INTERPLAY OF BRAIN-DERIVED NEUROTROPHIC FACTOR AND CYTOKINES IN SCHIZOPHRENIA

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MEĐUSOBNA DEJSTVA MOŽDANOG NEUROTROFIČNOG FAKTORA I CITOKINA U SHIZOFRENIJI

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ABSTRACT

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family and plays an important role in neuroplasticity, differentiation and survival of neurons, as well as their function. Neuroinflammation has been explored in the pathophysiology of many mental disorders, such as schizophrenia. Cytokines representing different types of immune responses have an impact on neurogenesis and BDNF expression. Cross-regulation of BDNF and cytokines is accomplished through several signalling pathways. Also, typical and atypical antipsychotic drugs variously modulate the expression of BDNF and serum levels of cytokines, which can possibly be used in evaluation of therapy effectiveness. Comorbidity of metabolic syndrome and atopic diseases has been considered in the context of BDNF and cytokines interplay in schizophrenia.

Keywords: *brain derived neurotrophic factor, cytokines, schizophrenia, metabolic syndrome, atopic diseases.*

SAŽETAK

Moždani neurotrofični faktor (Brain Derived Neurotrophic Factor-BDNF) pripada porodici neurotrofina i ima važnu ulogu u neuroplastičnosti, diferencijaciji i funkciji neurona. Neuroinflamacija je izučavana u etiopatogenezi mnogih mentalnih poremećaja, pa i u shizofreniji. Citokini različitih tipova imunskih odgovora utiču na neurogenezu i ekspresiju BDNF-a. Unakrsna regulacija BDNF-a i citokina se ostvaruje posredstvom nekoliko signalnih puteva. Pokazano je da tipični i atipični antipsihotici mogu drugačije da utiču na ekspresiju BDNF-a i serumske nivoe citokina, što može biti korisno u proceni efikasnosti terapije. Komorbiditet metaboličkog sindroma i atopijskih bolesti je razmatran i u kontekstu uzajamnog dejstva BDNF-a i citokina u shizofreniji.

Ključne reči: *moždani neurotrofni faktor, citokini, shizofrenija, metabolički sindrom, atopijske bolesti.*

ABBREVIATIONS

AD- Atopic dermatitis
BDNF- Brain Derived Neurotrophic Factor
CREB- Cyclic adenosine monophosphate Response Element- Binding
IFN-γ- Interferon-gamma
IL- Interleukin
MetS- Metabolic Syndrome
p75 NTR- p75 NeuroTrophin Receptor
PANSS- Positive and Negative Syndrome Scale
ST2- IL-1 receptor- related protein
TNF-α- Tumor Necrosis Factor-alpha
TrkB- Tropomyosin receptor kinase B

INTRODUCTION

The Brain Derived Neurotrophic Factor (BDNF) is a member of the nerve growth factor family (1). It plays an important role in neuronal survival and growth, modulates neurotransmission and participates as a crucial mediator in all aspects of neuroplasticity (2), such as neurogenesis (3), synaptogenesis (4) and vasculogenesis (5). BDNF participates in learning and memory organization, food intake and motor behaviour (6).

It was shown that BDNF is widely distributed in various regions of the brain, such as the olfactory bulb, cortex, hippocampus, basal forebrain, mesencephalon, hypothalamus, brainstem and spinal cord (2, 7, 8). BDNF promotes the survival of dopaminergic neurons of the substantia nigra (9), cerebellar granule neurons (10), motor neurons (11) and retinal ganglion cells (12).

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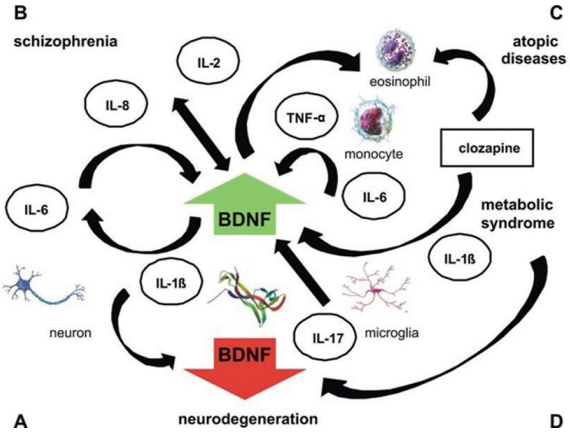

Figure 1. Brain-derived neurotrophic factor (BDNF) - cytokines interactions in schizophrenia and comorbid somatic states
In animal models application of IL-1β decreases BDNF levels in the nerve tissue and lead to degeneration. BDNF- IL-6 communication could be bidirectional. IL-17 up-regulates BDNF microglia production. (A) In schizophrenia was established significant positive association between BDNF and IL-2 and IL-8 levels. (B) TNF-α and IL-6 increase BDNF production in peripheral blood monocytes, that also underlies neuronal hyperreactivity in asthma. BDNF induces eosinophil increase in patients with atopic dermatitis and that could be a side effect of clozapine, an antipsychotic with BDNF- elevating properties. (C) In metabolic syndrome increase of inflammatory cytokines IL-6, TNF-α and IL-1β could reduce BDNF expression. (D)

Microglia and activated macrophages produce BDNF in the brain (13, 14). Human monocytes, but not lymphocytes, are the major cellular source of BDNF in peripheral tissues (15). Furthermore, it is found in the nonneuronal tissue such as lungs, heart, spleen, gastrointestinal tract and liver (16-18) and it is expressed in fibroblasts, vascular smooth muscle cells, and thymic stroma (5, 19, 20). BDNF is involved in activation of endothelial cells (21) and has an influence on the hematopoietic stem cells and thus supports haematopoiesis (22).

The BDNF gene is located on the short (p) arm of chromosome 11 at position 13 (23). As a basic dimeric protein (1), BDNF has a complex genomic structure, with sophisticated organization in terms of transcriptional, translational and post-translational regulatory mechanisms (24). Pro-BDNF is produced in endoplasmatic reticulum, transported to the Golgi apparatus and converted into mature BDNF (25). The receptor for BDNF is Tropomyosin receptor kinase B (TrkB), which exists in two isoforms: the full length receptor glycoprotein (gp145TrkB) with high affinity and truncated form gp-95TrkB lacking tyrosine kinase domain; and the Low affinity Nerve Growth Factor Receptor, also known as p75 NeuroTrophin Receptor (p75 NTR) (2).

BDNF levels in the cerebrospinal fluid in healthy controls were measured in the range of 98.1±83.99 (26). In healthy volunteers, mean plasma BDNF level was found to be ~92.5 pg/ml (8.0–927.0 pg/ml) (2). In schizophrenia, drug-naïve patients had a significant correlation between BDNF protein levels in plasma and cerebrospinal fluid (27). The BDNF can freely pass through blood-brain barrier and all of this suggests that BDNF blood levels can substantially reflect its levels in the central nervous system (28).

The role of BDNF and cytokines in central nervous system and peripheral tissues

Neuroinflammation has an important role in the pathophysiology of mental disorders and pro-inflammatory cytokines and BDNF may have a detrimental effect on neurogenesis, reviewed by Calabrese et al. (29). The impact of the pro-inflammatory cytokines on neurogenesis depends on their concentration, activation of specific cells and neurogenic factors (30). Different stimuli regulate BDNF production in neurons, such as Cyclic adenosine monophosphate Response Element-Binding protein (CREB) - dependent depolarization (31) and cytokines (32).

In study of Lapchak et al. (1993) the mRNA levels of BDNF were significantly decreased in the rat's hippocampus after 4 hours of intraperitoneal injection of interleukin (IL)-1β (33). Application of IL-1β reduces the expression of BDNF through suppression of apoptosis repressor with caspase recruiting domain, CREB and insulin receptor substrate 1 response or by increasing the phosphorilation of p38 mitogen-activated protein kinase (34). Similarly to IL-1β pathways insulin resistance in peripheral tissues (35), the "neurotrophic factor resistance" may be associated with elevation of proinflamatory cytokines, predisposing neurons to dysfunction and increased risk for degeneration (36), as shown in Figure 1A.

Some findings suggest that cytokines could not only inhibit, but also stimulate BDNF expression in neurons and thus improve neuronal survival. Intrathecal infusion of IL-6 in rats increases the concentration of BDNF mRNA in rat lumbal dorsal root ganglia (32) (Figure 1A). Tumor Necrosis Factor-alpha (TNF-α) and IL-6 increase BDNF production in human peripheral blood monocytes (Figure 1C), but IL-1β, Interferon-gamma (IFN-γ), IL-2, IL-4, IL-5, IL-13 and IL-15 did not have any effect on BDNF monocyte production (15). Treatment with IL-17 up-regulated the microglia production of neurotrophic factors (37) (Figure 1A).

The BDNF-cytokine communication seems to be rather bidirectional (presented in Figure 1A). In study of Lin et al. (2016) has been shown that application of BDNF in human Schwann cells increased the secretion of IL-6 through the Janus kinase- signal transducer and activator of transcription pathway activation (38), crucial for the development and function of the immune system (39). Also, wild type mice ($BDNF^{+/+}$) display higher IL-10 secretion in response to low-level stress compared to BDNF-deficient mice (40).

The role of BDNF and cytokines in schizophrenia

The BDNF ability to augment neuroplasticity implies that low BDNF levels may have a role in cognitive declining

observed in Alzheimer's disease, dementia (41, 42), schizophrenia (43), depression (44), and bipolar disorder (45). The influence of BDNF on dopaminergic neurons may be relevant to the pathogenesis of schizophrenia and reflect the severity or the neuronal degeneration in schizophrenia (9). BDNF increases neuronal dopamine content: modulates dopamine release relevant for neuronal plasticity in the ventral tegmental area (46) and also decreases dopamine in mesolimbic dopaminergic system (47). Reduction in BDNF expression was observed in the prefrontal cortex, striatum and hippocampus in animal models and patients with schizophrenia (48-50).

The microglia appeared to be activated in schizophrenia and have provided the main source of pro-inflammatory cytokines (51) and BDNF secretion (13, 14). The etiopathogenesis of schizophrenia is obviously related to the inflammatory responses mediated by microglia (52, 53).

Our previous results in early phases of schizophrenia suggested that type-1 and type-17 immune responses are decreased (54), type-2 response is increased and could be corrected with antipsychotics (55, 56), and higher serum levels of Transforming growth factor beta and IL-23 were measured regardless of applied therapy (57, 58).

BDNF regulation has been shown in many different types of inflammation and seems that it is not type-1 or type-2 restricted: serum levels of BDNF in schizophrenia are not in correlation with serum levels of IL-1β, IL-6, IL-8, IL-10, IL-12 and TNF-α (59), but Zhang (2016) showed a significant positive association between BDNF and IL-2 and IL-8 levels (60) (see in Figure 1B). These data are in correspondence with lower level of IL-2 in patients with early onset disease and predisposition for negative form of schizophrenia (61). Also, higher levels of IL-8 in second trimester have been linked to a higher risk for schizophrenia development (62).

The correlation between serum BDNF levels and Positive and Negative Syndrome Scale (PANSS) scores was not established in patients with schizophrenia (59, 63), but recently low BDNF levels were associated with impairment on the PANSS cognitive factor (60) and also with low cognitive scores on the Repeatable battery for the assessment of neuropsychological Status (64).

A recent meta analysis of Green at al. (2011) point out that blood levels of BDNF are reduced in both medicated and drug-naive patients with schizophrenia (65). Some studies have found a different regulation of BDNF mRNA expression in the rat hippocampus and neocortex after typical and atypical antipsychotic administration (66), where the typical antipsychotic drug haloperidol down-regulated BDNF mRNA expression and atypical antipsychotics olanzapine and clozapine up-regulated BDNF mRNA expression (67) (Figure 1C). Serum BDNF levels were higher in patients with chronic schizophrenia on clozapine or typical antipsychotics, than risperidone (68). Others showed significant decrease of IL-1β plasma levels and increase of TNF-α and BDNF after risperidone treatment (49). Some longitudinal studies have reported that lower serum BDNF levels did not increase after several weeks of antipsychotic treatment (63, 68).

Schizophrenia is associated with metabolic syndrome, expressed by type-2 diabetes and insulin insensitivity (69). This could be discussed as a consequence of unhealthy lifestyle or as a genetic predisposition that is potentiated with antipsychotic therapy (51). In schizophrenia, as in obesity, there is an imbalance between adiponectin and the pro-inflammatory cytokines TNF-α and IL-6 (70). Also, BDNF deficiency has been reported in increased food intake, hyperphagia and obesity (71). Obesity itself does not affect the value of BDNF in the serum in adults (72), but BDNF levels in plasma were decreased in patients with Metabolic Syndrome (MetS) compared with control subjects (73) (Figure 1D). For the first time, Zhang et al. (2013) tested the relationship between the BDNF Val66Met polymorphism and MetS in patients with schizophrenia under long-term clozapine treatment. BDNF serum levels appeared to be associated with clozapine-induced MetS, and that effect is only evident in male patients (71).

BDNF and cytokines in schizophrenia and atopic diseases

Results of Pedersen et al. (2012) indicated comorbidity of schizophrenia and atopic diseases, both with predominance of type-2 immune response (74). In humans, as well as in mouse models of asthma, allergen challenge increases BDNF levels in bronchoalveolar lavage fluid (75). Such increase may be a result of enhanced BDNF secretion by resident airway cells, immune cells including B-lymphocytes, eosinophils, mast cells and macrophages (75). BDNF in the presence of cytokines TNF-α and IL-13 increases proliferation of human airway smooth muscle in asthma (75). In vitro, increase of BDNF in sputum, in response to IL-13, suggests that type-2 cytokines regulate BDNF levels and activity in asthma (76). After antipsychotic treatment significant decrease of IL-13 was observed, suggesting that the BNDF- IL-13 interaction could be more thoroughly explored in schizophrenia (77). Also, IL-33, recently discovered IL-1 family member, plays a role in induction of airway contraction by stimulating expansion of IL-13-producing innate lymphoid cells (78). IL-33/ST2 signalling pathway regulates T cells, differentiation and activation of dendritic cells, activation of macrophages and mast cells and production of type 2 cytokine producing innate lymphoid cells, showed to be important in type-2 immune response in development of spontaneous obesity (79) and atopic disorders, particularly asthma (80).

As it is seen in asthma, BDNF levels are increased in serum, plasma and eosinophils in patients with atopic dermatitis (AD) (81). Patients with AD had higher eosinofilic expression of p75 NTR and TrKB in comparison with nonatopic control subjects (81). Furthermore, it has been shown that BDNF induces chemotaxis and inhibits apoptosis of eosinophils in patients with AD, indicating its role in proinflammatory actions (81). Increase in eosinophilic

count was also observed as a side effect of clozapine, an antipsychotic with BDNF- elevating properties (82). A common genetic variant of BDNF gene was associated with increased risk for developing allergic rhinitis (83). Mechanism of IL-6 and TNF-α induced neuronal hyperactivity in the allergic asthmatic patients is mediated by BDNF-secreting monocytes (15) (shown in Figure 1C).

CONCLUSION

Intriguing concept of neuroplasticity has introduced new approaches in basic and clinical research. The role of BDNF, as a member of nerve growth factor family, has been explored not exclusively in the central nervous system, but also in other peripheral tissues. Low BDNF levels or "neurotrophic factor resistance" associated with elevation of pro-inflammatory cytokines could have an impact in schizophrenia cognitive declining. The BDNF-cytokines interactions are not only restricted to type-1 or type-2 immune response. The role of IL-33/ST2 signalling pathway has been observed in MetS and atopic disorders, which are closely related to schizophrenia. This could be a rational for further research of IL-33 and BDNF interplay in schizophrenia, aiming to improve cognitive functioning and prevent metabolic dysfunction in patients with schizophrenia.

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Contributors

All authors contributed to and have approved the final manuscript.

Conflict of interest

The authors report no conflicts relevant to this paper.

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