Identifying novel neurotrophin analogs: from structural interventions to biological selectivity to promote neuroprotection and neurogenesis.

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ABSTRACT

Neurotrophins (NGF, BDNF, NT3, NT4/5) are secreted growth factors that have neuroprotective and neurogenic capacities. They exert their action by selectively binding to their respective high-affinity, pro-survival receptors TrkA, TrkB and TrkC. Furthermore, all mature neurotrophins and their pro-isoforms bind to $p75^{NTR}$ death receptor, resulting to the activation of pro-apoptotic signal transduction cascades. While these molecules have been shown to slow or prevent neurodegeneration, their reduced bioavailability and inability to penetrate the blood-brain-barrier limit their use as potential therapeutics. Our lab has previously shown that neurosteroid DHEA activates NGF receptors exerting neuroprotective and anti-apoptotic effects. Based on that finding, we have synthesized C17-spiroepoxy steroid derivatives of DHEA, named BNNs, that lack the endocrine side effects of the parent molecule. We have recently showed that BNN27 binds to and activates TrkA and $p75^{NTR}$ leading to neuroprotection.

In continuation of these findings, two sources of synthetic compounds are now screened to identify candidates of interest. The first source is a library of DHEA derivatives, designed to have increased neuroprotective action and neurotrophin receptor selectivity. The second source is a series of TrkB agonists, developed via *in silico* analysis to obtain non-peptide, small molecules with high potency and specificity. Neurotrophin mimetics were tested on neurotrophin-dependent, TrkA/TrkB/p75 expressing, cell lines, investigating receptors activation and downstream signaling, as well as cell survival. Based on biological evaluation of the compounds, we redesign structural changes and perform specific mutagenesis assays, in order to further improve their selectivity and neuroprotective actions.

The compounds that show greater survival rates and selective activation of the receptor will be further investigated for their pharmacological properties against neurodegenerative diseases, such as Alzheimer's Disease. We will test whether these molecules can ameliorate the detrimental effects of the toxic Amyloid-beta and therefore prevent neuronal cell death, behavioral defects and enhance neurogenesis.