Primary or idiopathic Parkinson's disease is the second most common late-onset neurodegenerative disease, characterized by several clinical features, such as resting tremor, akinesia, depression and sleep disturbances. These symptoms are in most cases related to a-synuclein aggregation leading to a marked depletion of dopaminergic neurons in substantia nigra and by a subsequent malfunction of the nigrostriatal circuitry. Several studies showed that the complex I inhibitor rotenone reproduces features of Parkinson’s disease, including nigrostriatal degeneration. In the present study, we investigated whether the activation of K_{Ca2} channels provides protective effects against rotenone-induced neuronal death in human dopaminergic neurons that were differentiated from a proliferating mesencephalic cell line. Western blot and RT-PCR analysis clearly demonstrated that the dopaminergic neurons did not express K_{Ca2.1} channels, low amounts of K_{Ca2.2} channels and high levels of K_{Ca2.3} channels, which was similar to the expression pattern of K_{Ca2} channel isoforms in primary dopaminergic cells. In the differentiated dopaminergic neurons rotenone promoted cellular death in a dose-dependent manner, as detected by an MTT-viability assay and quantification of apoptotic nuclei. Pharmacological treatment with NS309, an activator of K_{Ca2} channels, reduced rotenone toxicity and also prevented the depletion of ATP levels. In addition, the quantitative measurements of neurite outgrowth revealed that rotenone toxicity was associated with a pronounced degradation of the dendritic network, whereas NS309 preserved the neuronal network despite the presence of rotenone. Our findings suggest that activation of K_{Ca2} channels might be an efficient strategy for the treatment of neurodegenerative disorders linked to mitochondrial complex-I dysfunction.