

PROTECTIVE MECHANISMS OF BRAIN-DERIVED NEUROTROPHIC FACTOR AGAINST 3-NITROPROPIONIC ACID NEUROTOXICITY IN RAT CORTICAL NEURONS

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We have recently demonstrated that preconditioning of cortical neurons with brain-derived neurotrophic factor (BDNF, 100 ng/ml for 8 h) attenuated neurotoxicity induced by a mitochondrial inhibitor 3-nitropropionic acid (3-NP, 2.5 mM for additional 24 h) (Wu et al., *NeuroToxicology*, 30, 718-26, 2009). Results derived from inhibitor screening indicated that the BDNF effects may involve mitogen-activated protein kinases (MAPKs), nitric oxide synthase (NOS) and anti-apoptotic gene Bcl-2. However, the detailed underlying mechanisms remain to be fully delineated. In the present study, we further characterized the signaling cascades downstream of BDNF preconditioning. BDNF induced a biphasic increase in NO formation that peaked at 1 and 4 h. Furthermore, phosphorylation of endothelial NOS (eNOS) was induced to the maximal extent at 15 min following BDNF exposure. BDNF also induced a transient increase in the expression of neuronal NOS (nNOS) at 2 h and 6 h. Expression of inducible NOS (iNOS) was, however, not observed. BDNF induced phosphorylation of Akt and extracellular signal-regulated kinase-1/2 (ERK1/2) within 5 min. Furthermore, both PD98059 and Akt inhibitor suppressed BDNF-mediated neuroprotective effects against 3-NP. PKG is a well established mediator downstream of NO. BDNF induced the expression of PKG-1 and c-Jun. Application of 8-Br-cGMP, a PKG activator independent of NO, also increased expression of c-Jun. BDNF also induced the expression of anti-oxidative thioredoxin-1 and -2 and the anti-apoptotic proteins Bcl-xL and Bcl-2. The PKG activator 8-Br-cGMP alone was sufficient to induce the expression of thioredoxin-1, -2, Bcl-xL, and Bcl-2 with or without 3-NP. Together with our previous findings, we suggest that the BDNF-mediated neuroprotective effects may involve formation of NO, induction of PKG-1 and c-Jun, and as well as the expression of the anti-oxidative thioredoxin-1/-2 and the anti-apoptotic proteins Bcl-xL and Bcl-2.

Key word:

Bcl-2, mitochondrial toxin, neurotrophin, nitric oxide synthase, thioredoxin