

Pharmacological modulation of Kv3 potassium channels regulates the firing of parvalbumin-positive cortical interneurons

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Abstract:

Kv3-family potassium channels are expressed by fast spiking (FS) parvalbumin (PV)-positive interneurons that represent the major class of inhibitory interneuron in corticolimbic brain circuits. The channels activate in response to transient depolarization to positive potentials during an action potential in order to initiate rapid repolarisation. Thus the channels allow FS interneurons to fire accurately at high frequency to orchestrate the activity of cortical networks. Pharmacological manipulation of FS interneurons has considerable potential for the treatment of a range of neuropsychiatric disorders. We now report that the imidazolidinedione derivative, Compound 1, specifically increases currents mediated by recombinant Kv3.1 and Kv3.2 channels expressed in cell lines. In cortical slices, Compound 1 rescues the FS phenotype of parvalbumin-positive interneurons when their activity is reduced by low concentrations of the non-selective potassium channel blocker, tetraethylammonium (TEA). In cell lines, Compound 1 increased Kv3.1 and Kv3.2 currents in a concentration and voltage-dependent manner (EC<sub>50</sub> 4.7 and 4.9  $\mu$ M, respectively). In GAD67-GFP mice, which selectively express enhanced green fluorescent protein in PV-positive interneurons, immunofluorescence studies revealed that 75% of PV-expressing cells also contained Kv3.1b in layers II-III, and IV of mouse somatosensory cortex. In deep layers (V-VI), 81% of cells expressing PV also expressed Kv3.1b. Similarly, in the deep layers, 75% of cells expressing PV also expressed Kv3.2; however, in layers II-IV, only 44% of PV-expressing cells also expressed Kv3.2. Whole-cell current clamp recording from fluorescent PV-positive cells in the deep layers of the somatosensory cortex of GAD67-GFP mice confirmed their fast-spiking phenotype. Firing frequency and action potential half-width in response to depolarizing current pulses were both reduced by application of 0.5mM TEA, consistent with partial inhibition of Kv3 channels. Application of Compound 1 (10 $\mu$ M) reversed both of these effects of TEA. These results show that pharmacological, selective manipulation of fast-firing PV-positive interneurons may be achieved with a novel class of agents that modulate Kv3 channels.

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