Low molecular weight dipeptide analogue of BDNF, GSB-106, protected cells via the TrkB, Akt, Erk 1/2 activation

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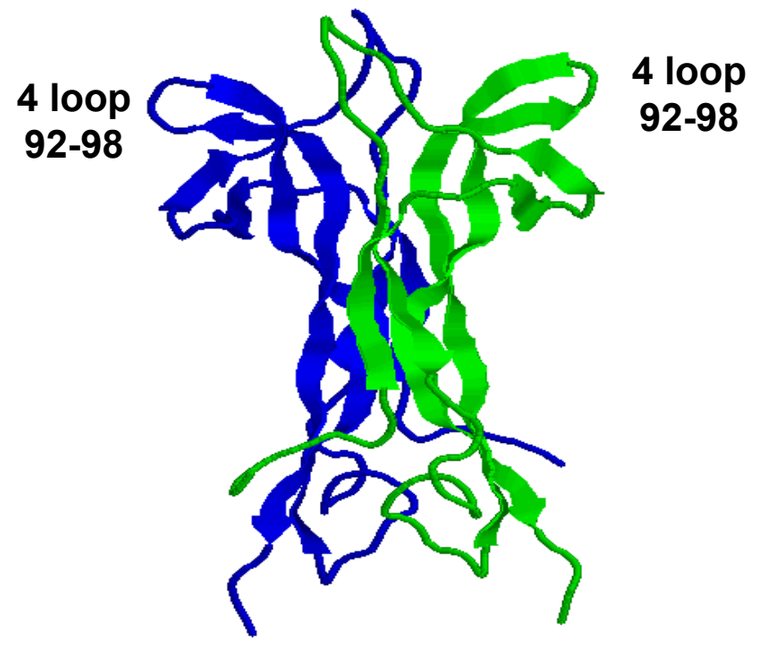
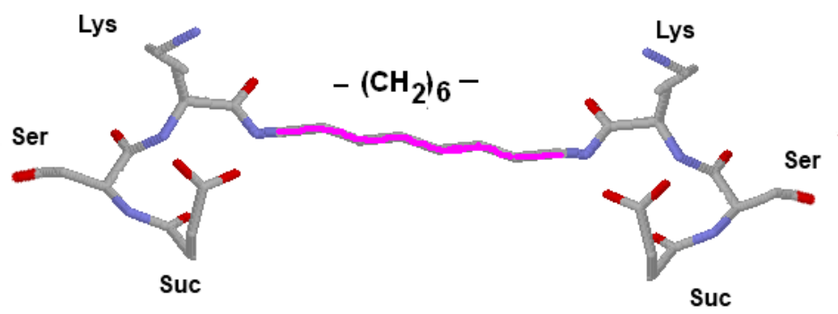
Purpose of study

In the pathogenesis most of neurodegenerative diseases and depression revealed reduction of brain-derived neurotrophic factor (BDNF) as endogenous neuroprotector. Has been show that BDNF rescues different types of neurons from ischemic, traumatic and toxic brain injury. The particular interest in BDNF is due to its involvement in the pathogenesis of depressions and possible antidepressant activity. The cellular actions of BDNF are mediated through the activation of the TrkB neurotrophin receptors. Pathways activated by BDNF include the Ras/Erk mitogen activated protein kinase (MAPK) pathway, the phosphatidylinositol-3-kinase (PI(3)K/Akt pathway and PLCγ pathway. MAPK pathway implicates in differentiation, neuroprotection, synaptic plasticity and antidepressant effect. Phosphatidylinositol-3-kinase (PI(3)K/Akt pathway leads to neuroprotection, neuritogenesis, synaptic plasticity, angiogenesis. Unfortunately, the pharmacological application of BDNF is limited because of its rapid degradation in the organism, low ability to penetrate the blood-brain barrier, and undesirable side effects. Therefore, in order to develop neuroprotective and antidepressant drugs, it seems urgent to synthesize low-molecular mimetics of BDNF, which are capable of activating the TrkB receptor signaling pathways and have no disadvantages of full-length BDNF protein. In Zakusov Institute of Pharmacology Russian Academy of Medical Sciences was synthesized low-molecular dipeptide analogue of BDNF - GSB-106 (bis(*N*-monosuccinyl-L-seryl-L-lysine hexamethylenediamide). We have previously shown that GSB-106 had neuroprotective effects in different models of cell damages: oxidative stress, glutamate toxicity or 6-hydroxydopamine-induced toxicity. Also GSB-106 showed the typical for BDNF antidepressant activity in several rodent tests. The objective of this study was to investigate the involvement of TrkB and two signaling pathways: MAPK/ERK1/2 and PI3K/Akt in neuroprotective and antidepressant effects.

BDNF (dimer)



GSB-106

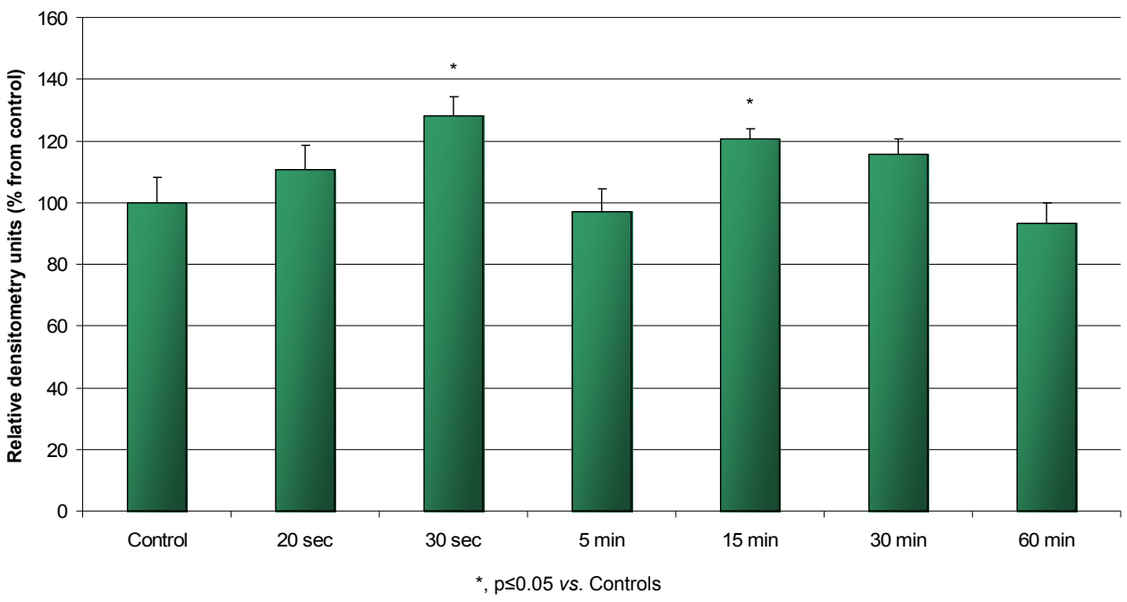


bis-(N-monosuccinil-seryl-lysine)
hexamethylenediamide

Methods

Experiments were carried out on hippocampal cell line HT-22. Cells were maintained at 37°C, 5% CO_2 in DMEM (Dulbecco's modified Eagle's medium) containing 5% FBS (fetal bovine serum). For experiments cells were passaged into 6-well plates. For this assay, cells were plated at $250x10^3$ cells per well in complete medium. Cultured HT-22 hippocampal neurons were incubated with GSB-106 (10^{-8}M) and BDNF (10^{-9}M) at the 20 sec, 30 sec, 5 min, 15 min, 30 min and 60 min time points. For detection phosphorylated TrkB, Akt and Erk 1/2 levels was used Western blot analysis by using specific antibodies against these proteins.

The level of phosphorylated Trk-B after addition GSB-106 in cell culture HT-22. Western blot densitometry.



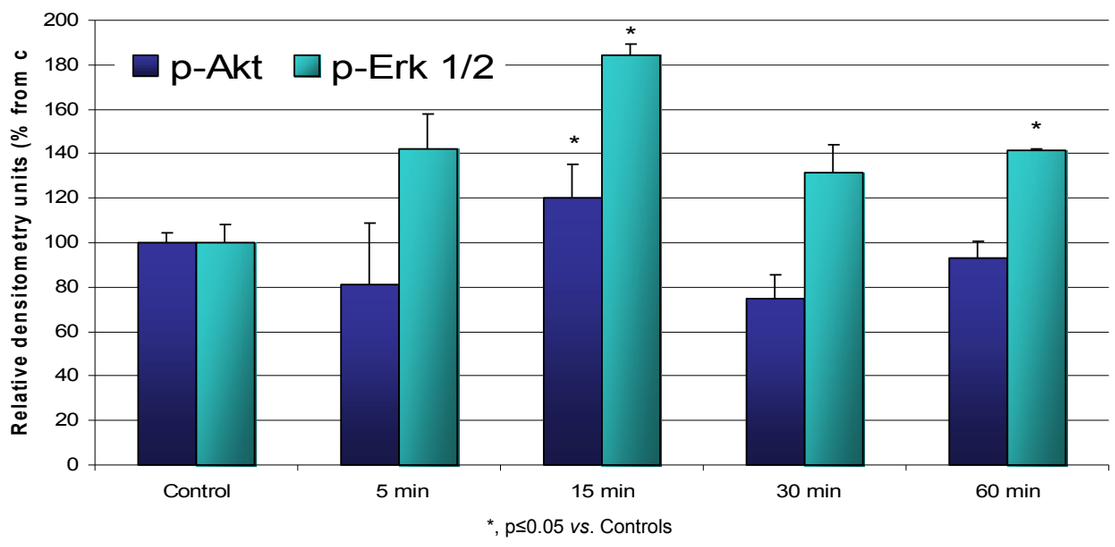
*, p≤0.05 *vs.* Controls

Results

BDNF binds to the TrkB receptor, which leads to its dimerization, autophosphorylation, and activation of a number of signal pathways. TrkB activation promotes neuronal survival, differentiation, and synaptic function. We have shown that GSB-106 caused a significant increase in phosphorylation of TrkB at 30 sec and 15 min of exposition HT-22 cells.

Two major signaling pathways have been implicated in responses underlying antidepressant effects: the phosphatidylinositol-3-kinase (PI(3)K/Akt signaling pathway and the MAPK/ERK signaling pathway. Numerous studies have implicated these two pathways in etiology and treatment of mood disorders. In our experiments GSB-106 indused the activation of Akt and Erk 1/2 signal pathways at the 15-minute time points in hippocampal neurons line HT-22.

The level of phosphorylated Akt and Erk 1/2 after addition GSB-106 in cell culture HT-22. Western blot densitometry.



*, p≤0.05 *vs.* Controls

Conclusion

Activation of TrkB, Akt, Erk 1/2 may be involved in neuroprotective and antidepressant effects of GSB-106.

Seredenin S.B., Gudasheva T.A.
Dipeptide mimetics of NGF and BDNF neurotrophins:
Russian patent № 2410392.
WO/2010/093284

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P.1.g.032

GSB-106, a low molecular weight dipeptide analogue of BDNF, protected cells via the TrkB, Akt, Erk 1/2 activation

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Methods: Experiments were carried out on hippocampal cell line HT-22. Cells were maintained at 37°C, 5% CO_2 in DMEM (Dulbecco's modified Eagle's medium) containing 5% FBS (fetal bovine serum). For experiments cells were passaged into 6-well plates. For this assay, cells were plated at 250×10^3 cells per well in complete medium. Cultured HT-22 hippocampal neurons were incubated with GSB-106 (10^{-8}M) and BDNF (10^{-9}M) at the 30s, 5min, 15min, 30min and 60min time points. For detection phosphorylated TrkB, Akt and Erk 1/2 levels was used Western blot analysis by using specific antibodies against these proteins.

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Conclusions: Activation of TrkB, Akt, Erk 1/2 may be involved in neuroprotective and antidepressant effects of GSB-106.

Citation: Eur Neuropsychopharmacol. 2014;24(Suppl 2):S221

Keywords

Neuropharmacology

Neuroprotection

Growth factors