanda y va acompañado de la liberación de hormonas. La respuesta fisiológica específica al estrés depende de factores como el tipo de estrés, las características del individuo, su sistema neuroendocrino y la combinación de estos elementos, que en conjunto determinan cómo reaccionan el cerebro y el cuerpo ante un factor estresante en particular. La activación del eje hipotalámico-pituitario-suprarrenal (HPA) es un mecanismo de respuesta desencadenado por el estrés. Las alteraciones del sueño, en particular el insomnio, son un efecto secundario común del estrés y varían en intensidad. El sueño desempeña un papel crucial en el mantenimiento del bienestar físico y mental, lo que hace que las conexiones fisiológicas entre el sueño y el estrés sean vitales para comprender el desarrollo de la fisiopatología inducida por el estrés. Los tratamientos actuales para el insomnio incluyen la terapia cognitivo-conductual, la mejora de la higiene del sueño y el empleo de intervenciones psicológicas y farmacológicas. Sin embargo, estos enfoques apuntan principalmente a mejorar los síntomas del insomnio en lugar de abordar su causa subyacente. En el contexto de la Homeopatía, el concepto de constitución se refiere a la estructura, composición, naturaleza y constitución física únicas de un individuo, influenciadas tanto por cualidades heredadas como por factores ambientales. Por tanto, es fundamental individualizar cada caso y administrar un remedio similar para conseguir una curación completa según los principios homeopáticos. Esta revisión tiene como objetivo explorar los cambios fisiológicos y neuroendocrinos que ocurren como resultado de la interacción entre el estrés y el desarrollo del insomnio.

Palabras clave - Estrés, Insomnio, Alteraciones Fisiológicas y Moleculares, Homeopatía

INTRODUCTION

Insomnia is a prevalent sleep disorder that affects many individuals. According to a survey conducted by the American Psychological Association, 43% of people reported experiencing insomnia induced by stress. Sleep reactivity refers to the disruption of sleep caused by exposure to stress, resulting in difficulties with both falling asleep and staying asleep. Individuals with highly reactive sleep systems experience a significant decline in sleep quality when under stress, whereas those with low sleep reactivity are less affected and can maintain relatively undisturbed sleep during stressful periods. Stress is a complex condition involving emotional, cognitive, and biological factors. Intense stress can lead to both short-term and long-term negative effects on the human body, activating the defensive mechanisms of the central nervous system. The response to stress varies depending on the type of stress and the individual's physiological reactions. These responses encompass neuroendocrine and behavioral changes, including alterations in the activity and immune function of the hypothalamic-pituitary-adrenal (HPA) axis.[2] Sleep plays a crucial role in maintaining overall human homeostasis, and sleep disorders are closely linked to significant medical, physiological, molecular, neuroendocrine, psychological, and social disturbances.

EPIDEMIOLOGY

The worldwide prevalence of insomnia ranges from 10% to 30% of the population, with some regions reporting even higher rates of 50% to 60%. In developed countries, approximately 6% of adults suffer from chronic insomnia. Recent data from countries like the UK and Germany suggest a rise in insomnia prevalence, affecting around 10% of the

population. The American Association of Sleep Disorders states that insomnia symptoms are experienced by approximately 33% to 50% of adults, with distress or impairment occurring in 10% to 15% of cases. According to the American Psychological Association, 43% of individuals experience insomnia triggered by stress. Studies indicate that 20% to 35% of the general population exhibit insomnia symptoms, and 10% to 20% display clinically significant insomnia symptoms. In an epidemiological study conducted in the USA, using the definition of insomnia, prevalence rates of 8.5% to 10.7% were found among adults aged 18 to 44 years.[4]

SEARCH STRATEGY - The literature reviews were obtained by conducting searches on various academic databases, including PubMed, Google Scholar, and Scopus. The searches were performed using specific keywords such as "Stress," "Insomnia," "Physiological and Molecular alterations," and "Homoeopathy."

RESULTS - Total of 40 articles were assessed for the review. Out of them 35 were selected for the study.

CIRCADIAN PROCESS OF SLEEP

The natural circadian rhythm of physical function follows a precise 24-hour cycle, even without external cues. People feel sleepy at night primarily due to fatigue from daily activities, rather than solely relying on the internal clock. Therefore, sleep can be delayed by appropriate stimuli. The control of the circadian rhythm, including REM (Rapid Eye Movement) sleep, is influenced by the low peak of body temperature in the early morning and is not directly related to sleep timing. The tendency to feel drowsy is regulated by a combination of homeostatic and behavioral factors, as well as the circadian rhythm. Disruption of the body temperature rhythm can result in an increased need for sleep in the early afternoon, leading to a nap. This distribution of sleep reflects the phase of the circadian cycle and is independent of external factors. The suprachiasmatic nucleus (SCN) is considered the "master clock" of the brain, responsible for regulating circadian rhythms. SCN neurons follow a 24-hour transcription and detoxification cycle. Animal studies have shown that removal of the SCN abolishes circadian rhythms of behavioral and physiological processes, which can interfere with sleep.[25] Under normal circumstances, melatonin secretion in the SCN will reset daily, with light entering through the eyes in the morning and from the pineal gland at night.[26] This light information is detected by ganglion cells containing melanopsin, which is then delivered to the SCN. The SCN information is further amplified in the sub-paraventricular zone (SPZ).[27] Neurons from the dorsomedial hypothalamus (DMH) transmit this information to neurons responsible for circadian hormone secretion, such as orexin neurons related to vigilance, as well as the ventrolateral preoptic nucleus (VLPO) involved in sleep, body temperature regulation, and corticosteroid and thyrotropin-releasing hormone regulation. Thus, changes in DMH activity affect sleep-wake patterns, activity levels, feeding behavior, core temperature, and corticosteroid rhythms.[28] Core body temperature is one of the physiological processes regulated by the circadian pacemaker. Sleep typically begins when core temperature reaches its lowest point and ends as it starts to rise. In addition to melatonin, corticosteroids are also involved in regulating the sleep-wake circadian rhythm. The endogenous rhythm influences the circadian secretion of the hypothalamic-pituitary-adrenal (HPA) axis through the SCN-adrenal pathway.[29] Cortisol secretion follows a rhythmic pattern, with lower levels during the day and early part of the night, but increasing towards morning. The nadir of cortisol secretion occurs within a couple of hours after sleep onset. In other words, sleep usually starts when cortisol levels are lowest and ends when they are highest. Physical or physiological stress can affect cortisol secretion by activating the HPA axis.[2]

STRESS AND RELATED SLEEP PHYSIOLOGY

Stress triggers the activation of the sympatho-adreno-medullary (SAM) and hypothalamic-pituitary-adrenal (HPA) systems, resulting in increased activity of cardiovascular, catecholamine, cortisol, ACTH, and CRH.[30] This hyperactivity of the stress system influences various aspects of the body, including endocrine, gastrointestinal,

immune systems, and feedback pathways.[31] Excessive cortisol secretion due to stress negatively impacts neural structures like the hippocampus, leading to memory deficits.[32] Moreover, it has a particularly detrimental effect on sleep by influencing the activity of the SAM and HPA systems.[33] The immune system is also affected by stress, as the autonomic nervous system activates genes involved in the production of immune substances like cytokines.[34] Increased activity in the autonomic nervous system and cortisol leads to heightened alertness, while increased ACTH influences awakening from sleep. For example, the receptor activity of mineral corticosteroids increases non-rapid eye movement (NREM) sleep, while the receptor activity of glucocorticosteroids promotes alertness and rapid eye movement (REM) sleep. In experiments involving mice subjected to immobilization or social stimulation, decreased slow wave sleep and REM sleep have been observed, with subsequent recovery sleep showing an increase in these sleep stages. Acute and chronic stress have been found to decrease slow wave sleep and REM sleep in mice exposed to stress, but a normal sleep pattern is restored during the recovery period. In acute stress situations, corticotropin-releasing hormone (CRH) acts as a neurotransmitter in the locus coeruleus (LC) and activates noradrenaline neurons. However, under chronic stress, elevated levels of corticosteroids disrupt sleep, and the impact on slow wave sleep and REM sleep is not significant. The immune system plays a crucial role in the relationship between stress and sleep. Acute or chronic stress significantly affects sleep through immune system modulation. Acute stress primarily activates the immune system mediated by catecholamines and natural killer (NK) cells.[35] Conversely, chronic stress down-regulates the immune system by reducing B and T cells and diminishing NK cell activity. This immune dysregulation is observed in conditions such as depression and post-traumatic stress disorder (PTSD). Immune-regulated feedback involving interleukin-1β (IL-1β) activates the HPA axis and contributes to the relationship between stress and sleep. IL-1β levels in the blood vary depending on the sleep-wake cycle, while blood tumor necrosis factor (TNF) levels are associated with slow wave brainwave activity. Additionally, there is a strong correlation between disrupted sleep continuity and impaired NK cell function. Conversely, insomnia elicits physiological responses similar to those seen in stressful situations. Sleep helps increase growth hormone and testosterone levels, while reducing metabolism and blood flow as a defense against stress. In a state of insomnia, cortisol, heart rate, central temperature, and oxygen consumption are increased, as well as glucose tolerance and cytokine levels. Sleep deprivation increases ghrelin (hunger hormone) and decreases leptin (satiety hormone), further exacerbating appetite. The existing evidence strongly suggests a close connection between stress and sleep. Stress induces psycho-physiological responses and activates the HPA system, which is incompatible with normal sleep.[2] Similarly, insomnia perpetuates a vicious cycle of stress and insomnia by further activating the HPA system.

INSOMNIA AND HOMOEOPATHY

According to a study, the prevalence rates of complementary and alternative medicine (CAM) varied widely, ranging from 5% to 74.8%. Homoeopathy and acupuncture were found to be more commonly used in German-speaking countries. Among the general population, chiropractic manipulation, herbal medicine, massage, and homoeopathy were the most frequently utilized CAM therapies, excluding spiritual prayer. Factors such as sex, age, and education were found to be predictors of CAM utilization, with higher usage among women, middle-aged individuals, and those with higher education levels. The most common ailments associated with CAM utilization included back pain, depression, insomnia, severe headaches or migraines, and gastrointestinal illnesses. Medical students tended to be more critical of CAM compared to students in other professions such as nursing and pharmacy.[23] CAM interventions have been increasingly studied for the treatment of sleep disorders.[21] A systematic review examined various CAM modalities, including herbal and nutritional medicine, acupuncture, acupressure, yoga, tai chi, massage, aromatherapy, and homoeopathy. Randomized controlled trials (RCTs) comparing homoeopathic medicines to placebo were limited and involved small patient numbers. However, some studies showed a trend favoring homoeopathic medicines, and a cohort study reported significant improvements from

baseline. An individual case study highlighted the detrimental effects of insomnia on multiple aspects of life and indicated that homoeopathic treatment for 3½ months restored the patient's quality of life to an optimal level, which had been diminished by chronic insomnia over a period of 10-12 years. This case study demonstrated the diverse applicability of homoeopathic remedies, as the same medicine that helped drowsy patients also proved beneficial for those who struggled to sleep, provided their symptoms matched. Overall, insomnia was shown to have a negative impact on work performance, decision-making, relationships, and overall quality of life.[22] CAM, including homoeopathy, has been explored as a potential treatment option for sleep disorders, and further research, particularly well-designed RCTs, is encouraged to evaluate the effectiveness of various CAM therapies.[24]

DISCUSSION

Insomnia caused by stress can be effectively prevented and managed by implementing healthy lifestyle habits. The management of daily life should address both mental and physical aspects, taking into account the comprehensive model of stress. It is important to analyze difficulties in initiating and maintaining sleep, as well as non-restorative sleep, separately, as they may be influenced by different factors in the psychosocial work environment over time. The reciprocal relationship between work stress and insomnia suggests a potential vicious cycle, highlighting the need for interventions targeting the work environment to reduce sleep difficulties and improve sleep quality. Sleep disturbances have been identified as potential causal and exacerbating factors in mood disorders.[3] Assessing and addressing sleep disturbances should be a priority in clinical practice to prevent and treat mood disorders, as they can impact neurodegenerative processes, neuroprogression, and neuroplastic adaptation. Stress-induced changes in sleep architecture can also contribute to cognitive dysfunction and psychiatric disorders. The COVID-19 pandemic has had a significant impact on the mental health of populations worldwide, leading to a high prevalence of depression, anxiety, insomnia, post-traumatic stress disorder (PTSD), and panic disorder (PD).[7] Negative family events and academic stress have been found to predict symptoms of insomnia, poor sleep quality, and lower academic performance in university students. Sleep quality, insomnia, and stress are interconnected phenomena that affect university students, with detrimental consequences for their mental health and academic performance. Research in human laboratory settings has provided strong evidence that acute psychological stress can lead to alterations in inflammation levels and the production of proinflammatory cytokines, indicating the impact of stress on the immune system and overall health.[13] Sleep plays a crucial role in regulating metabolic and hormonal processes, as well as appetite regulation. Adequate sleep duration and quality are essential for normal daily functioning. Chronic insomnia can be categorized into two phenotypes. The first phenotype is associated with physiological hyperarousal, shorter sleep duration, activation of the stress system, and significant medical complications. This phenotype tends to have a persistent course. The second phenotype is characterized by cognitive-emotional and cortical arousal, normal sleep duration, normal activity of the stress system, and a lower likelihood of medical complications. This phenotype is more likely to remit over time. Hyperarousal is a key component in modern models of insomnia disorder,[16] and stress-related cognitive-emotional reactivity can exploit the vulnerability of a highly reactive sleep system. Research on the effects of repeated stress on sleep in both males and females is limited. Studies in rats have shown that male rats exhibit behavioral and neuroendocrine habituation to repeated restraint stress over five days, while females require additional days of stress exposure to observe habituation.[20]

CONCLUSION

Excessive stress has detrimental effects on various aspects of human functioning, activating the defense system of the central nervous system. The physiological responses to stress vary depending on an individual's cognitive and psychological factors, leading to neuroendocrine and behavioral responses. Sleep is a crucial biological

process that involves numerous anatomical structures and biochemical substances. The regulation of sleep encompasses the circadian process, which determines the timing of sleep onset and offset, and the homeostatic process, which maintains the depth and duration of sleep. The HPA axis, which is activated by factors including stress and immune function, plays a role in sleep regulation. In the early stages of sleep, the activity of the HPA axis is suppressed, while in the latter part of sleep, HPA secretion activity increases. The increased activity of the HPA axis and the sympathetic nervous system influence the occurrence of rapid eye movement (REM) sleep. Components of the immune system, such as IL-1β, are also involved in the homeostatic regulation of sleep. IL-1β participates in an immune-regulating feedback loop that activates the HPA axis. Stress-related insomnia creates a vicious cycle by further activating the HPA system. As the response to stress and the development of insomnia vary from person to person, individualization is a fundamental principle in homoeopathy. Therefore, adopting a homoeopathic individualistic approach will be crucial in the treatment of stress-induced insomnia cases. By tailoring treatment to the unique needs of each individual, homoeopathy aims to address the underlying causes of insomnia and promote better sleep and overall well-being.

FUTURE DIRECTIONS

The bi-directional relationship between sleep and stress highlights the importance of addressing both aspects to improve overall health and well-being. To effectively manage stress-induced pathologies and sleep disturbances, it may be necessary to first focus on improving sleep health and implementing effective stress management strategies. Further rigorous research is needed to evaluate the effectiveness of Homoeopathy and other complementary and alternative medicine (CAM) therapies in the treatment of stress-induced insomnia. Understanding the mechanisms and effects of these therapies can provide valuable insights and potentially lead to the development of effective interventions for sleep disorders. Advancements in the knowledge of sleep-specific therapies and specialized interventions hold great potential for reducing the significant financial and emotional burdens associated with stress and trauma exposure. By developing targeted interventions that address sleep disturbances and effectively manage stress, healthcare professionals can help alleviate the negative impact of these conditions on individuals, their families, and society as a whole. Continued research and innovation in this field are crucial for improving outcomes and promoting better overall health.

CONFLICT OF INTEREST

The author declares no conflict of interest on the entire study.

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