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SUVN-G3031, H3 receptor inverse agonist modulates brain neurotransmitters with a role in the treatment of narcolepsy

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SUVN-G3031, a potent H3 receptor inverse agonist is being developed for the treatment of narcolepsy and other sleep-related disorders. SUVN-G3031 is one of the lead molecules with hKi of 8.7 nM and has more than 100 fold selectivity against the related GPCRs. SUVN-G3031 exhibited desired pharmacokinetic properties and brain penetration. First, in human, Phase 1 studies are completed under US IND and SUVN-G3031 has shown drug-like properties with a desirable pharmacokinetic profile, safety, and tolerability in healthy human volunteers. In the current study, SUVN-G3031 was evaluated in brain micro dialysis for evaluation of neurotransmitters like acetylcholine, histamine, dopamine, and norepinephrine in male Wistar rats. Additional neurochemical studies were carried out to evaluate the in vivo functional nature of the test compound and its effect on the tele-methylhistamine as a possible biomarker for clinical studies. SUVN-G3031 blocked R- α -methylhistamine induced water intake and produced a dose-dependent increase in tele-methylhistamine levels in rat and mice brain and cerebrospinal fluid. A single oral administration of SUVN-G3031 produced a significant increase in acetylcholine, histamine, dopamine and norepinephrine levels in the cortex. SUVN-G3031 produced no change in the dopamine levels of striatum and nucleus accumbens indicating that SUVN-G3031 may not have addiction liabilities. Results from the current studies and electroencephalographic (EEG) studies provide a strong evidence for the potential utility of SUVN-G3031 in the treatment of narcolepsy and other sleep-related disorders.

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