Neuroprotective microneurotrophins: selective agonists of Nerve Growth Factor (NGF) receptors.

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Summary
Neurotrophins, like NGF, are important factors for the development and maintenance of nervous tissue. Their decline has been associated to neurodegenerative disorders. Despite the demonstrated beneficial effects, the therapeutic usefulness of neurotrophins is compromised by their polypeptide nature and their restricted penetrance to the blood-brain barrier (BBB). We have recently developed synthetic C17-derivatives of neuroprotective neurosteroid Dehydroepiandrosterone (DHEA) (Charalampopoulos et al, PNAS 101:8209-8214, 2004), shown to interact with TrkA and $p75^{NTR}$ NGF receptors (Lazaridis et al, PLoS Biol 9(4):e1001051, 2011). Derivative BNN27 does not bind to TrkB and TrkC receptors, has nor affinity for steroid receptors and is deprived of any estrogenic or androgenic effects, described for endogenous DHEA (Calogeropoulou et al, J Med Chem 52:6569-6587, 2009). Derivative BNN27 effectively displaced binding of [^{3}H]DHEA to membranes isolated from HEK293 cells transfected with the cDNAs of TrkA and $p75^{NTR}$ receptors (IC_{50}: 1.86 and 3.9 nM respectively). BNN27 dose-dependently induces TrkA tyrosine phosphorylation in the functionaly relevant tyrosine residues, affecting downstream prosurvival kinases Akt and MAPKs in primary sympathetic neurons. BNN27 induces internalization and fast return of TrkA into neuronal cell membrane in a different manner than NGF, securing higher levels of surface TrkA and potentiating the efficacy of NGF. BNN27 promotes also the interaction of $p75^{NTR}$ receptor with its effector proteins RhoGDI, RIP2 and TRAF6 (Charalampopoulos et al, Cell Reports 2:1563-1570, 2013). BNN27 effectively rescues from apoptosis NGF receptor positive sensory neurons of Dorsal Root Ganglia (DRG) in *ngf-/-* mouse embryos. Our findings suggest that synthetic, lipophilic compounds, like BNN27, may represent lead molecules to develop BBB-permeable, neurotrophin agonists with potential therapeutic applications in neurodegenerative diseases and brain trauma (Gravanis et al, Science Signaling 16:5(246):pt8, 2012). The in vivo neuroprotective efficacy of microneurorotrophins is now tested in experimental animals models of human neurodegenerative diseases.