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GABA mechanisms and sleep.

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Abstract

GABA is the main inhibitory neurotransmitter of the CNS. It is well established that activation of GABA(A) receptors favors sleep. Three generations of hypnotics are based on these GABA(A) receptor-mediated inhibitory processes. The first and second generation of hypnotics (barbiturates and benzodiazepines respectively) decrease waking, increase slow-wave sleep and enhance the intermediate stage situated between slow-wave sleep and paradoxical sleep, at the expense of this last sleep stage. The third generation of hypnotics (imidazopyridines and cyclopyrrolones) act similarly on waking and slow-wave sleep but the slight decrease of paradoxical sleep during the first hours does not result from an increase of the intermediate stage. It has been shown that GABA(B) receptor antagonists increase brain-activated behavioral states (waking and paradoxical sleep: dreaming stage). Recently, a specific GABA(C) receptor antagonist was synthesized and found by i.c.v. infusion to increase waking at the expense of slow-wave sleep and paradoxical sleep. Since the sensitivity of GABA(C) receptors for GABA is higher than that of GABA(A) and GABA(B) receptors, GABA(C) receptor agonists and antagonists, when available for clinical practice, could open up a new era for therapy of troubles such as insomnia, epilepsy and narcolepsy. They could possibly act at lower doses, with fewer side effects than currently used drugs. This paper reviews the influence of different kinds of molecules that affect sleep and waking by acting on GABA receptors.

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