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Abstract:

Kv3.1 potassium channels are expressed in the auditory brainstem, where high firing rates and high

temporal accuracy are required for sensory processing. Kv3.1 channels typically activate at positive potentials and have a rapid rate of activation and deactivation in response to transient depolarization. We now report the first compounds to specifically modulate Kv3.1 channels. Compound 1 (AUT1) and Compound 2 (AUT2) are two novel imidazolidinedione derivatives. Using CHO cells stably expressing Kv3.1 channels, we have found that AUT1 (10μM) 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 in whole-cell patch clamp experiments. Consistent with the results from whole-cell recordings, single channel recordings showed that AUT1 increased the open probability of Kv3.1 channels at more negative potentials than in untreated conditions. 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, AUT2 (10μM) produced a sustained shift in voltage-dependence of inactivation to more negative potentials after three minutes of incubation, as well as altering the voltage-dependence of activation. Although Kv3.1 channels usually inactivate only very slowly during sustained depolarization, the rate of channel inactivation was 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 such as age-related hearing loss and tinnitus associated with central auditory deficits.