Pharmacological Reports
2007, 59, 393–401
ISSN 1734-1140

Inhibitory effects of 1,25-dihydroxyvitamin D_3 and its low-calcemic analogues on staurosporine-induced apoptosis

Magdalena Regulska[1], Monika Leśkiewicz[1], Bogusława Budziszewska[1], Andrzej Kutner[2], Danuta Jantas[1], Agnieszka Basta-Kaim[1], Marta Kubera[1], Lucylla Jaworska-Feil[1], Władysław Lasoń[1]

[1]Department of Experimental Neuroendocrinology, Institute of Pharmacology, Polish Academy of Sciences, Smętna 12, PL 31-343 Kraków, Poland

[2]Pharmaceutical Research Institute, Rydygiera 8, PL 01-793 Warszawa, Poland

Correspondence: Władysław Lasoń, e-mail: lason@if-pan.krakow.pl

Abstract:
The active form of vitamin D_3 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 D_3 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 D_3 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 D_3 (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 D_3 and PRI-2191 on staurosporine-induced caspase-3 activation. These data indicate that 1,25-dihydroxyvitamin D_3 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 D_3, staurosporine, caspase-3 activity, mitochondrial membrane potential, phosphatidylinositol 3-kinase, SH-SY5Y cells