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Pharmacologic blockade of MCH-R1 receptor reduces cataplexy and REM sleep in narcoleptic mice

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The sleep disorder narcolepsy is characterized by fragmented sleep and cataplexy and caused by a disrupted orexin signaling. Intermingled with orexin neurons in the lateral hypothalamus, there are cells producing melanin-concentrating hormone (MCH). MCH and orexin have opposite effects on sleep: MCH increases sleep, especially REM sleep while orexin decreases both NREM and REM sleep. Thus, we hypothesized that narcolepsy is a result of an imbalance between orexin and MCH system and a decrease in MCH signaling alleviates the symptoms of the disease. To study the role of MCH in narcolepsy, we used 14-16 weeks old, male, orexin neuron-deficient transgenic (TG) mice. The mice were instrumented with chronic EEG/EMG electrodes and an intracerebroventricular (icv) cannula. After 14 days recovery period, we injected the mice with the MCH-R1 antagonist Compound B (5 µg/animal, icv, Merck) or its vehicle at dark onset and recorded the sleep-wake behavior for the subsequent 24 hours. Blockade of the MCH-R1 receptor decreased the amount of cataplexy and REM sleep in TG mice. This reduction was due to a decrease in the number of cataplexy and REM sleep bouts, because the average length of these episodes remained unchanged. In addition, Compound B increased the amount of NREM sleep in TG mice during the dark phase. These results indicate that MCH plays an essential role in the initiation of REM sleep and cataplexy and suggests that these states are controlled by common neural mechanisms.