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The Role of Oxytocin in Maintaining Sleep Quality of Leprosy Patient: A Literature Review

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ABSTRACT

Around 80% of leprosy sufferers complain of pain that affects sleep quality and mental health, which has an impact on insomnia. Several factors impair the quality of life in leprosy, including skin lesions and social stigma, long treatment duration, leprosy reactions, disability, mental disorders, and chronic neuropathic pain complications The broad impact of leprosy on aspects of patients' lives has increased attention to the role of oxytocin which has an influence on many target organs. Oxytocin is a hormone that plays a vital role in various physiological and psychological processes in the body. Recent studies have shown a potential relationship between blood oxytocin levels and sleep quality. Improvement of sleep quality by oxytocin is related to inhibition of the HPA axis, melatonin, and orexin secretion. Besides that, social relation and emotional improvement also attributed to oxytocin's anxiolytic, anti-depressant, and tranquilizing effects as well as improved emotional stability. Oxytocin also affect smooth and skeletal muscle activity, as well as muscle condition in preparation for sleep.

Keywords: plasma oxytocin levels, multibacillary leprosy, sleep quality

INTRODUCTION

Leprosy is a disease that is feared because of the complications and disruption of quality of life it causes (Reis et al., 2013). Around 80% of leprosy sufferers complain of pain that affects sleep quality and mental health, which has an impact on insomnia (Alkan Melikoglu and Celik, 2017). Until now, no study has specifically assessed sleep quality in leprosy patients. The broad impact of leprosy on aspects of patients' lives has increased attention to the role of oxytocin which has an influence on many target organs. Oxytocin is a hormone that plays a vital role in various physiological and psychological processes in the body. Recent studies have shown a potential relationship between blood oxytocin levels and sleep quality, especially in patients with chronic pain (Doerr et al., 2022). Oxytocin has been found to be involved in regulating stress and anxiety responses, both of which can significantly affect sleep quality and contribute to chronic pain conditions (XH Li et al., 2021).

This means that, understanding oxytocin is important and it can be used to detect sleep disorders in leprosy patients. This understanding is expected to lead other researchers further to show oxytocin's role in sleep management.

DISCUSSION

ANATOMY AND PHYSIOLOGY OF SLEEP

Sleep is a physiological and repetitive form of reversible decreased consciousness, in which condition there is a global decrease in cognitive function so that the brain does not fully respond to surrounding stimuli (Lailiyya, 2018). In normal adults, the sleep cycle is divided into 5 phases, namely phases 1 to 4, known as Non-Rapid Eye Movement (NREM), and phase 5, called Rapid Eye Movement (REM). These five cycles can be repeated several times and a sleep period. Phases 1 and 2 are called light NREM, while phases 3 and 4 are called deep NREM, which are seen as delta waves or Slow-Wave Sleep (SWS).

The sleep-wake cycle relies on several brain areas that are widely distributed across the neural system connections. In recent years, the field has shown progress in the identification and characterization of new neuronal populations that can reveal the neurophysiological functions of sleep through selective activation, inhibition, and lesion of neuroanatomically defined neuronal subtypes that are widespread in the brain, such as GABAergic neurons and glutamatergic neurons (Fuller, Yamanaka and Lazarus, 2015; Drew, Lee and Kim, 2018).

SLEEP QUALITY

Sleep quality is a person's satisfaction with their sleep experience which includes aspects of initiation, maintenance, amount, and freshness upon awakening (Kline, 2013). Sleep quality can be divided into 4 parts of the approach as follows, namely: (Nelson, Davis, and Corbett, 2022):

a. Sleep efficiency is the ratio of the amount of sleep time compared to the amount of time the patient is in bed. Sleep efficiency of 85% or more is considered an indicator of good sleep quality, while <64% is an indicator of poor sleep quality.
b. Sleep latency is the transition time from waking to sleeping. Good sleep latency is 16 - 30 minutes, and poor sleep latency is > 60 minutes.
c. Sleep duration is the amount of sleep time curated by the time the patient wakes up during the night or throughout 24 hours. Sleep duration can vary from person to person due to activity, alcohol consumption, medication, illness, or working hours. According to The American Academy of Sleep Medicine and the Sleep Research Society, the recommended duration of sleep-in adults is >7 hours, children 13-18 years old 8-10 hours, and children aged 6-12 years should be able to sleep 9-12 hours.
d. *Wake after sleep onset* (WASO) is an objective calculation of sleep quality and focuses on the total amount of time waking up after sleep until the final time of waking up. WASO ≤20 minutes is considered good sleep quality.

The Pittsburgh Sleep Quality Index (PSQI) is an effective instrument for measuring sleep quality and patterns in adults. PSQI can distinguish “good” and “poor” sleep quality by measuring 7 components, namely: subjective sleep quality, sleep latency, sleep duration, efficiency of sleep habits, sleep disturbances, use of sleep medications, and daytime dysfunction during the last 1 month (Buysse *et al.*, 1989) (Mollayeva *et al.*, 2016).

Inadequate sleep quality is the fragmentation and interruption of sleep due to frequent and recurrent periods of nighttime wakefulness (Gofir, A., 2018). Poor sleep quality can result from systemic conditions or neurological diseases. Poor sleep quality will cause disorders in the body, such as cognitive impairment, anxiety, stroke risk, increased DM risk, depressive symptoms, and increased risk of cancer, heart disease, and weight (Davis, Ramani, and Quigg, 2020). Therefore, good sleep quality will have an impact on a good quality of life.

SLEEP DISTURBANCES IN LEPROSY

Leprosy is a disease that often reduces the quality of life. Several factors impair the

quality of life in leprosy, including skin lesions and social stigma, long treatment duration, leprosy reactions, disability, mental disorders, and chronic neuropathic pain complications (Menaldi et al., 2020). One of the impaired qualities of life is sleep quality. There is a positive correlation between pain and quality of life, with approximately 80% of patients with neuropathic pain having poor sleep quality, with female gender, pain severity, and pain duration being factors that correlate with poor sleep quality. In addition to pain, about 30% of people affected by leprosy in India experience mental health problems, especially among women, with lower education, lower socioeconomic status, and those with disabilities (Govindasamy et al., 2021). Psychiatric disorders, such as anxiety disorders and depression show a strong association with insomnia. The mechanism underlying the association between poor sleep quality and depression and anxiety is due to corticolimbic circuits that struggle with the regulation of affective reactivity (Oh et al., 2019) (Blake, Trinder, and Allen, 2018).

Treatment with oral glucocorticoids also affects sleep quality. Oral glucocorticoids are used in leprosy patients in the management of leprosy reactions in the long term (Menaldi et al., 2020). Glucocorticoid action on the suprachiasmatic nucleus (SCN) that drives sleep disturbances is due to serotonin depletion and reduced arginine vasopressin signaling in the Suprachiasmatic Nucleus (Szmyd B et al., 2021). In addition, its use can affect the diurnal cycle of cortisol release which also controls the stress response, and impacts mood and cognitive changes (Utami et al 22024).

OXYTOCIN

Oxytocin is a non-peptide hormone produced by the pituitary gland, which is well known for its role in lactation and postpartum. Oxytocin is not only a critical factor in the milk ejection reflex but also has various functions, such as regulating immunological, metabolic, and endocrine activities and many other peripheral functions as describes in figure.1 (Wang et al., 2022). Oxytocin is synthesized in magnocellular neurons located in the Supraoptic Nucleus (SO), Paraventricular Nucleus (PVN), and accessory nuclei in the hypothalamus (Sannino, Chini and Grinevich, 2017). Oxytocin is synthesized together with vasopressin and then sent to the area around the hypothalamus, encephalon, to the posterior pituitary gland, where these peptides are released into the systemic circulation. Oxytocin release can occur centrally (intracerebrally) or peripherally (in the systemic circulation). The daily cycle does not affect oxytocin level measurement due to its pulsatile release mechanism. (Van Dam et al., 2018; Kagerbauer et al., 2019).

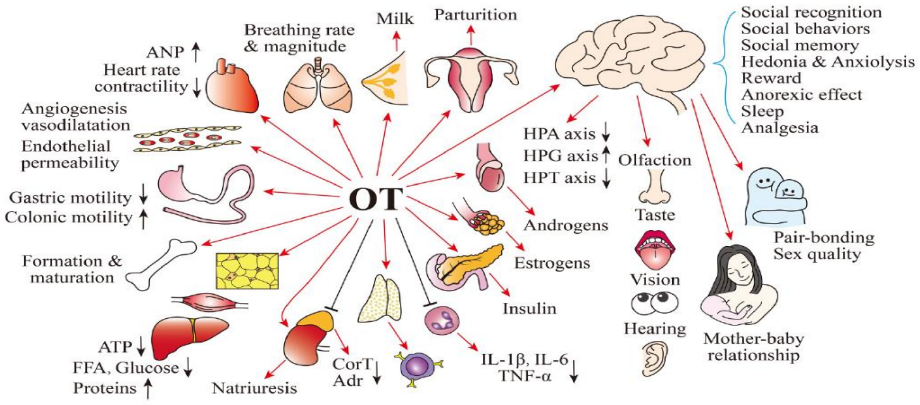

Figure 1. Summary of physiological effect of Oxytocin (OT). Abbreviations: Adrenaline (Adr), Atrial natriuretic peptide (ANP), Corticosteroids (CorT), Free fatty acids (FFA), Gonadotropin-releasing hormone (GnRH), Hypothalamic-pituitary-adrenal (HPA) axis, Hypothalamic pituitary gonad (HPG) axis, Hypothalamic pituitary thyroid (HPT) axis, Interleukin (IL), and Tumor necrosis factor (TNF)-α. (Wang et al, 2022).

OXYTOCIN ON SLEEP QUALITY OF LEPROSY PATIENTS

Oxytocin is known to be involved in nociception and pain responses. This involves both peripheral and central components. The main focus is on oxytocin neurons projecting directly into the C-type fibers of the DRG (Juif et al., 2013). In animal models, oxytocin release suppresses nociception and induces analgesia by specifically affecting inflammatory pain pathways (Eliava et al., 2016). In another study, the effects of oxytocin were mediated by its interaction with the TRPV 1 receptor, which is a receptor in the pain pathway. The ability of oxytocin to modulate pain is achieved by continuous activation of TRPV 1, resulting in decreased TRPV 1 activity through a desensitization process, thereby reducing TRPV 1-mediated inflammatory molecules (Nersesyan et al., 2017). A study by Li et al. also showed the effect of oxytocin on the Anterior Cingulate Cortex (ACC), which is the part that regulates emotional responses and sensory perception in chronic pain (XH Li et al., 2021).

In humans, oxytocin can improve sleep quality. In basal or diseased states, endogenous oxytocin facilitates sleep in postpartum women and among cancer survivors (Comasco *et al*., 2016) (Lipschitz *et al*., 2015). In animal experiments, sleep deprivation triggers an increase in oxytocin release at the Supraoptik nucleus, as an antagonist of wakefulness-provoking factors (Knöchel, Frickmann and Nürnberger, 2021). The sleep-wake cycle is related to the dynamics of activation and inhibition of neurotransmitters in the forebrain, which is regulated by the rhythmic release of hormones such as melatonin, cortisol, and orexin (Koop and Oster, 2022). Improvement of sleep quality by oxytocin is related to inhibition of the HPA axis and melatonin secretion (Teclemariam-Mesbah et al., 1997; Bülbül et al., 2011). The hormone orexin which functions in feelings of satiety, fear, as well as the wake-sleep cycle thus causing wakefulness, and by inhibition of oxytocin release in the paraventricular nucleus. (Maejima *et al*., 2017)

The effects of oxytocin are also attributed to oxytocin's anxiolytic, anti-depressant, and tranquilizing effects as well as improved emotional stability as shown in postpartum women (Comasco *et al*., 2016). As an emotion regulator, oxytocin also innervates the *mammillary body* complex which participates in the emotion, memory, emotion and regulation of sleep, thus, oxytocin may modulate sleep by modulating *mammillary body* cell activity (Liao *et al*., 2020).

Oxytocin can also affect smooth and skeletal muscle activity. In clinical trials of Obstructive Sleep Apnea (OSA) patients, Intranasal Oxytocin can increase respiratory rate and reduce the duration of obstructive events and oxygen desaturation by increasing upper airway muscle tone to the tongue and increasing the sensitivity of the chemoreflex so that the apnea condition stops immediately (Jain *et al*., 2017, 2020). Research by Joel et al, on intraperitoneal administration of oxytocin to mice, showed the effect of oxytocin causing *quiet-wakefullness* (Raymond *et al*., 2023). This is a state where the mice keep their eyes open with their body in a sleep-like position, without any movement. This shows the role of decreasing physical activity that usually occurs in sleep preparation conditions due to an acute increase in exogenous oxytocin, while maintaining alertness. (Mahalati *et al*., 1991; Raymond *et al*., 2023)

CONCLUSION

To date, no studies have specifically evaluated sleep quality in leprosy patients. The widespread impact of this disease on patients' lives raises attention to the importance of understanding the role of oxytocin in the effects of various organs. Several studies have provided information on how oxytocin can affect pain perception, sleep quality, mood, and social interactions. Therefore, research is needed that can identify differences in blood oxytocin levels in relation to sleep quality in leprosy

patients. Thus, understanding oxytocin can be increased and used to detect sleep disorders in leprosy patients. Hopefully, this knowledge can motivate other researchers to further explore the role of oxytocin in sleep management.

Declaration by Authors

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