Emerging role of GPR139 on sleep modulation and stress response in rodent models

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Background: We recently demonstrated that the essential amino acids L-tryptophan and L-phenylalanine, known to modulate mood and sleep, are physiological ligands for GPR139 (Liu et al., Mol. Pharmacol., 88: 911-25, 2015). GPR139 is exclusively expressed in the brain with highest expression levels measured in medial habenula and septum, and in pituitary gland in rodents and humans. The aim of the present study was to investigate the potential role of GPR139 on sleep and stress modulation in pharmacological and genetic models of GPR139 stimulation or inhibition.

Methods: EEG sleep effects of the selective GPR139 agonist JNJ-63533054 (3-30 mg/kg po) were evaluated after acute or 7-day repeated dosing in rats implanted with EEG/EMG electrodes. In GPR139 knockout (KO) and wild type (WT) littermate implanted mice, EEG sleep, locomotor activity, body temperature and plasma corticosterone levels were assessed under baseline conditions and under stress elicited by cage exchange.

Results: When acutely administered at the beginning of the light phase in rats, JNJ-63533054 dose-dependently reduced NREM latency and increased NREM sleep duration for 2h post-dosing without affecting REM sleep. This effect progressively dissipated upon repeated dosing, indicating a possibly functional desensitization of GPR139. Under baseline conditions, GPR139 KO mice spent less time in REM sleep than WT mice during the dark phase but not during the light phase. Cage exchange stress-induced hyperlocomotion, hyperthermia, EEG sleep alterations and plasma corticosterone release were not significantly different in GPR139 KO relative to WT mice.

Conclusions: Pharmacological activation of GPR139 promotes NREM sleep in rats whereas genetic inhibition of GPR139 (KO mice) has REM sleep suppressant effect. These data indicate an emerging role of GPR139 in the modulation of sleep. In a psychological stress model, physiological responses were not affected in mice lacking GPR139. GPR139 may act as a sensor to detect dynamic changes of L-tryptophan and L-phenylalanine in the brain.