Dimeric dipeptide mimetics of the neurotrophins NGF and BDNF: design, synthesis and pharmacological properties

Sergey B Seredenin¹, Tatyana A Gudasheva²

¹*Department of Pharmacogenetics, Federal State Budgetary Institution Research Zakusov Institute of Pharmacology, Russia,* ²*Department of Medicinal Chemistry, Federal State Budgetary Institution Research Zakusov Institute of Pharmacology, Russia*

The development of small molecule NGF and BDNF mimetics is a promising approach to overcome limitations in the use of the neurotrophin as a drug, which are poor pharmacokinetics and undesirable side effects.

We designed homodimeric dipeptide mimetics of beta-turns of separate NGF and BDNF loops (Ru Patent 2410392, 2010; US Patent US 9,683,014 B2, 2017; CN Patent CN 102365294 B, 2016). The central fragment of beta-turn was kept, and the preceding amino acid residue was substituted for by its bioisostere, C-terminal dimerization was performed using hexamethylenediamine spacer. It was shown by Western blot analysis that NGF and BDNF mimetics activate their specific receptors, TrkA and TrkB correspondingly.

The mimetic of NGF loop 4 (GK-2) and the mimetic of BDNF loop 1 (GSB-214) selectively activated AKT, and the mimetic of BDNF loop 2 (GTS-201) selectively activated ERK. Mimetics of NGF loop 1 (GK-6) and BDNF loop 4 (GSB-106) activated the both pathways. Mimetics, which activated the both cascades, were similar in their effects to the corresponding native neurotrophins. GK-6 exhibits both neuroprotective and differentiation activity and reduced the pain threshold in rats. For GSB-106, antidepressant activity characteristic of BDNF was revealed. On the other hand, GK-2, having a pronounced neuroprotective activity, did not induce differentiation and did not cause hyperalgesia, and GSB-214 and GTS-201 exhibited neuroprotective, but not antidepressant activity. None of the mimetics have influence on the body weight. Thus, the patterns of activation of the post-receptor pathways completely corresponded to the spectrum of observed pharmacological effects. The evidences, that activation of both PI3K / AKT and MAPK / ERK is necessary for the manifestation of antidepressant activity, and activating of the PI3K / AKT is essential for neuroprotection, are crucial and priority.

There were selected two the most active compounds: dipeptide mimetic of the NGF loop 4, bis-(N-monosuccinyl-glutamyl-lysine) hexamethylenediamide (GK-2) as a potential anti-stroke drug and dipeptide mimetic of the BDNF loop 4, bis(N-monosuccinyl-L-seryl-L-lysine) hexamethylenediamide (GSB-106) as a novel antidepressant drug.

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