Daytime Sleepiness and Narcolepsy

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At the end of the First World War a disastrous influenza epidemic took a higher toll in human lives than the war itself. Constantin von Economo described sleep disturbances in some of the victims associated with characteristic lesions in the hypothalamus (Von Economo, 1930): hypersomnia “Encephalitis lethargica” was associated with destruction of neurons in the posterior hypothalamus comprising, as we know now, the histamine and the orexin/hypocretin neurons. There were also cases of fatal insomnia associated with lesions in the preoptic area, which contains sleep-active GABAergic neurons that inhibit the waking systems. This inhibition of the wake-active neurons is enhanced by barbiturates, benzodiazepines, ethanol and general anesthetics like propofol. The drowsiness (and weight gain) caused by antihistamines and by many drugs used in the therapy of neuropsychiatric disorders is attributed to the block of histamine H1 receptors (Lin et al., 2011). Simple daytime sleepiness such as brief sleep attacks while driving is very common and often has serious consequences. More spectacular and much rarer is narcolepsy/cataplexy, which features, in addition to irresistible daytime sleep attacks, sudden onset of REM sleep with paralysis upon waking (cataplexy) and hypnagogic hallucinations (dreams before losing consciousness) (Mignot & Nishino, 2005). Most narcoleptic patients suffer from a likely autoimmune-induced loss of orexins/hypocretins from neurons in the periventricular area of the hypothalamus. Recent experimental data suggest that both the orexin/hypocretin and the histamine systems may be affected in full-blown narcolepsy with cataplexy (Anaclet et al., 2009).

Treatment of these ailments with, e.g., amphetamines, GHB and antidepressants is so far not satisfactory (Mignot & Nishino, 2005). With the recognition of the major role of the

histamine system in waking and the widespread innervation of other systems involved in sleep-wake control it became obvious that an enhancement of histaminergic activity and the release of other transmitters, including glutamate, acetylcholine, serotonin and the catecholamines, would be an adequate strategy. This is possible through blocking the H3 autoreceptors and heteroreceptors and thus disinhibiting transmitter release. Several H3 receptor antagonists/partial agonists with a wide range of indications in neuropsychiatric disorders are on their way to the clinic at present for this purpose (Lin et al., 2011).

References

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