Pharmacological modulation of Kv3.1 potassium currents

Maile R. Brown1, Charles H. Large2, Giuseppe Alvaro2, Leonard K. Kaczmarek1
1Department of Pharmacology, Yale School of Medicine, New Haven, CT
2Autifony Therapeutics Ltd., Via Fleming 4, Verona, Italy

Kv3-family potassium channels such as Kv3.1 are typically expressed in rapidly spiking neurons and in brain regions such as the auditory brainstem, where firing at high rates with high temporal accuracy is absolutely required for sensory processing. One characteristic that distinguishes these channels from other voltage-dependent potassium channels is their very rapid rate of activation and deactivation in response to transient depolarization. In addition, Kv3 channels typically activate only at positive potentials (>-10mV). These features allow neurons to fire at high frequencies (up to ~800 Hz). Until now, manipulations of levels of Kv3 currents in neurons have required genetic manipulations or use of the non-specific potassium channel blocker tetraethylammonium ions (TEA). We now report that two imidazolidinedione derivatives, Compound 1 and Compound 2, specifically increase and decrease Kv3.1 currents respectively.
Using CHO cells stably transfected with Kv3.1, we have found that 10μM Compound 1 shifts the voltage of activation of Kv3.1 currents towards negative potentials, producing as much as a 131.3% increase in current at membrane potentials close to -10mV. Numerical simulations of the firing properties of auditory brainstem neurons, predict that increasing concentrations of Compound 1 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, the compound Compound 2 produced a sustained shift in voltage-dependence of inactivation to more negative potentials, 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 Compound 2. Thus the net effect of this compound is to suppress Kv3.1 currents in the physiological range of membrane potentials. In numerical simulations, Compound 2 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. Modulation of Kv3.1 currents represents a novel avenue for manipulation of neuronal excitability.

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