Proceedings of the 3rd International Conference on Biological Engineering and Medical Science
DOI: 10.54254/2753-8818/22/20230932

Research on the symptoms, causes, and available treatments of narcolepsy

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Abstract. The classic tetrad of hypnagogic hallucinations, cataplexy (sudden bilateral loss of muscle tone), excessive daytime sleepiness, and sleep paralysis characterizes narcolepsy, a chronic sleep disorder. Narcolepsy affects 0.05 percent of the population. It lowers the quality of life for those who have it and can prevent them from engaging in certain occupations and pastimes. Therefore, this paper focuses on the symptoms, causes, and available treatments of narcolepsy. Through literature reading and analysis, it can be concluded that narcolepsy with cataplexy is caused by disruptions in signals within the central nervous system and a lack of hypocretins. There is currently no known cure for narcolepsy, and medication along with lifestyle modifications is the basis of therapy. Moreover, several innovative therapies are being created and tested.

Keywords: narcolepsy, cataplexy, hypocretins, deep brain stimulation (DBS), MCH receptor antagonists, cognitive-behavioral therapy.

1. Introduction

Narcolepsy is a lifelong, severely handicapping condition of rapid eye movement (REM) sleep [1]. The characteristic tetrad of hypnagogic hallucinations, sleep paralysis, cataplexy, and severe daytime sleepiness with uncontrollable sleep episodes characterizes it. Narcolepsy impacts school and work functioning, driving, interpersonal relationships, and quality of life. The goals are to help patients with narcolepsy receive a proper diagnosis and to offer clinical management advice, including information on the use of psychostimulants and their safety, as well as the indications for their use and the best antipsychotic medications. This article discusses how to treat narcolepsy, its causes and symptoms, and how to alleviate its negative effects on daily living.

2. Causes and symptoms of narcolepsy

From a neurological perspective, the brain activity in individuals with excessive daytime sleepiness differs significantly from that of normal individuals. The electroencephalogram (EEG) of individuals with EDS displays a more relaxed brain state than the wakeful state observed in normal individuals [2].

First, research on the abnormal function of the brainstem suggests that narcolepsy may be associated with dysfunction within this area [3].The brainstem is one of the major regions that controls sleep and wakefulness states. Activation of the brainstem can promote wakefulness, while inhibition can induce sleep.

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Second, the visual and circadian rhythms in the hypothalamus perform an essential part in regulating sleep. Vision plays a crucial role in wakefulness. Light enters the hypothalamus through the optic nerve, which can promote wakefulness and inhibit sleep, thus allowing for the normal switch between wakefulness during the day and sleep at night.

Third, dopamine is a neurotransmitter that plays a role in regulating attention, movement, emotions, and pleasure. Narcolepsy may be associated with changes in the degradation pathway of dopamine, leading to a decrease in dopamine levels and affecting the maintenance of wakefulness.

Forth, the DMN is a system of connected brain areas that show increased activity when a person is not focused on what is happening around them, as shown in Figure 1.

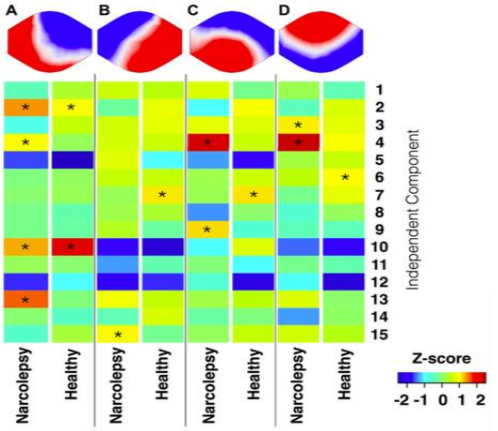

Figure 1. Temporal correlation of EEG microstates and functional magnetic resonance imaging (fMRI) RSNs.

Results of the temporal sorting of the RSNs using the time courses of the four EEG microstates. Results are stratified in terms of microstate and study group, with results for the narcolepsy patients and controls displayed separately. The temporal sorting regression coefficients are displayed in terms of Z-scores. *Indicates a temporal correlation with a Z-score >1 [3].

Fifth, narcolepsy with cataplexy is caused by a lack of hypocretins, key brain chemicals that help sustain alertness and prevent REM sleep from occurring at the wrong times [4]. Hypocretins are released during wakefulness and increase activity in target neurons that promote wakefulness and suppress rapid-eye-movement (REM) sleep. In people who have narcolepsy with cataplexy, most of the hypocretin-producing neurons die off, as shown in figure 2, the patient has much less hypocretins in the brain, resulting in poor control of REM, which may result in reduced or inconsistent activity in these target neurons [4].

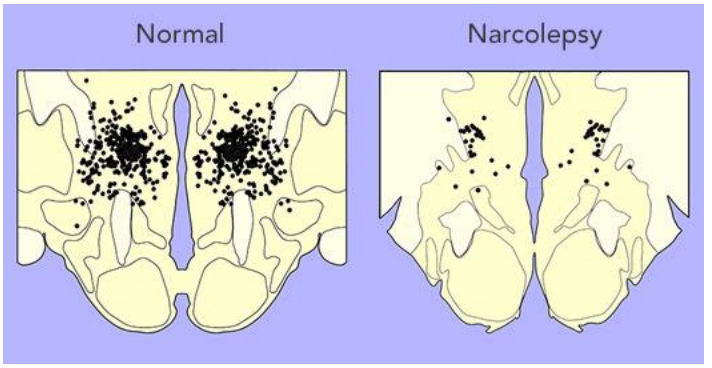

Figure 2. The number of hypocretin-producing neurons in the brain is markedly reduced in the brains of people with narcolepsy [4].

An essential first step in correctly diagnosing and treating this persistent and sometimes crippling sleep disease is to understand the symptoms of narcolepsy.

The clinical symptoms of narcolepsy include:

First, excessive sleep, the symptom of being unable to get enough sleep no matter how much one sleeps.

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Second, patients often experience excessive daytime sleepiness regardless of the situation, with varying degrees of irresistible sleep onset, which leads to a worsening of the quality of their awakeness.

Third, sleep inertia, i.e., after regular sleep or a nap, is a period of time where certain functions may be impaired or alertness lowered upon awakening.

Forth, patients with narcolepsy usually fall asleep quickly, but they may experience difficulty awakening in the morning and sometimes appear to be confused, which is indicative of sleep inertia (or sleep drunkenness), a state of diminished alertness transitioning from sleep to wakefulness.

In addition, some patients with narcolepsy have a normal main sleep cycle (6-9 hours), but their characteristic symptom is several unintentional daytime naps, which may be relatively long but nonrestorative. Some individuals with narcolepsy have a family history of the disorder and also exhibit symptoms of autonomic nervous system dysfunction, such as recurrent vascular headaches, abnormal peripheral vascular responses.

3. The treatment of narcolepsy

Currently, the treatment methods for narcolepsy can be mainly divided into medication therapy and non-medication therapy, which will be introduced separately below.

3.1. Medication therapy

A. Modafinil.

Current research shows that the main mechanism of action of modafinil is to increase the levels of neurotransmitters such as dopamine, norepinephrine, and glutamate, thereby improving wakefulness and attention and alleviating symptoms of narcolepsy. Modafinil primarily acts in multiple regions of the brain, including the hypothalamus, amygdala, brainstem, and cortex. Its wake-promoting ability in the hypothalamus is widely considered to be the core mechanism by which it improves symptoms of narcolepsy. In addition, modafinil may also increase the activity of neurotransmitters such as norepinephrine and dopamine, and increase glutamate concentration by inhibiting the activity of glutamate transferase.

Modafinil can improve symptoms of narcolepsy, and increase wakefulness and attention. A daily dose of 200-400mg of modafinil can usually help improve wakefulness with good tolerability. It can reduce the frequency and duration of sleep attacks and daytime napping in patients with narcolepsy [5].

B. Amantadine

The specific mechanism of action of Amantadine is not clear, but it may affect the dopamine levels in the central nervous system, inhibit glutamate release, and affect activity of sodium channels. In the treatment of narcolepsy, Amantadine has been found to be less effective compared to modafinil.

3.2. Non-pharmacological therapies

A. Pulsed light therapy.

This therapy uses light of specific wavelengths and pulse intensities to irradiate the patient's eyes, adjusting the patient's biological clock to improve symptoms of narcolepsy and quality of life. Pulsed light therapy can increase the body's sensitivity to periodic light signals, synchronizing the patient's biological clock with the 24-hour day-night rhythm. Trials targeting narcolepsy have shown that after pulsed light therapy, patients had an increase of approximately 20 minutes in their continuous sleep time, and a decrease in fatigue during the evening [6].

B. Cognitive-behavioral therapy.

Cognitive Behavioral Therapy (CBT) is one of the psychological treatment methods that aims to improve the mental and physical health of patients by changing unhealthy patterns of thinking and behavior. When treating narcolepsy, cognitive behavioral therapy typically involves the following two aspects:

1) Sleep habit changes: the treatment objective of this aspect is to increase the quality and quantity of sleep by cultivating healthy sleep behaviors, including adjusting the time of sleep and waking up, maintaining a quiet, comfortable, and dark sleep environment, reducing activities in bed, etc. [7].

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2) Cognitive restructuring: the treatment objective of this aspect is to help patients alleviate anxiety and worry and improve sleep quality by identifying and changing unhealthy sleep concepts and beliefs and correcting unhealthy cognitive patterns. For example, through cognitive training, patients can change their views and expectations about sleep, their unreasonable expectations and excessive worries about sleep, reducing negative emotions and stress related to sleep [8].

The researchers intervened with CBT on 164 elderly people, and the results showed that after one year of CBT treatment, the participants' sleep time, sleep efficiency, and anti-anxiety ability were significantly improved).

3.3. Lifestyle adjustments

Narcolepsy patients can make lifestyle adjustments to enhance treatment efficacy. The following are specific measures regarding lifestyle adjustments for the treatment of narcolepsy.

A. Maintaining a balanced and regular diet, with smaller meals spread throughout the day and avoiding overconsumption of alcohol and unhealthy eating habits. Studies have shown that increasing the intake of magnesium and vitamin B12 can serve as an adjunctive treatment for narcolepsy by improving sleep quality and relieving negative emotions in narcolepsy patients.

B. Moderate-intensity aerobic exercise, such as brisk walking, jogging, swimming, and so on, is particularly effective in improving sleep. These exercises can stimulate the body to produce hormones such as dopamine, and reduce harmful stress hormones such as cortisol, further reducing anxiety and tension and enhancing the body's immunity [8] .

C. Proper use of relaxation techniques such as meditation, deep breathing, etc. can effectively relieve stress and anxiety, thereby improving sleep quality [7]. Multiple studies have shown that meditation can lower stress levels, relieve anxiety, and have a certain alleviating effect on sleep disorders [8] .

Although non-pharmacological therapies have certain advantages, such as improving self-management abilities and helping to adapt to the external environment, they also have some limitations. Therefore, although lifestyle changes are an effective adjunctive treatment method, they cannot fully replace the importance of drug treatment and behavioral therapy. A comprehensive approach using a variety of treatment methods can better help control narcolepsy symptoms and improve patients' quality of life [8] .

4. New research and treatment plan

Currently, research on treating narcolepsy with deep brain stimulation and MCH receptor antagonists is still relatively limited, and further research and validation are needed.

A. Deep Brain Stimulation (DBS) is a surgical treatment method that involves implanting electrodes into specific regions of the brain to produce high-frequency electrical stimulation, which can affect the neural excitability of different brain areas and produce therapeutic effects for certain diseases. DBS is widely used to treat conditions such as Parkinson's disease, Tourette syndrome, epilepsy, and is currently being explored for use in treating narcolepsy.

Specifically, DBS may have the following effects:

1) Regulating the normal arousal pathway: DBS may regulate the normal arousal system, including the activity of the thalamus, brainstem reticular formation, and other related neural areas, thereby enhancing brain alertness and attention.

2) Regulating neurotransmitter levels: DBS may increase levels of neurotransmitters such as dopamine, norepinephrine, and serotonin in the brain, which are associated with arousal and wakefulness.

3) Regulating the sleep-wake cycle: DBS may regulate regions of the brain associated with the sleep-wake cycle, thereby helping to restore the biological rhythm and improve sleep quality [9].

B. MCH receptor antagonists are a novel type of drug that can be used to treat narcolepsy.

MCH is a neuropeptide that can regulate physiological processes such as appetite and sleep. Existing data suggest that MCH may be a key factor in the pathogenesis of narcolepsy because it can suppress activity in the brain's sleep center, leading to a state of drowsiness.

MCH receptor antagonists primarily act on MCH receptors by blocking the binding of MCH to its receptors to exert therapeutic effects. Specifically, MCH receptor antagonists can alleviate narcolepsy symptoms, improve alertness and quality of life in patients. Additionally, it can also improve negative emotions and cognitive functions such as depression, anxiety and memory impairments.

MCH receptor antagonists are currently produced through chemical synthesis and undergo preliminary clinical and animal testing confirmation. However, more research is needed to confirm the efficacy and safety of MCH receptor antagonists in the treatment of narcolepsy [10].

Overall, research on the use of deep brain stimulation and MCH receptor antagonists to treat narcolepsy is still in the exploratory stage and further studies are needed to demonstrate their treatment potential and safety.

5. Conclusion

In conclusion, the causes, symptoms, and techniques of narcolepsy therapy are discussed in this article. Rapid eye movement sleep disorder narcolepsy is a chronic, profoundly disabling illness that greatly affects work, study, and quality of life, and has a profound impact on the physical and mental health of patients. Medication therapies, non-pharmacological therapies, and lifestyle adjustments can be done to alleviate the symptoms, but they also have their own advantages, disadvantages, and applicability. Therefore, in the specific treatment process, various factors must be considered comprehensively based on the patient's specific situation to achieve the best treatment results. Although there has been great progress in the treatment of narcolepsy, it still faces many unknowns. Future research and treatment should focus more on deepening the understanding of the pathogenesis of narcolepsy and developing more targeted, effective, and safe treatments.

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