Mechanisms underlying the effects of $GABA_A$ sedative-hypnotic drugs

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The predominant inhibitory transmitter, gamma-aminobutyric acid (GABA), and its $GABA_A$ receptors play an important role in the neuronal systems regulating sleep. In particular, the most effective hypnotics, benzodiazepines (BZ) and BZ-like compounds, target $GABA_A$ receptors. However, many hypnotics display side-effects. Therefore, there is a need to develop new compounds to treat insomnia. Interestingly, the effects of $GABA_A$ receptor agonists on sleep are substantially different from those evoked by BZ or BZ-like compounds. One of our aims is to decipher in mice the mechanisms underlying the specific effects of $GABA_A$ agonists, e.g. THIP/Gaboxadol and muscimol, on behavior and the electroencephalogram (EEG).

Traditional hypnotics target synaptic $GABA_A$ receptors mediating "phasic" inhibition. We were able to demonstrate *in vivo* that THIP acts at extrasynaptic $GABA_A$ receptors mediating a non-desensitizing "tonic" inhibition in the brain. In addition, we demonstrated a relationship between regional electroencephalogram synchronization and the alteration of behavior induced by muscimol. Understanding the mechanisms underlying physiological and "pharmacological" sleep could provide a better basis to develop new compounds to treat sleep disorders, as well as to characterize their effects on the EEG and performance in human subjects.

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