Inactivation of the A-type current is inhibited by ERK5 phosphorylation of Kv4.2 in PC12 cells.

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Extracellular signal-regulated kinase (ERK) 5, a member of mitogen-activated protein kinase, plays important roles in the neuronal development. In our previous studies, we demonstrated that ERK5 mediates neurite/axon outgrowth and catecholamine biosynthesis in PC12 cells and sympathetic neurons. However, the regulation of membrane excitability by ERK5 remains unclear. Thus, we examined the effect of ERK5 on Ca^{2+} and K^+ channels in PC12 cells. In order to activate ERK5 signaling selectively, ERK5 and the constitutively active MEK5 mutant were overexpressed in PC12 cells. In these cells, the gene expression of L-, P/Q- and N-type Ca^{2+} channels was not increased. In contrast, those of Kv4.2 and Kv4.3 were enhanced by ERK5 signaling. Although the protein levels of Kv4.2 were not correlated to mRNA levels, phosphorylation levels of Kv4.2 were increased by ERK5 activation. Because Kv4.2 is a pore-forming subunit of A-type K^+ channels, which play essential roles in membrane excitability, we measured the A-type K^+ current by a whole-cell patch clamp method. The electrophysiological data showed that ERK5 inhibits inactivation of the A-type current, which may be involved in the neural differentiation process by affecting membrane excitability.