Inhibitory effects of 1,25-dihydroxyvitamin D₃ and its low-calcemic analogues on staurosporine-induced apoptosis

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Abstract:
The active form of vitamin D₃ and some of its related compounds show neuroprotective effects in various models of neuronal damage, however, mechanism of their anti-apoptotic action has not been elucidated. Therefore, the present study was designed to investigate the effects of 1,25-dihydroxyvitamin D₃ and its low-calcemic analogues, PRI-2191, PRI-1890 and PRI-1901 on staurosporine-induced apoptosis in human neuroblastoma SH-SY5Y cells. Twenty-four hour incubation with staurosporine (1 μM) enhanced the caspase-3 activity, decreased mitochondrial membrane potential and increased the number of apoptotic cells as visualized by Hoechst staining. 1,25-Dihydroxyvitamin D₃ and PRI-2191 attenuated the staurosporine-induced caspase-3 activity at 5, 50 and 500 nM, whereas PRI-1890 and PRI-1901 were active only at higher concentrations. Furthermore, 1,25-dihydroxyvitamin D₃ (50 and 500 nM) and PRI-2191 (500 but not 50 nM) reversed the staurosporine-evoked decrease in mitochondrial membrane potential. Hoechst and calcein staining confirmed the neuroprotective effects of the secosteroids under study. Further study revealed that a selective inhibitor of phosphatidylinositol 3-kinase (PI3-K), wortmannin, at concentration of 100 nM antagonized the effect of 1,25-dihydroxyvitamin D₃ and PRI-2191 on staurosporine-induced caspase-3 activation. These data indicate that 1,25-dihydroxyvitamin D₃ and its low-calcemic analogues at nanomolar concentrations inhibited mitochondrial pathway of apoptosis in SH-SY5Y neuronal cells, though with different potency. Moreover, the activation of PI3-K/Akt signaling pathway appears to play a role in anti-apoptotic effects of the secosteroids.

Key words:
1,25 dihydroxyvitamin D₃, staurosporine, caspase-3 activity, mitochondrial membrane potential, phosphatidylinositol 3-kinase, SH-SY5Y cells