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Narcolepsy: Identifying its Causes and Assessing Novel Therapeutic Targets

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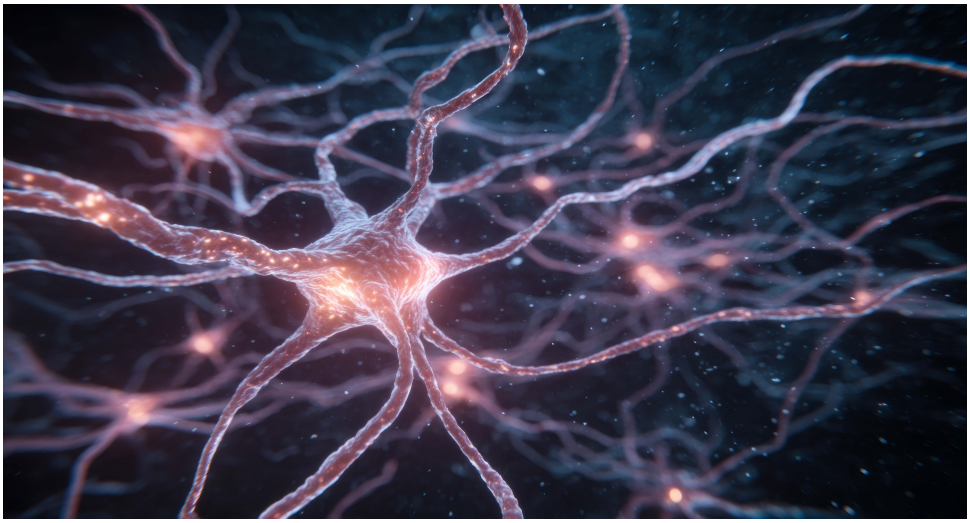

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Abstract

Narcolepsy is a dysfunction of the orexin neurons commonly associated with excessive sleepiness and cataplexy, which is characterized by the abrupt loss of muscle control. Two types of narcolepsy exist. Type 1 narcolepsy is narcolepsy with cataplexy, while Type 2 narcolepsy is associated with the same drowsiness as Type 1 narcolepsy, but no cataplexy is observed. There has been substantial research into the causes and development of narcolepsy, with current hypotheses focusing on both genetic expression and competition, as well as dysfunction in the hypocretin (HCRT) system. Orexin neuropeptides within this system regulate the sleep-wake cycle; therefore, abnormal production of these peptides may lead to narcolepsy. The aim of this paper is to examine the mechanisms underlying narcolepsy in order to provide a comprehensive evaluation of current and emerging treatments.

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1. Introduction

According to a 2023 report by Medical News Today[1], an estimated 150,000 to 200,000 individuals in the United States have been diagnosed with narcolepsy. However, these numbers are difficult to pin down for two reasons: narcolepsy is easily misdiagnosed as a side effect of other disorders, and many patients refrain from seeking treatment. Narcolepsy is a sleep disorder caused by low hypocretin levels, which are associated with excessive drowsiness and cataplexy. There are a variety of risk factors outlined by the National Institute of Health[2], ranging from genetic mutations to autoimmune disorders, that lead to the low hypocretin and orexin levels that cause narcolepsy.

The first description of narcolepsy appeared in 1877 as "sleepiness" and "episodes of muscle weakness triggered by excitement" in reports by German scientists Westphal and Fischer[3]. These early descriptions were followed by more than 150 years of research into the development and treatment of narcolepsy. In 1930, researchers proposed that lesions in the posterior hypothalamus were responsible for the condition, shifting the focus of subsequent studies toward neurological causes rather than external ones.[4]

Later, in 1957, a team of scientists developed imipramine, a pharmacological treatment utilizing a dual stimulant/antidepressant formula, which is still prescribed today.[5]

In current society, narcolepsy remains a neurological disorder that requires continued research. The economic burden on those affected alone justifies the need for more efficient and cost-effective care. A study by the National Institute of Health found that "annual direct medical costs are approximately twice as high in patients with narcolepsy as in controls without this condition ($11,702 vs. $5,261)."[6] More recent studies showed that dysfunction of the orexin neuron is associated with other conditions, such as addiction and eating disorders. Thus, further study of narcolepsy may also advance treatment and developments in those fields.[7]

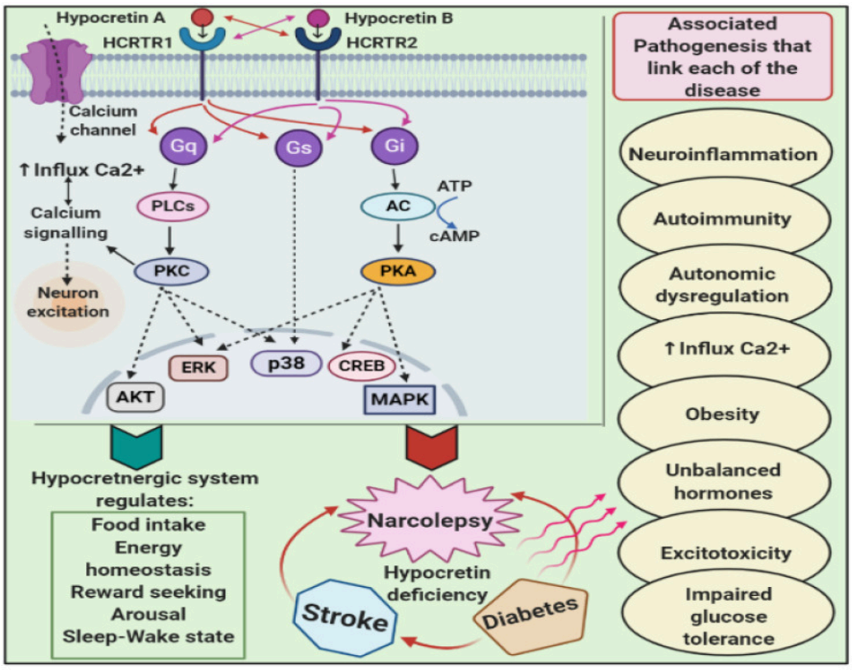

Figure 1: Demonstrates the physiological function of the hypocretin neurotransmitters and the relationship between narcolepsy and other medical conditions affected by the hypocretin system.

2. Types of Narcolepsy

It is estimated that about 200,000 Americans and 3 million people worldwide are affected by narcolepsy, but only 25% of those affected by narcolepsy are diagnosed and receiving treatment. Type 1 narcolepsy is characterized by excessive daytime sleepiness (EDS) combined with cataplexy. In its most extreme form, Cataplexy refers to a condition in which an abrupt loss of muscle tone causes an individual to collapse. However, on a less severe scale, it may present as a slack jaw. Type 2 narcolepsy shares similar symptoms with Type 1, except that cataplexy is typically absent.

There are ultimately three recognized types of narcolepsy. The first is narcolepsy with cataplexy, which involves the characteristic sudden loss of muscle tone or control, often triggered by strong emotions. Symptoms can range from mild weakness to a complete body collapse.

The second is narcolepsy without cataplexy, which is marked by persistent EDS without the muscle weakness associated with cataplexy. Due to the absence of this hallmark symptom, it can be more challenging to diagnose. The third type is secondary narcolepsy, which results from direct injury to the hypothalamus, a deep-seated brain structure that regulates sleep, wakefulness, and other functions. Such injuries often lead to a more severe form of narcolepsy, accompanied by additional neurological issues and significant sleep disturbances. Each type presents unique challenges and may require different approaches to management and treatment.

3. The Pathophysiology of Narcolepsy

Hypocretin is an excitatory neurotransmitter that plays a crucial role in regulating sleep and arousal states. These neurotransmitters bind to HCRT receptors in the posterior hypothalamus and serve an excitatory and facilitatory role in gamma-aminobutyric acid (GABA) and glutamate-mediated neurotransmission. Across different medical literature, these neurotransmitters are referred to by various names—orexin, hypocretin, or HCRT—depending on the source.

For clarity, this paper will strive to maintain consistency by referring to the neurotransmitter associated with narcolepsy as hypocretin, while preserving the original language in directly cited sources.

Orexin neuropeptides are responsible for signaling in the HCRT system. These neuropeptides interact with orexin receptors to regulate circadian rhythms—not only maintaining the distinction between sleep and wakefulness, but also managing the REM cycle. A study in *Sleep*[6] details the oscillation between phasic states—characterized by brief, orexigenic neuronal excitation—and tonic states, which uphold continuous conscious awareness. For individuals with narcolepsy, fluctuations in orexigenic neural firing interrupt the tonic state, leading to loss of muscle tone and sudden onset of sleep.

Ever since the discovery of narcolepsy, scientists have proposed different possible pathophysiological causes of the condition. The autoimmune hypothesis proposes a link between infection and the

loss of HCRT neurons, but studies have shown no significant evidence to support this claim. The most widely accepted theories explaining the cause of HCRT-orexin fluctuation discuss external stimuli and genetics. The concept of external stimuli overwhelming the central nervous system is a theory that has been circulating ever since some of the earliest recorded cases of narcolepsy, where moments of excitement or stress immediately preceded cataplectic attacks.

More recent studies involving HCRT neuron-ablated mice and humans with narcolepsy have shown a correlation between the condition and the presence of the QRFP gene. These studies suggest that the HCRT and QRFP genes may compete for transcription factors.[7] Because of this competition, there is indication that the HCRT gene and the QRFP gene colocalize, meaning that they overlap, and the tissues expressed by these genes "codistribute in proportion to one another within and between structures".[8]

This is a potential hypothesis for the cause of narcolepsy: if the QRFP gene can outcompete the HCRT gene, then the orexin neuropeptides will not be produced at the rate needed to maintain wakefulness, and narcolepsy will ensue.

The HCRT gene specifically is a specific target of some research, and researchers have proposed that DNA methylation and histone modification are responsible for HCRT gene silencing and promotion. The HCRT gene was found to have 13 CpG sites.[11] CpG sites describe areas of DNA where cytosine is directly followed by guanine. These sites are the most common sites affected by DNA methylation.

DNA methylation is a heritable epigenetic mark involving the covalent transfer of a methyl group to the C-5 position of the cytosine ring of DNA by DNA methyltransferases.[12] Through DNA methylation, the expression of the HCRT gene shifts, causing fluctuations in hypocretin production, and thus causing narcolepsy.

4. Current Treatments for Narcolepsy

Current pharmacological treatments for narcolepsy include FDA-approved medications such as Modafinil and Armodafinil. These are used to stimulate the central nervous system to preserve wakefulness.

There are several benefits and disadvantages of this medication. On the positive side, it effectively promotes wakefulness and is associated with minimal side effects in most patients. However, clinical trials have shown that modafinil can produce euphoric and psychoactive effects, which may increase the risk of addiction. Another drawback is that by solely stimulating the central nervous system, the medication addresses the symptoms rather than the underlying cause of narcolepsy.

5. Future Therapies of Interest

5.1 Smart Neurofeedback System

The Smart Neurofeedback System (SNS) is a therapy that aims to intertwine the potential of orexin hormone therapy with cutting-edge technology.

SNS employs biofeedback to help patients gain control over their sleep-wake cycles, using a wearable device that both detects sleep episodes and administers medication at just the right moment. In biofeedback training, patients undergo biofeedback sessions where they learn to monitor and influence their physiological states. Through EEG-based neurofeedback, they gain more control over their sleep-wake cycle by altering brain wave patterns associated with alertness and relaxation.

A wearable device could be developed to detect the onset of sleep episodes and provide gentle, non-disruptive cues to the user to help maintain wakefulness during the day. At night, it could use different stimuli to promote sound sleep. For targeted medication management, we could integrate a smart medication delivery system within the wearable that releases medication based on the user's

physiological data. This approach may optimize timing and dosage, reduce side effects, and enhance the overall effectiveness of narcolepsy treatments.

5.2 Genosync Therapy Program

Gene therapy for narcolepsy is a theoretical approach to treat narcolepsy at the molecular level. Although the therapy is still in the preclinical phase, it shows great promise as a personalized treatment for narcolepsy.

By genetically profiling each patient, scientists and healthcare professionals can tailor gene therapy to address the specific genetic variances contributing to narcolepsy. In genetic profiling, patients undergo comprehensive genetic testing to identify specific genetic markers associated with narcolepsy, particularly those affecting the hypocretin (orexin) system. Personalized gene therapy strategies involve optimizing viral vector platforms for hypothalamic delivery. By tailoring the vector to the patient's genetic architecture, scientists can effectively supplement or restore the physiological activity of hypocretin-producing neurons. This precision medicine approach aims to address the root cause of narcolepsy in patients.

Researchers could also investigate non-invasive methods for delivering the gene therapy directly to the brain, such as focused ultrasound or intranasal delivery systems, minimizing risks associated with traditional neurosurgical approaches.

5.3 Gaba(b) Modulation

JZP-258 is a drug designed to modulate the GABA(b) receptor, specifically by targeting its allosteric site. This modulation in the central nervous system inhibits neural signals that may otherwise lead to cataplexy. A current treatment that holds a sizable market share is Xyrem[11], an oral drug that similarly modulates the GABA(b) receptor using sodium oxybate.

The compound name JZP-258 refers to its listing in Jazz Pharmaceuticals' proprietary database—JZP for Jazz Pharmaceuticals and 258 as its entry number. Once the compound showed promise in clinical trials, it proceeded to receive a commercial name. In Phase III trials, JZP-258 demonstrated statistically significant efficacy over placebo in treating narcolepsy symptoms, supporting Jazz Pharmaceuticals' successful FDA application in late 2020.[12]

"Preliminary data from phase III trials suggest that the low-sodium oxybate preparation JZP-258 offers a more favorable tolerability profile than sodium oxybate, especially in patients experiencing cataplexy and EDS. This study found that patients taking Xyrem reported inflamed gastrointestinal tracts and stomach problems.

6. Conclusion

The promise of future therapies opens up potential pathways for more personalized and effective interventions. Ongoing research into advancements in narcolepsy treatment also provides insights into related neurological and sleep disorders. It is an exciting time for narcolepsy research, with the anticipation that emerging therapies will go beyond traditional symptom management and move toward more precise, targeted strategies.

The lack of ongoing studies into novel narcolepsy treatments raises concerns, particularly in the event of drug shortages, which could significantly impact patient quality of life. The innovative approaches outlined in this study present a promising transition from symptom management to disease-modifying therapies, substantially decreasing the overall disease burden.

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