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Wake-promoting agents and anti-cataplectic medication

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Narcolepsy is a chronic sleep disorder characterized by excessive daytime sleepiness (EDS) and symptoms of dissociated rapid eye movement sleep such as cataplexy (sudden loss of muscle tone), hypnagogic hallucinations (sensory events that occur at the transition from wakefulness to sleep), sleep paralysis (inability to perform movements upon wakening or sleep onset), and nocturnal sleep disruption. As these symptoms are often disabling, most patients need life-long treatment. The treatment of narcolepsy is well defined, and, traditionally, amphetamine-like stimulants (i.e., dopaminergic release enhancers) have been used for clinical management to improve EDS and sleep attacks, whereas tricyclic antidepressants have been used as anticataplectics. Disruption of neurotransmission through the hypocretin/orexin (Hcrt) system, usually by degeneration of the Hcrt-producing neurons in the posterior hypothalamus, results in hypersomnia and cataplexy in narcolepsy. The cause of Hcrt neurodegeneration is unknown but thought to be related to autoimmune processes. Current treatments for narcolepsy are symptomatic, including wake-promoting therapeutics that increase presynaptic dopamine release and anticataplectic agents that activate monoaminergic neurotransmission. Sodium oxybate, sodium salt of gamma-hydroxybutyrate, is the only medication approved by the European and US that alleviates both sleep/wake disturbances and cataplexy. it is hypothesized that its therapeutic effects may occur through gamma-aminobutyric acid receptor type B-mediated effects at noradrenergic, dopaminergic, and thalamocortical neurons. These therapies are almost always needed in combination with non-pharmacologic treatments (i.e., behavioral modification). A series of new drugs is currently being tested in animal models and in humans. Animal models have also aided understanding the neurobiology of the Hcrt system, mechanisms of cataplexy, and the pharmacology of narcolepsy medications. Transgenic rodent models will be critical in the development of novel therapeutics for the treatment of narcolepsy, particularly efforts directed to overcome challenges in the development of hypocretin replacement therapy. Recent developing agent for narcolepsy include a wide variety of hypocretin agonists, melanin-concentrating hormone receptor antagonists, antigen-specific immunopharmacology, and histamine H3 receptor antagonists/inverse agonists (e.g., pitolisant). Even though current treatment is strictly symptomatic, based on the present state of knowledge of the pathophysiology of narcolepsy, we expect that more pathophysiology-based treatments will be available in the near future.

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