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Antidepressant-like Activity of Dimeric Dipeptide Mimetics of different BDNF Hairpin loops is Determined by the ActivationPattern of TrkB Receptor Signaling Pathways

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Abstract

Background: A growing number of evidence suggest that brain derived neurotrophic factor (BDNF) and signaling at its receptor, TrkB, are involved in the pathogenesis of depression. Earlier, we created dimeric dipeptides on the basis of the beta-turns of BDNF loops 1, 2 and 4 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). All these dipeptides were shown to elevate the TrkB phosphorylation level while having different post-receptor signaling patterns. GSB-106 increased the levels of ERK and AKT kinase phosphorylation, whereas GTS-201 only increased the level of ERK phosphorylation and GSB-214 only increased the level of AKT phosphorylation. All dipeptides have demonstrated neuroprotective activity in vitro. An interesting observation was that GSB-106 exhibited significant antidepressant activity in the forced swimming test in mice, while GTS-201 and GSB-214 did not. These data suggests that the activation of both MAPK/ERK and PI3K/AKT pathways are essential for the manifestation of antidepressant-like activity by BDNF mimetics. To test this assumption we studied the antidepressant-like activity of GSB-106, GSB-214 and GTS-201 in the social defeat model of depression in mice.

Methods: C57BL/6 mice were exposed to 10 days of social defeat stress. Dipeptides GSB-106, GSB-214 and GTS-201 were administered intraperitoneally (ip) immediately after the each stress exposure session. In twenty-four hours since the last injections of the drugs, the forced swim test was conducted.

Results: Among the studied dipeptide BDNF mimetics only GSB-106 statistically significantly attenuated the increase of immobility time in forced swimming test in stressed mice compared with untreated control.

Conclusions: The antidepressant-like activity of the studied dipeptide BDNF mimetics is dependent on activation of both PI3K/AKT and MAPK/ERK signaling cascades, whereas selective activation of PI3K/AKT or MAPK/ERK pathway does not produce antidepressant effects.

Keywords: BDNF, Depression, low-Molecular Mimetics, Dipeptides, TrkB, ERK, AKT, Selective Activation of Signaling Pathways

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Background

Major depressive disorder (MDD) is a leading cause of global disease burden that affects over 300 million individuals worldwide [1]. There is a well-established body of clinical evidence implicating the involvement of BDNF in the pathobiology of depression [2]. BDNF has a role in processes such as neuronal maturation, synapse formation, synaptic plasticity and neurogenesis among others in the brain [2]. The neurotrophic hypothesis of depression claims that decreased levels of BDNF result into the hippocampal atrophy observed in depressed patients [3]. Numerous data suggests that altered BDNF level contributes to the atrophy, synaptic disconnection, and dysfunction of MDD-related circuits [3,4]. Current evidence strongly implicates BDNF-TrkB signaling in the response to clinically used antidepressant drugs including ketamine [3].

BDNF exerts its main biological actions through TrkB receptors. 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. 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 [5,6].

We hypothesized [6,7] that by interacting with the same receptor, different neurotrophin hairpin loops can activate various intracellular signaling cascades and are therefore responsible for different biological effects.

To put this hypothesis to test, we designed the dimeric dipeptides on the basis of 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) [6], bis-(N-hexanoyl-L-seryl-L-lysine) hexamethylenediamide (GTS-201) [8,9] and bis-(N-monosuccinyl-L-seryl-L-lysine) hexamethylenediamide (GSB-106) [6] [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.

It was shown by Western blot analysis that the all obtained dipeptides activate TrkB receptor and that they each have different post-receptor signaling patterns [8,10]. GSB-106 increased the levels of ERK and AKT kinase phosphorylation, whereas GTS-201 only increased the level of ERK phosphorylation and GSB-214 only increased the level of AKT phosphorylation. All these compounds in concentrations of 10^{-5}–10^{-8} M protected HT22 neuronal cells from the H_2O_2-induced oxidative stress [6,8]. The neuroprotective activity of the dipeptide mimetics of BDNF was confirmed in an in vivo model of transient middle cerebral artery occlusion in rats at ip administration [10]. Pharmacokinetic studies of GSB-106 showed that this compound penetrate the blood-brain barrier (unpublished data).

An interesting observation was that GSB-106 exhibited significant antidepressant activity in the forced swimming test in mice, while GTS-201 and GSB-214 did not [6,9,11]. These data suggests that that the activation of both MAPK/ERK and PI3K/AKT pathways is necessary for the manifestation of antidepressant activity mediated by TrkB receptors.

In order to test the assumption above, in our present study we studied the antidepressant-like activity of GSB-106, GSB-214 and GTS-201 in a model of depression in mice induced by repeated social defeat stress.

Methods

Drugs: The dimeric dipeptides GSB-214 ((bis-(N-monosuccinyl-l-methionyl-l-serine) heptamethylenediamide (Tm =160°C–162°C, $[\alpha]D^{20}$=-21.75° (c=0.4%; MeOH)), GSB-106 ((bis-(N-monosuccinyl-l-seryl-l-lysine) hexamethylenediamide (Tm =143°C–145°C, $[\alpha]D^{20}$=-24.7° (c=0.4%; dimethylformamide)) and GTS-201 ((bis-(N-hexanoyl-L-seryl-L-lysine) hexamethylenediamide ($[\alpha]D^{30}$=-21.59° (c=0.6%; MeOH)) were synthesized at the V.V. Zakusov Institute of Pharmacology (Moscow, Russia). Amitriptyline was purchased from Federal state unitary enterprise "Moscow Endocrine Plant" (Moscow, Russia).

Animals: Male adult C57BL/6 mice weighing 18 - 20 g were used in the study. The animals were obtained from the "Stolbovaya" Central Laboratory for Animal Breeding (Moscow Region, Russia). The animals were housed under controlled temperature of 22°C ± 2°C and 12 h light-dark cycle (lights on at 08:00 hours). All mice were maintained on a standard diet with food and water available ad libitum. The study was carried out in accordance with the Order of the Ministry of Health Care and Social Development of the Russian Federation № 708n of 23.08.2010 "Approval of the Rules of Good Laboratory Practice". All of the experiments were approved by the Institutional Animal Care and Use Committee of Zakusov Institute of Pharmacology (Moscow).

Social defeat stress: The social defeat procedure was adopted from the sensory contact model of social defeat stress (SDS), originally described by Kudryavtseva N.N. and co-workers [12]. Initially, mice were individually housed for 5 days to achieve abolish group effects. Then all individuals were randomly placed in pairs in cages separated with perforated Plexiglas walls, which divide the cage into two separate compartments to allow visual, olfactory, and auditory contact of mice for the 24-h period. Behavioral testing started two days after the animals were acclimated to the new conditions in pairs. During testing, the separator was removed for 10 min to allow agonistic interactions. During the three consecutive screening tests, the aggressor and defeated mice were determined. For each stress session the defeated mice were exposed to aggressors for 5-10 min every day for 10 days in total. This treatment leads to the development of marked social avoidance associated with behavioral and physiological changes reminiscent of depressive symptoms [13].

Since the first day stress session defeated mice have been divided into 6 experimental groups (10 animals in each). GSB-106, GSB-214 and GTS-201 (1 mg/kg) were administered intraperitoneally (ip) immediately after the each stress exposure sessions for 10 days. The dose was chosen based on previous in vivo studies. Stressed and non-stressed control groups received distilled water. The classical tricyclic antidepressant Amitriptyline, which was used as a positive control, was administered ip in the same order at a dose of 10 mg/kg [14]. In twenty four hours since the last injections of the drugs the forced swim test (FST) was conducted.

Forced swim test: A modified protocol was used as described by Porsolt et al [15]. The FST was conducted by placing the mice in a cylinder (30 cm in height ×10 cm in diameter) containing 19 cm of water at 22°C. The FST paradigm includes two sections: an initial 10-min pretest followed by a 5-min test 24 h later. The immobility time (including passive swimming) during the test was recorded. Immobilization and passive swimming were defined when a mouse was floating on the surface without struggling, making only the movements necessary to keep its head above the water.

Statistical analysis: For the in-between group comparisons statistical significance was assessed by the one-way analysis of variance (ANOVA) with Dunn's multiple comparison test. Values of $p<0.05$ were considered to indicate statistical significance.

Results

After 10 days of stress, untreated stressed mice "SDS group" showed a significantly ($p < 0.05$) higher immobility time in the FST compared to the «control», non-stressed group. The data obtained are in good accordance with literature data and confirm the depressive-like state of stressed mice [16]. The administration of GSB-106 (1 mg/kg, ip) for 10 days has significantly attenuated the increase of immobility time in FST by 1.4 fold (Fig.1). There was no statistically significant differences between "SDS+GTS-201", "SDS+GSB-106" and the "control" groups. GSB-214 and GTS-201 has no effect on the immobility time. The administration of amitriptyline (10 mg/kg, ip) to stressed mice significantly decreased immobility time in the FST compared with the "stress" group by 1.9-fold (Fig. 1).

Thus, dipeptide GSB-106 induced an antidepressant effect in a social defeat stress model of depression in mice, while GSB-214 and GTS-201 does not.

Discussion

Thus, earlier we created dimeric dipeptide mimetics of BDNF loops 1, 2 and 4 [6,8]. It has been established that all these compounds activate the specific BDNF receptor TrkB and they each have different post-receptor signaling patterns. Mimetic of BDNF loop 4 (GSB-106) activated both the main TrkB signaling pathways - PI3K/AKT and MAPK/ERK [10], mimetic of BDNF loop 1 (GSB-214) selectively activated PI3K/AKT [10] and mimetic of BDNF loop 2 (GTS-201) selectively activated MAPK/ERK signaling [8].

All the BDNF mimetics obtained, with selective or nonselective activation of PI3K/AKT and MAPK/ERK pathways, demonstrated neuroprotective activity in vitro. It is widely known that PI3K/AKT and MAPK/ERK pathways are two major intracellular signaling networks activated by growth factors responsible for the cell survival [17]. It has been reported that NGF mediated neuroprotective signaling is most likely to depend on PI3K/AKT rather than MAPK/ERK signaling [18-21]. As for the BDNF, the majority of reports suggest that the both pathways are significant for neuronal survival [22-24]. The results of this study suggest that the PI3K/AKT and MAPK/ERK pathways play independent roles in neuroprotective activity associated with the activation of TrkB receptors.

Unlike neuroprotective properties, antidepressant-like activity in the forced swimming test in mice was detected only in GSB-106 [6,8,9]. The results of the examination of GSB-214, GTS-201 and GSB-106 in this test are presented in Table 1.

Group	Duration of immobility, % of control group
Control	100
Imipramine, 25 mg/kg	36*
GSB-106, 0.1 mg/kg	79*
GSB-106, 1.0 mg/kg	80*
GSB-214, 0.1 mg/kg	95
GSB-214, 1.0 mg/kg	93
Control	100
Imipramine, 25 mg/kg	44*
GTS-201, 0.1 mg/kg	105
GTS-201, 1.0 mg/kg	92

Table 1: Effect of BDNF mimetics GSB-106, GSB-214 and GTS-201 (ip) on the duration of immobility in forced swimming test in mice [6,8,9].

***** - p<0.05 comparison with the control group (Mann-Whitney U test)

The results obtained suggest that the antidepressant-like activity of BDNF dipeptide mimetics is dependent on activation of both the PI3K/AKT and MAPK/ERK signaling cascades, whereas selective activation of the PI3K/AKT or MAPK/ERK pathway does not produce antidepressant effects. These data were confirmed in the present study in a model of depression in mice induced by repeated social defeat stress (Fig.1).

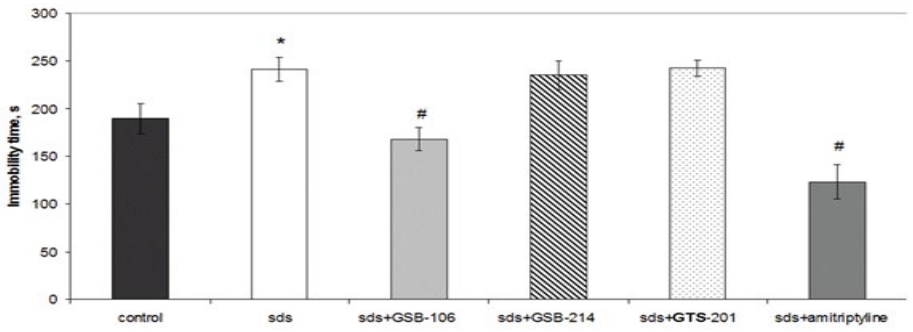

Figure 1: Effects of the dipeptides GSB-106, GSB-214 and GTS-201 in the forced swimming test in male mice C57Bl/6 in the social defeat model of depression.

Notes: Data are presented as mean ± SEM. ***** - p < 0,05 – compared with control group; # - p < 0,05 – compared with sds group (one-way analysis of variance (ANOVA) with Dunn's multiple comparison test).

The revealed need of engaging the both PI3K/AKT and MAPK/ERK pathways for the manifestation of antidepressant activity by BDNF mimetics is in good agreement with the literature data [3, 25-27] on the implication of both these signaling pathways in the depression and treatment response. Postmortem studies have reported decreased levels of MEK, ERK and AKT in the hippocampus of the subjects who committed suicide due to depression, consistent with the hypothesis that the reduction of both MAPK/ERK and PI3K/AKT pathways contribute to depressive symptoms [3]. Inhibition of AKT or MAPK pathway abolishes effect of a number of antidepressants, in particular desipramine, paroxetine and ketamine [26,28-30]. Acute administration of the MAP kinases inhibitor PD184161 produces depressive-like behavior in C57Bl/6 mice [26]. There are literature data indicating that the both MAPK/ERK and PI3K/AKT pathways are essential for the regulation of neurogenesis and synaptogenesis [27,31], which impairments are considered to be among the main etiopathological factors of depression [32]. In this regard, it should be noted that GSB-106 was found to prevent stress-induced impairments of hippocampal neurogenesis [33] and stimulates hippocampal synaptogenesis [34] in mice.

The patterns of signaling pathways activation of BDNF mimetics and their pharmacological properties are presented in Table 2.

Laboratory code	BDNF loop	Protein kinases activation			Neuroprotective activity in vitro	Antidepressant-like activity in FST in mice	
		TrkB	Akt	Erk		Forced swimming test	Social defeat model of depression
GSB-214 [6,10]	1	+	+	0	+	0	0
GTS-201 [8,9]	2	+	0	+	+	0	0
GSB-106 [6,10]	4	+	+	+	+	+	+

Table 2: Patterns of signaling pathways activation and pharmacological properties of BDNF mimetics
Notes: (+)—positive effect, 0—no effect

The data obtained through the present study confirms our hypothesis [6] that by interacting with the same receptor different neurotrophin hairpin loops can activate various intracellular signaling cascades and are therefore responsible for different biological effects. This hypothesis is also supported by the data we obtained earlier for NGF mimetics. We found out that dimeric dipeptide mimetics designed based on the NGF loop 1 and 4 β-turn sequences have different patterns of signal transduction and different profiles of biological activity [35]. By using these compounds, we revealed the possibility of separation of the neuroprotective and differentiating effects of NGF. In addition to that, we established that the selective activation of the PI3K/AKT pathway is sufficient for the manifestation of neuroprotective activity by NGF mimetics and is not associated with hyperalgesia, which is one of the main side effects of NGF, whereas the activation of the both PI3K/AKT and MAPK/ERK pathways generates nociceptive effects [35].

Conclusions

In the current study by using the social defeat model of depression in mice it was confirmed that the antidepressant-like activity of dipeptide BDNF mimetics is dependent on the activation of both PI3K/AKT and MAPK/ERK signaling cascades, whereas selective activation of the PI3K/AKT or MAPK/ERK pathway does not produce antidepressant effects.

List of abbreviations

BDNF – brain derived growth factor
TrkB - tyrosine kinase B
ERK - extracellular signal-regulated kinase
FST – forced swim test
MAPK, MEK1, MEK2 - mitogen-activated protein kinases
NGF - nerve growth factor
PI3K - phosphatidylinositol 3-kinase
SDS - social defeat stress

Declarations

Ethics approval and consent to participate

The all studies involving animals were carried out in accordance with the Order of the Ministry of Health Care and Social Development of the Russian Federation № 708n of 23.08.2010 "Approval of the Rules of Good Laboratory Practice" and were approved by the Institutional Animal Care and Use Committee of V.V. Zakusov Institute of Pharmacology (Moscow).

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

TAG conceived of the study, participated in its design and coordination and drafted the manuscript. PP participated in the study of dipeptides GSB-214, GTS-201 and GSB-106 antidepressant-like activity in the social defeat model of depression in mice and drafted the manuscript. AVT carried out the study of dipeptides GSB-214, GTS-201 and GSB-106 antidepressant-like activity in the social defeat model of depression in mice, performed the corresponding statistical analysis and participated in the drafting of the manuscript. SBS participated in the study design and coordination. All authors read and approved the final manuscript.

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References

1. Phillips C. Brain-Derived neurotrophic factor, depression, and physical activity: Making the Neuroplastic Connection. Neural Plast. 2017;2017. doi:10.1155/2017/7260130

2. Lee BH, Kim YK. The roles of BDNF in the pathophysiology of major depression and in antidepressant treatment. Psychiatry Investig. 2010;7(4):231-235. doi:10.4306/pi.2010.7.4.231.

3. Duman R.S., Voleti B. Signaling pathways underlying the pathophysiology and treatment of depression: novel mechanisms for rapid-acting agents. Trends Neurosci. 2012 Jan; 35(1): 47–56. doi: 10.1016/j.tins.2011.11.004

4. Duman RS, Monteggia LM. A neurotrophic model for stress-related mood disorders. Biol Psychiatry. 2006;59(12):1116-27. doi:10.1016/j.biopsych.2006.02.013

5. Fletcher JM, Hughes RA. Novel monocyclic and bicyclic loop mimetics of brain-derived neurotrophic factor. J Pept Sci. 2006;12(8):515-24. doi:10.1002/psc.760

6. Gudasheva TA, Tarasiuk AV, Pomogaĭbo SV, Logvinov IO, Povarnina P, Antipova TA, Seredenin SB. Design and synthesis of dipeptide mimetics of the brain-derived neurotrophic factor. Russ J Bioorganic Chem. 2012;38(3):243-252. doi:10.1134/S1068162012030053

7. Gudasheva TA, Antipova TA, Seredenin SB. Novel low-molecular-weight mimetics of the nerve growth factor. Dokl Biochem Biophys. 2010;434:262-5. doi: 10.1134/S160767291005011X

8. Gudasheva TA, Tarasiuk A V., Sazonova NM, Povarnina PY, Antipova TA, Seredenin SB. A novel dimeric dipeptide mimetic of the BDNF selectively activates the MAPK-Erk signaling pathway. Dokl Biochem Biophys. 2017;476(1):291-295. doi:10.1134/S1607672917050027

9.Sazonova NM, Tarasiuk AV, Shumskiy AN, Povarnina P., Kruglov S.V., Antipova T.A. et al. Synthesis and biological evaluation of the dipeptide mimetic of the BDNF loop 2 (in Russian). Chem Pharm. 2018;52(8).

10. Gudasheva TA, Povarnina P, Logvinov IO, Antipova TA, Seredenin SB. Mimetics of brain-derived neurotrophic factor loops 1 and 4 are active in a model of ischemic stroke in rats. Drug Des Devel Ther. 2016;10:3545-3553. doi:10.2147/DDDT.S118768

11. Gudasheva TA, Logvinov IO, Povarnina PY, Antipova TA, Seredenin SB. Analysis of dependence of antidepressant properties of TrkB receptor ligands on MAP-kinase pathway activation. Dokl Biochem Biophys. 2015;460(1):20-22. doi:10.1134/S1607672915010068

12. Kudryavtseva NN, Avgustinovich DF. Behavioral and physiological markers of experimental depression induced by social conflicts (DISC). Aggress Behav. 1998;24(4):271-286. doi:10.1002/(SICI)1098-2337(1998)24:4<271::AID-AB3>3.0.CO;2-M

13. Golden SA, Covington HE, Berton O, Russo SJ. A standardized protocol for repeated social defeat stress in mice. Nat Protoc. 2011;6(8):1183-1191. doi:10.1038/nprot.2011.361

14. Abdelhamid RE, Kovács KJ, Nunez MG, Larson AA. Depressive behavior in the forced swim test can be induced by TRPV1 receptor activity and is dependent on NMDA receptors. Pharmacol Res. 2014;79:21-27. doi:10.1016/j.phrs.2013.10.006

15. Porsolt RD, Anton G, Blavet N, Jalfre M. Behavioural despair in rats: A new model sensitive to antidepressant treatments. Eur J Pharmacol. 1978;47(4):379-391. doi:10.1016/0014-2999(78)90118-8

16. Iñiguez SD, Aubry A, Riggs LM, et al. Social defeat stress induces depression-like behavior and alters spine morphology in the hippocampus of adolescent male C57BL/6 mice. Neurobiol Stress. 2016;5:54-64. doi:10.1016/j.ynstr.2016.07.001

17. Kaplan DR, Miller FD. Neurotrophin signal transduction in the nervous system. Curr Opin Neurobiol. 2000;10(3):381-391. doi:10.1016/S0959-4388(00)00092-1

18. Crowder RJ, Freeman RS. Phosphatidylinositol 3-kinase and Akt protein kinase are necessary and sufficient for the survival of nerve growth factor-dependent sympathetic neurons. J Neurosci. 1998;18(8):2933-2943. http://www.ncbi.nlm.nih.gov/pubmed/9526010

19. Liu L, Sun T, Xin F, Cui W, Guo J, Hu J. Nerve Growth Factor Protects Against Alcohol-Induced Neurotoxicity in PC12 Cells via PI3K/Akt/mTOR Pathway. Alcohol Alcohol. 2017;52(1):12-18. doi:10.1093/alcalc/agw077

20. Wei K, Liu L, Xie F, Hao X, Luo J, Min S. Nerve growth factor protects the ischemic heart via attenuation of the endoplasmic reticulum stress induced apoptosis by activation of phosphatidylinositol 3-kinase. Int J Med Sci. 2015;12(1):83-91. doi:10.7150/ijms.10101

21. Salinas M, Diaz R, Abraham NG, De Galarreta CMR, Cuadrado A. Nerve growth factor protects against 6-hydroxydopamine-induced oxidative stress by increasing expression of heme oxygenase-1 in a phosphatidylinositol 3-kinase-dependent manner. J Biol Chem. 2003;278(16):13898-13904. doi:10.1074/jbc.M209164200

22. Nakazawa T, Tamai M, Mori N. Brain-derived neurotrophic factor prevents axotomized retinal ganglion cell death through MAPK and PI3K signaling pathways. Invest Ophthalmol Vis Sci. 2002;43(10):3319-3326. http://www.ncbi.nlm.nih.gov/pubmed/12356841

23. Almeida RD, Manadas BJ, Melo CV, Gomes JR, Mendes CS, Grãos MM et al. Neuroprotection by BDNF against glutamate-induced apoptotic cell death is mediated by ERK and PI3-kinase pathways. Cell Death Differ. 2005;12(10):1329-1343. doi:10.1038/sj.cdd.4401662

24. Hetman M, Kanning K, Cavanaugh JE, Xia Z. Neuroprotection by brain-derived neurotrophic factor is mediated by extracellular signal-regulated kinase and phosphatidylinositol 3-kinase. J Biol Chem. 1999;274(32):22569-22580. doi:10.1074/JBC.274.32.22569

25. Hashimoto K. Brain-derived neurotrophic factor as a biomarker for mood disorders: An historical overview and future directions. Psychiatry Clin Neurosci. 2010;64(4):341-357. doi:10.1111/j.1440-1819.2010.02113.x

26. Duman CH, Schlesinger L, Kodama M, Russell DS, Duman RS. A Role for MAP Kinase Signaling in Behavioral Models of Depression and Antidepressant Treatment. Biol Psychiatry. 2007;61(5):661-670. doi:10.1016/j.biopsych.2006.05.047

27. Jiang C, Salton SR. The role of neurotrophins in major depressive disorder. Transl Neurosci. 2013;4(1):46-58. doi:10.2478/s13380-013-0103-8

28. Réus GZ, Vieira FG, Abelaira HM, Michels M, Tomaz DB, dos Santos MA et al. MAPK signaling correlates with the antidepressant effects of ketamine. J Psychiatr Res. 2014;55(1):15-21. doi:10.1016/j.jpsychires.2014.04.010

29. Pazini FL, Cunha MP, Rosa JM, Colla AR, Lieberknecht V, Oliveira Á et al. Creatine, similar to ketamine, counteracts depressive-like behavior induced by corticosterone via PI3K/Akt/mTOR pathway. Mol Neurobiol. 2016;53(10):6818-6834. doi:10.1007/s12035-015-9580-9

30. Xu D, Sun Y, Wang C, Wang H, Wang Y, Zhao W et al. Hippocampal mTOR signaling is required for the antidepressant effects of paroxetine. Neuropharmacology. 2018;128:181-195. doi:10.1016/j.neuropharm.2017.10.008

31. Park H, Poo M. Neurotrophin regulation of neural circuit development and function. Nat Rev Neurosci. 2012;14(1):7-23. doi:10.1038/nrn3379

32. Wainwright SR, Galea LAM. The neural plasticity theory of depression: Assessing the roles of adult neurogenesis and psa-ncam within the hippocampus. Neural Plast. 2013;2013. doi:10.1155/2013/805497

33. Gudasheva TA, Povarnina PY, Seredenin SB. Dipeptide mimetic of the brain-derived neurotrophic factor prevents impairments of neurogenesis in stressed mice. Bull Exp Biol Med. 2017;162(4):454-457. doi:10.1007/s10517-017-3638-9.

34. Gudasheva TA, Povarnina PY, Antipova TA, Seredenin SB. Dipeptide mimetic of the BDNF GSB-106 with antidepressant-like activity stimulates synaptogenesis. Dokl Biochem Biophys. 2018;481(1):225-227. doi:10.1134/S1607672918040130

35. Gudasheva TA, Povarnina PY, Antipova TA, Firsova YN, Konstantinopolsky MA, Seredenin SB. Dimeric dipeptide mimetics of the nerve growth factor Loop 4 and Loop 1 activate TRKA with different patterns of intracellular signal transduction. J Biomed Sci. 2015;22(5):106. doi:10.1186/s12929-015-0198-z