



Dimeric Dipeptide Mimetics of Brain-Derived Neurotrophic Factor: Design and Biological Properties



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Abstract

BDNF may represent a beneficial therapeutically agent against a variety of neurological and psychiatric disorders, but bad pharmacokinetics complicate its clinical use. This article focuses on the design and BDNF-like biological properties of low-molecular weight dimeric dipeptide mimetics of BDNF free of these disadvantages.

Keywords: BDNF; GCB-106; Dipeptide; Low-molecular weight mimetic; Neuroprotection; Antidepressant-like activity

Abbreviations: TrkB: Tropomyosine-related Kinase B; BDNF: Brain-Derived Neurotrophic Factor; PI3K/AKT: Phosphatidylinositol 3-kinase/Protein Kinase B; MAPK/ERK: Mitogen-Activated Protein Kinase/Extracellular Signal-Regulated Kinase; MCAO: Middle Cerebral Artery Occlusion

Introduction

Brain-derived neurotrophic factor (BDNF) regulates the development and maintenance of the peripheral and the central nervous system predominantly through binding to the transmembrane receptor tyrosine kinase TrkB [1]. Moreover, BDNF is synthesized and released by pancreatic beta-cells and produces the insulinotropic effect [2]. Binding of BDNF with TrkB leads to the activation of various intracellular signaling pathways, including the PI3K/AKT and MAPK/ERK pathways, which are the most critical for the biological effects of BDNF [3].

BDNF is a potential therapeutic target in numerous neurological, mental and psychiatric disorders including depression [4]. However, the outcomes of several clinical trials using recombinant BDNF are disappointing [5,6] possibly because of the poor delivery and short in vivo half-life of BDNF. To address this problems, tremendous effort has been made to generate selective agonists of TrkB including peptide mimetics [7]. Bioactive BDNF exists in a form of a noncovalently linked homodimer. Each monomer contains seven beta strands connected by four hairpin loops, three of which are exposed outside (loops 1, 2, 4) and therefore may play a major role in the interaction with the receptor [8].

We designed the dimeric dipeptides based on the beta-turns of BDNF loops 1 (-D³⁰-M³¹-S³²-G³³-), 2 (-V⁴⁴-S⁴⁵-K⁴⁶-G⁴⁷-) and 4 (-D⁹³-S⁹⁴-K⁹⁵-K⁹⁶-); respectively bis-(N-monosuccinyl-L-methionyl-L-serine)

heptamethylenediamide (GSB-214), bis-(N-hexanoyl-L-seryl-L-lysine) hexamethylenediamide (GTS-201) and bis-(N-monosuccinyl-L-seryl-L-lysine) hexamethylenediamide (GSB-106) [9-11] [Ru Patent №2410392, 2010; US Patent US 9,683,014 B2, 2017; CN Patent CN 102365294 B, 2016]. The beta-turn sequences of BDNF hairpin loops were chosen as the basis of design because they are most likely to interact with the receptor due to their accessibility.

These compounds were constructed according to the uniform plan the central fragment of beta-turn was saved, and the preceding amino acid residue was substituted by its bioisostere, C-terminal dimerization was performed using oligomethylenediamine spacer. We studied the biological properties of GSB-214, GTS-201 and GSB-106. It was shown that all of them activate TrkB receptor and that they each have different post-receptor signaling patterns [10-13]. GSB-106 increased the levels of ERK and AKT kinase phosphorylation, whereas GSB-214 only increased the level of AKT phosphorylation and GTS-201 activated MAPK/ERK signaling cascade without affecting PI3K/AKT signaling.

The all dipeptides in concentrations of 10⁻⁵-10⁻⁸ M protected HT22 neuronal cells from the H₂O₂-induced oxidative stress [9,10,14]. Neuroprotective activity of the active in vitro compounds was studied in vivo in a model of ischemic stroke, induced by transient middle cerebral artery occlusion (MCAO) in rats. The dimeric dipeptides GSB-106 and GSB-214 statistically significantly

decreased infarct volumes at the treatment beginning 4 hour after surgery [15] bis-(N-monosuccinyl-L-seryl-L-lysine). GSB-106 reduced this volume by ~66% and GSB-214 by ~28%. Loop 2 mimetic GTS-201 was inactive.

An interesting observation was that GSB-106 exhibited significant antidepressant activity in the forced swimming test in mice, while GSB-214 and GTS-201 did not [9,10]. These data suggest that the both MAPK/ERK and PI3K/AKT signaling pathways are necessary for the manifestation of antidepressant activity mediated by TrkB receptors. There is literature data that describes 7,8-dihydroxyflavone (7,8-DHF), a small molecular TrkB agonist with antidepressant-like properties that provokes the PI3K/AKT and MAPK/ERK activation [16,17].

The antidepressant-like activity of GSB-106 was confirmed in a number of rodent tests [18] including forced swim test in rats and mice, tail suspension test in mice, in Nomura water wheel test in rats and in a social defeat stress model of depression in mice. Notably it is orally bioactive (0.05-5mg/kg) and is safe for chronic treatment [19,20]. GSB-106 was found to prevent stress-induced impairments of hippocampal neurogenesis [21] and stimulates hippocampal synaptogenesis [22] in mice.

Study of the antidiabetic effects (estimated from the degree of hyperglycemia and dynamics of body weight in C57Bl/6 mice with the streptozotocin -induced diabetes mellitus) of dipeptide mimetics of BDNF demonstrated [23] that GSB-214 which selectively activated PI3K/AKT possessed robust antidiabetic activity. GTS-201 selective activator of MAPK/ERK does not demonstrated any antidiabetic activity. GSB-106 activating both signaling pathways exhibited weak antidiabetic activity.

Like BDNF [24] dipeptide GSB-106 demonstrated antinociceptive effect. It significantly enhanced the pain threshold in the hot plate (by 29%) and tail flick (by 50%) tests in rats at 24h point at dose 0.1mg/kg i.e. [25]. As a result, we created dimeric dipeptide mimetics of BDNF loops 1, 2 and 4. It has been established that all these compounds activate the specific BDNF receptor TrkB and they each have different post-receptor signaling patterns. Mimetic loop 4 GSB-106 acts as a good lead compound for further development as a promising therapeutic.

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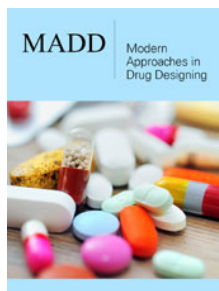
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