Involvement of PI3-K in neuroprotective effects of the 1,25-dihydroxyvitamin D₃ analogue – PRI-2191

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Abstract:
The active form of 1,25-dihydroxyvitamin D₃ prevents neuronal damage in vitro and in vivo, however, it induces also hypercalcemia and hyperphosphatemia. Side-chain-modified analogues of 1,25-dihydroxyvitamin D₃, which show low calcemic activity, may be potentially useful in the treatment of some neurodegenerative diseases. Previously, we have found that PRI-2191 more potently than 1,25-dihydroxyvitamin D₃ protects human neuroblastoma (SH-SY5Y) cells against hydrogen-peroxide-induced toxicity. In the present study, we evaluated effects of two other 1,25-dihydroxyvitamin D₃ analogues – PRI-1890 and PRI-1901 on the neuronal degeneration in the same cell model. In line with the previous study, 24-h incubation with hydrogen peroxide (0.5 mM) was toxic to cells, as evidenced by an enhanced efflux of lactate dehydrogenase into the culture medium, and these effects were prevented by PRI-1890 and PRI-1901 at concentration of 5, 50 and 500 nM. Comparing the neuroprotective effects of secosteroids, we found that all three analogues were efficient at lower concentration than 1,25-dihydroxyvitamin D₃ and among them the PRI-2191 showed the most evident concentration-dependent effect. In the second part of this study, an involvement of mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3-K), kinases which play a crucial role in neurodegenerative processes, in neuroprotective action of 1,25 dihydroxyvitamin D₃ and its the most potent analogue PRI-2191 has been investigated. The inhibitor of c-Jun N-terminal kinase (JNK)-MAPK (SP600125, 1 µM), inhibitor of p38-MAPK (SB-203580, 1 and 10 µM) and inhibitor of extracellular signal-regulated kinase (ERK)-MAPK (PD-98059, 15 and 30 µM) attenuated the hydrogen peroxide-induced toxicity. Moreover, PD-98059 (30 µM) enhanced neuroprotective effects of 1,25 dihydroxyvitamin D₃, but not that of PRI-2191. In contrast, the inhibitor of PI3-K (wortmannin, 10, 100 nM) did not affect hydrogen peroxide-induced cell damage itself, however, it significantly antagonized the effect of PRI-2191. On the other hand, wortmannin did not affect the neuroprotective effects of 1,25 dihydroxyvitamin D₃. This suggests that the activation of PI3-K/Akt signaling pathway plays an important role in the mechanism of inhibitory action of PRI-2191 on hydrogen peroxide-evoked toxicity in SH-SYSY cells. Furthermore, these data point to differential involvement of ERK-MAPK and PI3-K in neuroprotective effects of 1,25 dihydroxyvitamin D₃ and its low-calcemic analogue – PRI-2191.

Key words:
1,25 dihydroxyvitamin D₃, PRI-2191, PRI-1890 and PRI-1901, hydrogen peroxide, neurotoxicity, protein kinases, SH-SYSY cells