Potential anti-manic efficacy of a Kv3 channel modulator in a model of amphetamine-induced hyperactivity and in *CLOCKΔ19* mutant mice

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Kv3.1 and Kv3.2 voltage gated potassium channels are expressed on parvalbumin-positive GABAergic interneurons in corticolimbic brain areas, where they contribute to the ability of these neurons to fire actions potentials at high frequencies. The channels are also expressed on GABAergic neurons of the basal ganglia, substantia nigra, and ventral tegmental area where they regulate firing pattern, critical for movement control, reward, and motivation. Modulation of Kv3.1 and 3.2 channels thus may have potential in the treatment of disorders in which these systems have been implicated, such as bipolar disorder. Following the recent development of an imidazolidinedione derivative, Compound 1, which specifically increases currents mediated by Kv3.1 and Kv3.2 channels, we now report that the drug is able to reverse "mania-like" behavior in two mouse models: amphetamine-induced hyperactivity and the *Clock-Δ19* mouse. Compound 1 (10 - 60mg/kg, p.o.), administered to male CD-1 mice 30 minutes prior to a single injection of d-amphetamine (2mg/kg, i.p), completely prevented amphetamine-induced hyperactivity in a dose-dependent manner, similar to the atypical antipsychotic, clozapine (3mg/kg, i.p.). Similar efficacy was also observed in Kv3.2 knockout mice. In contrast, Compound 1 (60 mg/kg, p.o.) was unable to prevent amphetamine-induced hyperactivity in mice lacking Kv3.1 channels. Notably, Kv3.1 null mice, displayed baseline hyperlocomotion, increased reaction to novelty, and reduced anxiety. In *Clock-Δ19* mice, which contain a point mutation in the circadian gene, *Clock*, that gives rise to a persistent mania-like behavioral phenotype, a single oral dose of Compound 1 (60mg/kg, p.o.) reduced hyperlocomotion to wild-type levels. Analysis of Kv3.1 protein levels in the ventral tegmental area of *Clock-Δ19* mice found a significant increase, suggesting a possible compensation for the known increase in dopaminergic neural activity in this brain area. Taken together, these results suggest that the modulation of Kv3.1 channels may provide a novel approach to the treatment of bipolar mania.