Subcellular expression and neuroprotective effects of SK channels in human dopaminergic neurons.

Small-conductance Ca(2+)-activated K(+) channel activation is an emerging therapeutic approach for treatment of neurological diseases, including stroke, amyotrophic lateral sclerosis and schizophrenia. Our previous studies showed that activation of SK channels exerted neuroprotective effects through inhibition of NMDAR-mediated excitotoxicity. In this study, we tested the therapeutic potential of SK channel activation of NS309 (25 ?M) in cultured human postmitotic dopaminergic neurons in vitro conditionally immortalized and differentiated from human fetal mesencephalic cells. Quantitative RT-PCR and western blotting analysis showed that differentiated dopaminergic neurons expressed low levels of SK2 channels and high levels of SK1 and SK3 channels. Further, protein analysis of subcellular fractions revealed expression of SK2 channel subtype in mitochondrial-enriched fraction. Mitochondrial complex I inhibitor rotenone (0.5 ?M) disrupted the dendritic network of human dopaminergic neurons and induced neuronal death. SK channel activation reduced mitochondrial membrane potential, while it preserved the dendritic network, cell viability and ATP levels after rotenone challenge. Mitochondrial dysfunction and delayed dopaminergic cell death were prevented by increasing and/or...
stabilizing SK channel activity. Overall, our findings show that activation of SK channels provides protective effects in human dopaminergic neurons, likely via activation of both membrane and mitochondrial SK channels. Thus, SK channels are promising therapeutic targets for neurodegenerative disorders such as Parkinson's disease, where dopaminergic cell loss is associated with progression of the disease.