Neurotrophic Factors and Depression: Pathophysiology and Beyond

Salih Gümrü, Feyza Arıcıoğlu

Marmara Universitesi Eczacılık Fakultesi, Farmakoloji Anabilim Dalı ve Psikofarmakoloji Araştırma Birimi, Haydarpaşa, İstanbul-Türkiye

Yazışma Adresi / Address reprint requests to: Feyza Arıcıoğlu
Marmara Üniversitesi Eczacılık Fakültesi, Farmakoloji Anabilim Dalı ve Psikofarmakoloji Araştırma Birimi, Haydarpaşa, 34668, İstanbul-Türkiye
Telefon / Phone: +90-216-418-9573 Faks / Fax: +90-216-345-2952 Elektronik posta adresi / E-mail address: feyza.aricioglu@gmail.com
Kabul tarihi / Date of acceptance: 28 Mayıs 2012 / May 28, 2012

ÖZET

Nörotrofik faktörler ve depresyon: Patofizyoloji ve ötesi

Depresyon toplumda yaygın bir psikiyatrik bozukluk olmasına rağmen, patofizyolojisi henüz aydınlatılamamıştır. 1970'li yıllardan beri depresyon üzerine birçok hipotez tartışılmış; son yıllarda bu alanda birçok yeni görüş ortaya çıkmıştır. Majör depresyon hipokampus ve prefrontal kortekste hacim azalmalarıyla belirgindir ve antidepresan ilaçlar hipokampusta nörojenez, sinaptojenez ve nöronal matürasyon dahil nöronal plastisitenin pek çok çeşidini tetiklemektedir. Son yıllarda elde edilen bazı bulgular, nörotrofik faktörlerin nöronal plastisiteyi çift yönlü olarak düzenleyebildiğini göstermektedir. Bu durum, nörotrofik faktörlerin depresyonun hem patofizyolojisinde, hem de tedavisinde rol oynuyor olduğu şeklinde yorumlanabilir.
Anahtar sözcükler: Nörotrofik faktörler, beyin-kaynaklı nörotrofik faktör (BDNF), plastisite, depresyon

ABSTRACT

Neurotrophic factors and depression: pathophysiology and beyond

Although depression is one of major psychiatric disorders in society, its neurobiology remains still unclear. Since 1970's, many hypotheses on depression have been discussed. In recent years, many new points of view have emerged in this research area. Major depression is associated with reduced volumes in the hippocampus and prefrontal cortex, and antidepressant drugs promote many forms of neuronal plasticity, including neurogenesis, synaptogenesis and neuronal maturation in hippocampus. Recent evidences indicate that neurotrophic factors may regulate neuronal plasticity bidirectionally, meaning they may play role in pathophysiology and treatment of depression.
Key words: neurotrophic factors, brain-derived neurotrophic factor (BDNF), plasticity, depression

INTRODUCTION

Depression is a highly prevalent and mostly recurrent disorder associated with significant disabilities and increased mortality, explaining the high ranking of the disease in the Disability Adjusted Life Years (DALY) in Europe and the United States (1). This common psychiatric disorder affects 21% of the world population during their lifetime (2). Thus, depression has been recognized as a disorder with major epidemiological and economic consequences (3). Since all hypotheses have come up short on explaining some components of depressive disorder, scientists are in quest of new theories to fill this gap in the field.

Neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), are small proteins involved in neuronal survival, development, function and plasticity (4). Because these are also involved in hippocampal plasticity and increase in synaptic strength, neurotrophic hypothesis of depression has become very popular in the last decade (5). It is claimed that reduced brain BDNF levels cause depression, whereas increases in brain BDNF levels produce an antidepressant action. However, recent investigations, together with information gained on the basic role of neurotrophins in the brain, suggest a modified neurotrophic hypothesis, emphasising the role of BDNF as a tool of experience-dependent modifications in neural networks that regulate different aspects of mood (6). This unique understanding brought the idea of "neuronal plasticity", through which neurotrophic factors show their effects in depressive disorder.

In this editorial, neurotrophic hypothesis of depression and the role of neurotrophins in management of disorder are in short discussed.

The role of neurotrophic factors and neuroplasticity in pathophysiology of depression

Since 1970's, different hypotheses on pathophysiology of depression have gained recognition by scientists. The first one was "Monoamine Hypothesis", claiming underactivity of monoamines, such as noradrenaline, serotonin and dopamine, results in depression. Most of drugs used in depression treatment are aiming to change the levels of monoamines through different mechanisms. It often takes two to three weeks for antidepressant drugs to effectively treat depression. This is a difficult phenomenon to explain within the context of the monoamine hypothesis, because classical antidepressants provide a quick change of neurotransmitter levels in synaptic cleft only in a couple of hours. This phenomenon gave rise to another hypothesis, called "Neurotransmitter Receptor Hypothesis", claiming the main arises from signaling pathways, which play critical role in the signal transfer through receptors of monoamines. This point of view provided a basis to "Monoamine Hypothesis of Gene Expression", supporting the genetic basis of these signaling disturbances. The latter hypothesis also attracted attention on neurotrophic factors, whose shortage due to genetic expression causes atrophy and apoptosis of hippocampus (7), which is a critical cerebral area linked to major depressive disorder (MDD) (8).

The neurotrophic hypothesis of neuronal development was formulated several decades ago, and has been largely confirmed by genetic studies (9,10). It states that neurons, which are initially made in excess, compete for access to the neurotrophic factors that are produced by target cells in limited amounts (10,11). However, it is important to note that the physiological role of neurotrophins is not directly to keep neurons alive, but to select from competing neurons those which have achieved best connections with the target tissue, and thereby optimize the numbers of neurons required for target innervation. Additionally, BDNF has a critical role in selecting well-functioning synapses in central nervous system (10).

The selection procedure explained above implicates neuronal plasticity in the pathophysiology of mood disorders and in the recovery from depression (6,12). Depression is directly connected to neuronal degeneration and volume reduction without an alteration in cell numbers (13) of some important brain areas, such as hippocampus and prefrontal cortex. The reversible nature of this degeneration and clinical symptoms linked to impaired information processing are the main markers for the possible involvement of neuronal plasticity in depression (14).

There are too many recent evidences, suggesting that neurotrophic factors play a critical role in the regulation of neuronal plasticity in the brain (9, 15). This bidirectional regulation occurs through binding of two different receptor types. "Anabolic" plastic changes, such as neuronal survival, axon branching and elongation, dendritic sprouting, synaptogenesis and long-term potentiation (LTP) are provided by activation of tyrosine kinase receptors (Trk) (16). The binding results in dimerization and autophosphorylation of the receptor,

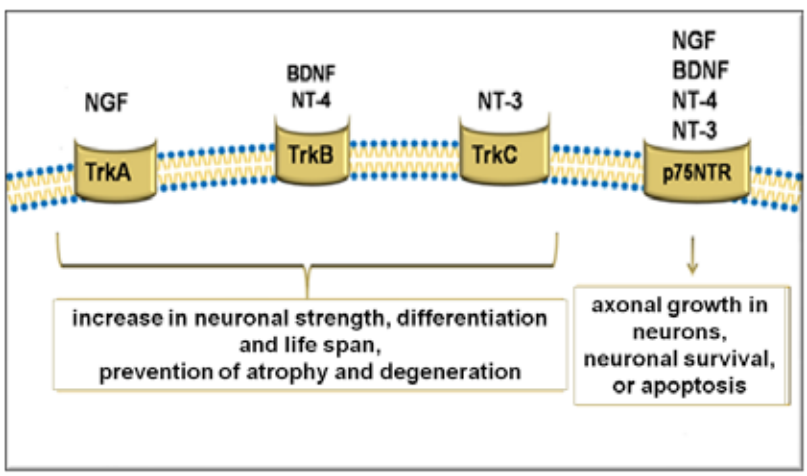

Figure 1: Neurotrophic factors, their receptors and fuctions. They show their effects by binding 3 types of tyrosine kinase receptors (TrkA, TrkB, TrkC) and pan-neurotrophic receptor p75.

which is followed by activation of different signaling pathways. Signaling is promoted by phosphorylation of additional thyrosine residues to create docking sites for adapter proteins which couple the receptors to intracellular signal transduction mechanisms. All of these phosphorylation steps provide the activation of Ras/mitogen activated protein kinase (Ras/MAPK), phosphoinositide 3-kinases (PI3K) and phospholipase C-c1 (PLC-c1)-mediated signaling pathways (17,18,19). As a result, anabolic plastic changes occur. In contrast, "catabolic" plastic responses, such as cell death, synaptic loss and long-term depression (LTD), are mediated by activation of pan-neurotrophic receptor 75 (p75) (Fig. 1).

Neurotrophic factors and antidepressant activity

Many studies have suggested that regular BDNF signaling is necessary and sufficient for antidepressant drug action. Different groups of antidepressants have been found to increase TrkB activation and signaling rapidly within an hour after drug administration (20,21). Antidepressant-induced tyrosine phosphorylation of TrkB doesn't activate extracellular kinase pathways, but activates Phospholipase Cγ signaling, leading the phosphorylation of cAMP-related element binding protein (CREB). CREB is a transcription factor regulating gene expression of plasticity-related protein, such as neurotrophic factors and Bcl-2, a protein blocking apoptosis pathways in the cell. A chronic antidepressant treatment increases hippocampal CREB levels and the period needed for the induction of CREB equals 10-21 days, which also refers to the length of the period for clinical observation of the antidepressant drug effect. The effects of CREB and BDNF have been observed on the same type of hippocampal neurons. It is also reported, that a decrease in levels of CREB may cause decrease in levels of BDNF. These findings indicate that CREB and BDNF may have synergistic effects on hippocampus and that antidepressants show their effects through the activation of CREB and BDNF. After a couple of weeks of treatment, all antidepressant treatments, including electroconvulsive shock treatment, increase BDNF mRNA expression in hippocampus and prefrontal cortex (12). It can be said, that every kind of antidepressant therapy has the ability to rapidly activate TrkB signaling and provide long-term increase in BDNF production. All of these data guided scientists to accept "Neurotrophin Hypothesis of Antidepressants", which explains some questions about antidepressant treatment.

Neurotrophic factors as antidepressant drugs

Neurotrophic factors are thought as candidate antidepressant agents, since antidepressant treatments increase levels of them in brain. Different routes of administration have been studied to make it clear, if neurotrophic factors are valuable as drug candidates. A study summarized that, intact BDNF in the peripheral circulation after i.v. injection crosses the BBB by a high-capacity, saturable transport system. Intracerebroventricular injection has been found effective, too (23).

A neurotrophic factor, insulin-like growth factor-I (IGF-I), has been thought as a possible drug for depression therapy. Its CNS delivery capacities following intranasal and intravenous administrations have been compared and intranasal administration was more favorable (24). Data have shown that BDNF plus IGF-I is more effective than either neurotrophin alone in activating neurotrophic cascades and promoting survival of hippocampal neurons. Up to now, intranasal IGF-I has been used only in animal models of cerebral ischemia, in which it reduced infarct volume by inhibiting apoptosis (25).

An obstacle in front of the safe use of neurotrophic factors as drugs is their lately discovered involvement in drug abuse. Studies demonstrate that, BDNF plays a role in survival of midbrain dopaminergic neurons. Since midbrain dopaminergic system is essential in mediating drug addiction, increase in BDNF levels may have a significant role in this process. It is found that, BDNF infusion into rat midbrain enhances the rewarding effects of cocaine. Furthermore, plasma BDNF concentrations of methamphetamine users were significantly higher than those of controls. Although the increased central BDNF activity hypothesis of drug addiction may provide new insights for improved therapeutic strategies for the prevention and treatment of drug addiction, their possible addictive nature may threathen their strong candidate status in depression therapy.

CONCLUSION

Major depression is associated with reduced volumes in hippocampus and prefrontal cortex, and negative contagion of neurons in these areas triggers depression. Stress-induced vulnerability decreases the expression of genes that make neurotrophic factors such as BDNF, which are critical for the survival and function of key neurons. Treatment strategies to increase the levels of neurotrophic factors in the brain may be a useful way to improve recurrent and treatment-resistant depression cases. Today, there are also some experimental therapy options such as BDNF mimetics, and the value of neurotrophic factors as a target of future drug development could not be neglected.

REFERENCES

1. Ustün TB, Ayuso-Mateos JL, Chatterji S, Mathers C, Murray CJ. Global burden of depressive disorders in the year 2000. Br J Psychiatry. 2004;184: 386-392.
2. Kotan Z, Sarandöl A, Saygın Eker S, Akkaya C. Depresyon, Nöroplastisite ve Nörotrofik Faktörler: Psikiyatride Güncel Yaklaşımlar. Current Approaches in Psychiatry. 2009;1: 22-35.
3. Belmaker RH, Agam G. Major depressive disorder. N Engl J Med. 2008;358: 55-68.
4. Sofroniew MV, Howe CL, Mobley WC. Nerve growth factor signaling neuroprotection, and neural repair. Annu Rev Neurosci. 2001;24: 1217-1281.
5. Frodl T, Meisenzahl E, Zill P, Baghai T, Rujescu D, Leinsinger G, Bottlender R, Schüle C, Zwanzger P, Engel RR, Rupprecht R, Bondy B, Reiser M, Möller HJ. Reduced hippocampal volumes associated with the long variant of the serotonin transporter polymorphism in major depression. Arch Gen Psychiatry. 2004;61: 177-183.
6. Castrén E, Võikar V, Rantamäki T. Role of neurotrophic factors in depression. Curr Opin Pharmacol. 2007;7: 18-21.
7. Stahl SM. Essential Psychopharmacology Neuroscientific Basis & Practical Applications. 2nd Edition. Cambridge University Press; 2002. p.179-188.
8. Rot M, Mathew S, Charney DS. Neurobiological mechanisms in major depressive disorder. CMAJ. 2009;180: 305-313.
9. Huang EJ, Reichardt LF. Neurotrophins: roles in neuronal development and function. Annu Rev Neurosci. 2001;24: 677-736.
10. Castrén E, Rantamäki T. Neurotrophins in depression and antidepressant effects. Novartis Found Symp. 2008;289: 43-52.
11. Levi-Montalcini R. The nerve growth factor: thirty-five years later. EMBO J 1987;6: 1145-1154.
12. Duman RS, Monteggia LM. A neurotrophic model for stress-related mood disorders. Biol Psychiatry. 2006;59: 1116-1127.
13. Drevets WC. Neuroimaging and neuropathological studies of depression: implications for the cognitive-emotional features of mood disorders. Curr Opin Neurobiol. 2001;11: 240-249.
14. Berton O, Nestler EJ. New approaches to antidepressant drug discovery: beyond monoamines. Nat Rev Neurosci. 2006;7: 137-151.
15. Lu B. BDNF and activity-dependent synaptic modulation. Learn Mem. 2003;10: 86-98.
16. Huang EJ, Reichardt LF. Trk receptors: roles in neuronal signal transduction. Annu Rev Biochem. 2003;72: 609-642.
17. Furmaga H, Carreno FR, Frazer A. Vagal Nerve Stimulation Rapidly Activates Brain-Derived Neurotrophic Factor Receptor TrkB in Rat Brain. PLoS One. 2012;7: e34844.
18. Doksat MK. Evrimsel Perspektiften Depresyon ve Sitokinler. Klinik Psikofarmakoloji Bülteni. 2003;13: 97-108.
19. Allen SJ, Dawbarn D. Clinical relevance of the neurotrophins and their receptors. Clinical Scinece; 2006;110: 175-191.
20. Rantamaki T, Knuuttila JE, Hokkanen ME, Castren E. The effects of acute and long-term lithium treatments on TrkB neurotrophin receptor activation in the mouse hippocampus and anterior cingulate cortex. Neuropharmacology. 2006;50: 421-427.
21. Saarelainen T, Hendolin P, Lucas G, Koponen E, Sairanen M, MacDonald E, Agerman K, Haapasalo A, Nawa H, Aloyz R. Ernfors B, Castrén E. Activation of the TrkB neurotrophin receptor is induced by antidepressant drugs and is required for antidepressantinduced behavioral effects. J Neurosci. 2003;23: 349-357.
22. Gürpınar D, Erol A, Mete L. Depresyon ve nöroplastisite. Klinik Psikofarmakoloji Bülteni. 2007;17: 100-110.
23. Pan W, Banks WA, Fasold MB, Bluth J, Kastin AJ. Transport of brain-derived neurotrophic factor across the blood-brain barrier. Neuropharmacology. 1988;37: 1553-1561.
24. Thorne RG, Pronk GJ, Padmanabhan V, Frey II WH. Delivery of insulin-like growth factor-I to the rat brain and spinal cord along olfactory and trigeminal pathways following intranasal administration. Neuroscience. 2004;127: 481-96.
25. Kooijman R, Sarre S, Michotte Y, De Keyser J. Insulin-like growth factor I: a potential neuroprotective compound for the treatment of acute ischemic stroke? Stroke. 2009;40: 83-88.
26. Tsai SJ. Increased central brain-derived neurotrophic factor activity could be a risk factor for substance abuse: Implications for treatment. Medical Hypotheses. 2007;68: 410-414.