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Parkinson's disease (PD) is a widespread neurodegenerative disorder. Even though PD has been studied in many aspects, it is still unknown the molecular signaling mechanisms linking reactive oxygen species (ROS) and neuronal apoptosis in PD. A better understanding of cellular mechanisms that occur in Parkinson's disease is essential for development of new therapies. In this study we investigated the signaling molecules involved in neuronal apoptosis induced by 6-hydroxydopamine (6-OHDA) in human SK-N-SH neuroblastoma cells as a model cellular system. Treatment of SK-N-SH cells with 6-OHDA increased nitric oxide generation and apoptosis. N(G)-monomethyl-L-arginine (NMMA), a NOS inhibitor, prevented 6-OHDA-induced cell death. In addition, 6-OHDA also induced time-dependent phosphorylation of extracellular signal-regulated protein kinase (ERK1/2) and cyclic AMP regulatory binding protein (CREB), which was not dependent on phosphatidylinositol 3-kinase(PI3-K). Furthermore, 6-OHDA also increased Bax expression but decreased bcl-2 level. Blocking of ERK1/2 activation with the upstream inhibitor PD98059 prevented 6-OHDA-induced cell death and changes of the ratio between Bax and Bcl-2. These data suggest that ERK1/2 play an important role in 6-OHDA-induced neurotoxicity.

[PB3-2] [04/18/2003 (Fri) 09:30 - 12:30 / Hall P]

A novel potassium channel opener, KR-31378, protects cortex neurons from oxidative injury by restoring antioxidant enzyme activities and glutathione levels

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Neuronal hyperexcitability followed by high level of intracellular calcium and oxidative stress play critical roles in neuronal cell death in stroke and neurotrauma. Hence, KR-31378, a novel benzopyran derivative was designed as a new therapeutic strategy for neuroprotection possessing both anti-oxidant and potassium channel modulating activities. In the present study, we tested for its neuroprotective efficacy against oxidative stress-induced cell death in primary cortical cultures and further investigated its neuroprotective mechanism.
Incubation of cortical neurons with KR-31378 protected FeSO4-induced apoptotic as well as necrotic cell death in a concentration dependent manner. The protective effect of KR-31378 was neither mimicked by other potassium channel openers nor abolished in the presence of KATP channel blockers, indicating that its effect was not related K+ channel opening activity. The mechanism of protection is rather attributable to the antioxidant property of KR-31378 since it suppressed the intracellular accumulation of ROS and ensuring lipid peroxidation caused by FeSO4. We further studied its effect on antioxidant defense, enzymatic and nonenzymatic system. Prooxidant, FeSO4, resulted in decrease of catalase and glutathione peroxidase activities, which were restored by KR-31378 treatment. In addition, it attenuated the depletion of glutathione contents caused by FeSO4. Taken together, modulation of antioxidant enzyme activities and glutathione metabolism may contribute to the antioxidant property of KR-31378 by which it exerts a beneficial effect in oxidative stress-induced brain injury and it represents a potentially useful therapeutic agent for the ischemic brain injury

[PB3-3] [04/18/2003 (Fri) 09:30 - 12:30 / Hall P]