REVIEW OF CLINICAL PHARMACOLOGY AND
PHARMACOKINETICS INTERNATIONAL
EDITION 24: 102 (2010)

Nerve Growth Factor Receptors Mediate the Neuroprotective Effects of Neurosteroid Dehydroepiandrosterone

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Key words: Neurosteroids, neurotrophins, apoptosis, membrane receptors, cell signaling

SUMMARY

Neurosteroid DHEA is biosynthesized in neurons and glia, regulating neuronal survival and neurogenesis during development and in aging. We provide evidence that DHEA acts as a neurotrophic factor, protecting neuronal cells against apoptosis via activation of TrkA and $p75^{NTR}$, membrane receptors of neurotrophin NGF. Specifically, we have shown that siRNA against pro-survival TrkA receptors blocked the anti-apoptotic effect of DHEA and reversed its stimulatory action on anti-apoptotic Bcl-2 proteins. Radiolabeled [^{3}H]DHEA bound with high affinity to membranes isolated from HEK293 cells transfected with the cDNAs of TrkA and $p75^{NTR}$ receptors (Kds 0,9 and 5.6 nM respectively). Membrane binding of DHEA on $HEK293^{TrkA}$ and $HEK293^{p75NTR}$ transfectants was also shown with flow cytometry and immunofluoresence microscopy, using the membrane impermeable DHEA-BSA-FITC conjugate. DHEA-polyethylene-glycol beads effectively pulled down recombinant TrkA and $p75^{NTR}$ proteins, and precipitated both proteins from extracts prepared from cells expressing both receptors. DHEA was mimicking NGF in stimulating the phosphorylation of TrkA and in controlling TrkA and $p75^{NTR}$ protein levels. Furthermore, DHEA effectively activated NGF receptor-mediated signaling; Shc, Akt, and ERK1/2 kinases down-stream to TrkA receptors and TRFA6, RIP2 and RhoGDI effectors of $p75^{NTR}$ receptors. Finally, DHEA rescued from apoptosis sensory neurons of dorsal root ganglia in NGF null embryos and compensated NGF in rescuing sympathetic neurons of embryonic superior cervical ganglia. Our findings suggest that DHEA and NGF cross-talk via their activation of NGF receptors to afford brain shaping and maintenance. Phylogenetic findings on the evolution of neurotrophins, their receptors and CYP17, the enzyme responsible for DHEA biosynthesis, combined with our data support the hypothesis that DHEA served as a phylogenetically ancient neurotrophic factor.