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BIOMARKERS OF DEPRESSION: NEW CHALLENGES

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As one of the most widespread illnesses today, depression has a big social and economical significance. Therefore, enormous efforts are made in getting deeper insights into its etiology and pathogenesis, which are still unknown to us. Owing to the fast technological development, neurosciences have started to develop intensively. Neuroimaging technologies and new sensitive laboratory tests enable the discovery of active molecules that take part in pathophysiological processes so that they can be considered as potential biomarkers.

Although the biomarker which would be specific for depression has not been isolated yet, there are a lot of studies that confirm the existence of changes of the level of active substances in depressive patients with the regard to control ones. In this paper, we will take a look into potential biomarkers that ere in the centre of the research: the factors of growth, that is, brain-derived neurophic factor (BDNF), inflammatory and neuroendocrine biomarkers, as well as potential indicators of the oxidative and nitrosative stress.

This kind of the possibility of the insight into biological bases of the depressive processes would enable new ranges in diagnostics, therapies and prognosis of this disorder and would contribute to the better quality of life of patients and their families. *Acta Medica Medianae 2017;56(1):44-49.*

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Introduction

After all these years, mood disorders, especially depression, still remain in the focus of the public attention. Maybe the reason for this is the fact that no other psychiactic illness brings so much suffering as depression. According to the estimates of the World Health Organization (WHO) from the year 2000, depression is on the fourth place of all illnesses in medicine according to the number of years of living and productive working that a person loses because of the illness. Estimates are that by the year of 2020, depression will be on the second place, right behind ischemic heart disease (1).

Because this illness is so widespread and common and is of great medical and social importance, efforts of the scientists to discover both its etiology and pathogenesis are obvious. It is considered that pathogenesis is multifactorial, i.e. that biological, psychological and social factors contribute to the occurence of depression.

Owing to the development of neurosciences and numerous methods that reach the molecular level of the research, greater emphasis is put on discovering biological factors significant for the development and/or maintaining depression. The classical monoamine theory of depression (disorder on the level of serotonine, noradrenaline and dopaminergic transmission) (2-7) was put behind as a result of new findings resulting from the research of the cell genome (8) as well as neuroimaging methods (9, 10), and other molecular mechanisms including glutamineric transmission and melatonine (11).

In the last few years the focus of the researches are inflammations, due to both oxidative and nitrosative stress, that are considered to play an important role in the pathogenesis of depression (12, 13).

Biomarkers and their significance in depressive disorders

The working group (including the members of the Food and Drug Administration (FDA), Natio-

nal Institutes of Health (NIH), extramural academia and pharmaceutical industry) defined "biomarkers" as "a characteristics that is objectively measured and estimated as an indicator of the normal biological process, pathological process or pharmacological response to a therapeutic intervention" (14, 15).

In order to be clinically useful, these markers must have high sensibility and specificity as well as the possibility of reproduction and need to be acceptable for a patient i.e. examinee (14, 16). They can be detected in different ways: by testing of bodily fluids or cells, by neuroimaging, etc.

The pheripheral biomarkers are based on examining samples of blood i.e. serum or plasma. Their examining has its practical value. They are relatively noninvasive (apart from the need of taking a blood sample) and are easier for measuring, and because of this they have a greater potential for the application in a routine clinical practice than other researches such as generic and imaging ones (17).

Discovering the biomarkers of depression that could be used in the future as a routine procedure is a big challenge for the researchers. It is known that depressive disorders are heterogeneous and are diagnosed based on the symptoms (e.g. anhedony, bad mood, insomnia, suicidal ideas) and not on the basis of the laboratory tests. The research for the biological markers of depression is partly a result of the need for the additional diagnostic means. The determination of biological markers is useful in many ways. First of all, biomarkers can give the insight into the biological basis of the depressive process. Psychiatrists would get the possibility to discover the specific depressive profile for each patient and could choose the optimal treatment. The insight of the seriousness and prognosis of the illness would be made easier as well as the potential reaction to pharmacological treatment. One of the biggest problems of antidepressive treatment is the problem of the delayed effect, as for the obvious clinical improvement of the patient more than two weeks are usually necessary. The particular significance of biomarkers would be the possibility of the insight into the early improvement under the influence of medicine (within the first days, maybe hours) (18).

In the further text we will focus on the potential biomarkers whose change during the depressive conditions of a patient has been proven in numerous preclinical and clinical studies.

Brain-derived neurotrophic factor (BDNF)

BDNF or neurotrophic brain factor is a protein, coded as BDNF genom, and it is a member of the family of the growth factors. It has an effect on the neurons in the central and peripheral nervous system, supports the survival of the existing ones and growth and differentiation of new neurons and synapses (neurogenesis i.e. incitement and control of the development of new neuro cells out of stem cells). In the brain, it is active in the cortex, hippocampus and basic ganglia, as well as in regions of the brain that are of the vital significance for learning, memory, and complex thinking processes. It is its neuroplastic function i.e. the function of the regulator of the plasticity of the synapses of neural networks that connects it to the pathogenesis of the depressive disorder (19, 20). The stress-induced deficiency in the structural and synaptic plasticity of the adult brain, which is the basis for the development of the depressive disorder can be regulated i.e. reversed by the BDNF. In that way, the cognitive flexibility is reached as well as the increased possibility of adapting to living conditions and challenges that can cause or worsen depressive episodes (20).

Apart from the brain, this peptid is also present at the periphery – in the retina, kidneys, saliva and prostate. BDNF is also present in the blood where it is mostly stored in thrombocytes, but it can be measured both in serum and plasma. Karege et. al were the first who demonstrated in 2002 that the levels of BDNF in plasma of depressive patients are lower than in healthy control group patients (21, 22). Numerous studies have confirmed significantly a lower level of this molecule in the serum (23-25) of depressive people. These findings matched with the findings of the postmortem studies, where the changed BDNF levels were found in hippocampus (18), as well as in hippocampus and prefrontal cortex (26, 27). At the same time, there was a question about its normalization after antidepressive treatment, which was reported not only in some single studies but also in meta-analyses (20, 21, 23, 24, 28, 29). It is interesting that some studies suggest that there are gender difference changes of BDNF (28) i.e. that there is a significant change of BDNF in the female population during the depression as well as the normalization after the antidepressive treatment. Due to the existence of the opposite claims, these findings are to be tested on a large number of the examinees/respondents.

Finally, it is necessary to point out that changed i.e. lowered level of BDNF was recorded in other neuropsychiatric illnesses, especially in those that have joined depressive symptomatology – schizophrenia, bipolar disorder, eating disorders, etc. (21, 30).

Cytokines and inflammatory marker

Chronic inflammation and oxidative stress are connected with the pathophysiology of many illnesses e.g. cardiovascular (31, 32), kidney infections (33), rheumatoid arthritis (34), malignant illnesses (35), etc. The normal physiology of aging of cells is also connected to the immune processes (36-39).

Connecting depressive conditions to the immunology dates back to the beginning of the nineties of the last century when Smith (1991)

(39) reported about the rise of the inflammatory factors in depressed patients.

Since then, there are more and more proofs that inflammation can have an important role in pathophysiology of the depressive disorder. Inflammatory factors are included in almost all pathophysiological mechanisms in the brain, including the metabolism of neurotransmitters, as well as in neuroendocrine and neural plasticity. It is considered that the activation of the inflammatory pathways in the brain contributes to the lowering of the neutrophilic support, to the change of glutamate absorption mechanisms, as well as the oxidative stress, that leads to the toxic characteristics and lessening of glial elements in accordance with neuropathological findings that characterize depressed patients (40).

In accordance with previously listed theories, in many metha-analyses it was proven that there was the rise of proinflammatory factors in the serum of depressed patients. For example, in one of the meta-analyses based on 8 researches that included 14.832 patients, a significant connection between the increase in CRP and depressive symptomatology was detected.

In the analysis of IL-6 in three studies with 3.695 examinees, the correlation was not so clearly obvious (41). Some other meta-analysis confirms the significant connection with the level of IL-6, while similar correlation between depression and other interleukins was not found (IL-1beta, IL-4, IL-2, IL-6, IL-8, IFN-gama) (42). Numerous studies demonstrate that different therapeutic strategies (including pharmacotherapy, psychotherapy and electroshock) have a tendency to ease the inflammatory activity and depressive symptomatology, thus suggesting that lessening of the inflammation would contribute to a better response to the treatment (43-48). The data that patients resistant to treatment with antidepressants have higher levels of IL-6 in comparison with the depressed that react to the treatment (43, 44) can inspire new researches and therapeutic possibilities.

One more evidence of the connection of the inflammation and depression is that antagonists of the leukins have the antidepressive effect. TNF antagonist etanercept and inflixmab lower the symptoms of depression induced by the immune activation during psoriasis (49, 50). It has also been detected that cyclooxygenase-2 (COX-2) inhibitor of celexocib, which inhibits the production of proinhibitory cytokines, including TNF and IL-1b, produces fast antidepressive response in patients with major depression (MD) (51).

Taken together, these results raise the possibility that the reduction of the inflammatory process can improve the therapeutic response and that inhibition of the pro-inflammatory molecules can be a promising strategy for treating depressed patients with the higher level of cytokine profiles (20).

Markers of the oxidative and nitrosative stress

Parallel with the inflammatory factors in the last few years, there is intensive research of the markers of the oxidative and nitrosative stress and their role in pathogenetic processes in depression. There are more and more pieces of evidence that depression is followed by the lowered antioxidative status. In plasma of depressive patients there is a lower level of many key antioxidants such as vitamin E, zinc, coenzyme Q 10, as well as the total of the oxidative status. A lowered antioxidant enzyme activity e.g. glutathione preoxidase (GPX) is another characteristic of depression. The abovementioned lowered antioxidative capacity can worsen the protection against free radicals (ROS), which damage fatty acids, proteins and DNA. The damage caused by the oxidative and nitrosative stress is manifested by the higher level of malondialdehyde (MDA), which is a product of peroxidation of polyunsaturated fatty acids and arachidonic acid and the rise in the level of 8 hydroxy 2 deoxiguanosine, which is an indicator of oxidative damage of DNA. These changes serve as a trigger of the immune tolerance i.e. they cause immune i.e. autoimmune response (13).

Neuroendocrine markers

Depressive patients have a changed neuroendocrine function i.e. changed regulation of HTA axis that leads to the higher release of the corticotrophin hormone (CRP) and in some cases maintains the level of cortisol (52). Glucocorticoids (cortisol in people and corticosteron in rodents) bind their receptors of HPA (hypothalamic–pituitary–adrenal) axis and have the effect of negative regulators of HPA activity. It is considered that the higher level of cortisol in depressed patients is a compensatory mechanism as a response to the lessening of the function of glucocorticoid receptor and expression in the brain.

Cortisol is not high in all depressed people. According to some data, people who belong to melancholic subtype of depression (melancholic, psychomotorically slowed down) have a greater chance to have a rise in the activity of HPA axis than people who are not melancholic i.e. psychomotorically agitated patients (20, 53).

The inflammatory markers, including cytokines, regulate the neuroendocrine function (40). They can jeopardize the function of the HPA axis and its negative feedback. It was noticed long ago that the acute administration of cytokines raises the release of CRH, adrenocorticotropic hormone ACTH and cortisol (54). Glucocorticoids have a clear effect on inflammations, (55), which is widely used in therapeutic purposes.

Because of a close connection between inflammation and neuroendocrine factors, there are a lot of biomarkers that can be followed, in the

sense of following pathways by which the immune system has the effect on the brain. Cytokines can be monitored as well as inflammatory mediators (COX-2, prostaglandins), reactive molecules of nitrogen (nitrogen monoxide), and the receptors e.g. glucocorticoid receptors. Monitoring of these potential markers during an anti-depressive treatment can help to identify the population of patients who react to anti-inflammatory therapy (40).

Conclusion

In spite of the great promises of biomarkers in all fields of medicine, less than 150.000 recorded biomarkers were confirmed and qualified for the routine clinical practice. Common difficulties are the deficiency of standardization in collecting and storage of samples, inadequate accommodation of samples (from the examined and control group), inadequate number of samples etc. (14). Psychiatry has long been at the back of all these researches, but in the last few years there has been a fast development of neurosciences. Here, first of all, we have to point out the neuroimaging technologies (structural, functional, biochemical and neurophysiological methodologies). Sensitive and specific tests discover in serum active molecules that take part in pathogenesis of the depressive disorder - indicators of the oxidative stress, inflammations, factors of growth. It is considered that significant results have been achieved. There is a realistic possibility for the further development of technology together with computer statistics and other services, which will lead to important improvement in both diagnostics and therapy. "The personalized" therapy i.e. therapy adjusted to each single patient thanks to the development of biomarkers is no longer an unattainable goal.

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BIOMARKERI DEPRESIJE- NOVI IZAZOVI

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Kao jedna od najrasprostranjenijih bolesti današnjice, depresija ima veliki socijalni i ekonomski značaj. Zato se značajni napori ulažu u rasvetljavanje njene etiologije i patogeneze, koja je još uvek nepoznata. Zahvaljujući brzom tehnološkom razvoju poslednjih godina, dolazi do intenzivnog razvoja neuronauka. Neuroimidžing tehnologije i novi osetljivi laboratorijski testovi omogućavaju otkrivanje aktivnih molekula koji učestvuju u patofiziološkim procesima, pa se zato mogu smatrati potencijalnim biomarkerima.

Iako još nije izolovan biomarker koji bi bio specifičan za depresiju, u velikom broju studija je potvrđeno postojanje promena nivoa aktivnih supstanci kod depresivnih u odnosu na kontrolu. U ovom tekstu osvrnućemo se na potencijalne biomarkere koji su u fokusu istraživanja: faktore rasta, tj. brain-derived neutrophic factor (BDNF), inflamatorne i neuroendokrine biomarkere, kao i potencijalne indikatore oksidativnog i nitrozativnog stresa.

Ovakva mogućnost uvida u biološke osnove depresivnog procesa omogućila bi nove domete u dijagnostici, terapiji i prognozi ovog poremećaja i doprinela boljem kvalitetu života bolesnika i njihovih porodica. *Acta Medica Medianae 2017;56(1):44-49.*

Ključne reči: *depresija, biomarkeri, inflamacija, oksidativni stres*