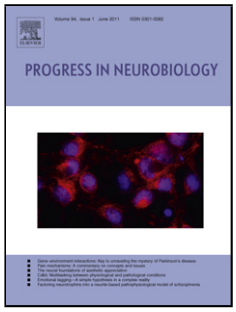

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CHALLENGES IN THE DEVELOPMENT OF THERAPEUTICS FOR NARCOLEPSY

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Highlights

- Historical perspective: narcolepsy symptoms, subtypes and diagnosis
- Comorbidities, risk factors and links with the immune system
- Discovery of hypocretins/orexins and the neurodegenerative basis for narcolepsy
- Neural circuitry of sleep, wakefulness and cataplexy
- Animal models of narcolepsy
- Pharmacotherapeutics: past, present and future
- Challenges in the development of narcolepsy therapeutics and new approaches

Abstract
Narcolepsy is a neurological disorder that afflicts 1 in 2000 individuals and is characterized by excessive daytime sleepiness and cataplexy-a sudden loss of muscle tone triggered by positive emotions. Features of narcolepsy include dysregulation of arousal state boundaries as well as autonomic and metabolic disturbances. Disruption of neurotransmission through the hypocretin/orexin (Hcrt) system, usually by degeneration of the HCRT-producing neurons in the posterior hypothalamus, results 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 is the only medication approved by the U.S. Food and Drug Administration that alleviates both sleep/wake disturbances and cataplexy. Development of therapeutics for narcolepsy has been challenged by historical misunderstanding of the disease, its many disparate symptoms, and until recently, its unknown etiology. Animal models have been essential to elucidating the neuropathology underlying narcolepsy. These 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.

Keywords
Narcolepsy, Cataplexy, Orexin, Hypocretin, Neurodegeneration, Animal models