Pharmacological activators and inhibitors of Kv3.1 potassium currents

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Kv3 potassium channels are expressed in the auditory brainstem and in rapidly spiking neurons throughout the brain, where firing at high rates with high temporal accuracy is required for sensory processing. Kv3.1 channels typically activate at positive potentials and have a very rapid rate of activation and deactivation in response to transient depolarization. We now report the first compounds to specifically modulate Kv3 channels. These compounds are imidazolidinedione derivatives, Compound 1 (AUT1) and Compound 2 (AUT2). Using CHO cells stably expressing Kv3.1 channels, we have found that 10μM AUT1 shifts the voltage of activation of Kv3.1 currents towards negative potentials such that currents are activated around -20 mV and produce a 131% increase in current at test potentials of -10mV. Numerical simulations of the firing properties of auditory brainstem neurons, predict that increasing concentrations of AUT1 would be expected to decrease firing rate in response to high frequency stimulation (400 Hz), but to increase the temporal accuracy with which actions potentials are phase-locked to the stimuli. In contrast, 10μM AUT2 produced a sustained shift in voltage-dependence of inactivation to more negative potentials after three minutes of incubation, as well as altering voltage-dependence of activation. Although Kv3.1 channels usually inactivate only very slowly during sustained depolarization, the rate of channel inactivation is also markedly increased in the presence of AUT2. Thus the net effect of this compound is to suppress Kv3.1 currents in the physiological range of membrane potentials. In numerical simulations, AUT2 had a biphasic effect on excitability. Low concentrations increased the rate of firing in response to 400 Hz stimulation whereas higher concentrations prevented neurons from responding to high-frequency stimulation, as is found in mice in which Kv3.1 has been deleted. Pharmaceutical modulation of Kv3.1 currents represents a novel avenue for manipulation of neuronal excitability, and has the potential for therapeutic benefit in the treatment of hearing disorders associated with central auditory deficits.