REVIEW

Comparative Analysis of Pathobiochemical Changes in Major Depression and Post-Traumatic Stress Disorder

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Abstract—Comparative analysis of available literature data on the pathogenetic neuroendocrine mechanisms of depression and post-traumatic stress disorder (PTSD) is provided in this review to identify their common features and differences. We discuss the multidirectional modifications of the activity of cortical and subcortical structures of the brain, levels of neurotransmitters and their receptors, and functions of the hypothalamic-pituitary-adrenocortical axis in depression and PTSD. The analysis shows that these disorders are examples of opposite failures in the system of adaptive stress response of the body to stressful psychotraumatic events. On this basis, it is concluded that the currently widespread use of similar approaches to treat these disorders is not justified, despite the significant similarity of their anxiety-depressive symptoms; development of differential therapeutic strategies is required.

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INTRODUCTION

Depression, or major depressive disorder (MDD) is currently one of the most wide-spread diseases in the world, and not only among the psychiatric ones. A less common disease, post-traumatic stress disorder (PTSD), has also a post-stress nature. Despite the great role of genetic predisposition and belonging to different nosologic groups (F33.2 and F43.1 according to the International Classification of Diseases, ICD-10, respectively), the common feature of these disorders is their development as a result of intense or chronic exposure to stress (psychotraumatic nature), as well as a number of similar symp-

toms. Moreover, there is a high degree of comorbidity between PTSD and depression [1] that suggests the presence of common etiological factors leading to the development of these states. Yehuda and Antelman [2] have reported that duration and intensity of exposure to the traumatic agent is of great importance for formation of PTSD or depression-like state in animals. At the same time, a short-term exposure of high intensity leads to the development of PTSD more frequently, whereas depressive disorders develop as a result of prolonged exposure to stressful situations of mild intensity. However, despite a number of common symptoms and etiological factors, these two states have pronounced pathophysiological differences, and to some extent, even can be considered as opposites. This issue is discussed in the present review as an attempt to demonstrate that the considered post-stress conditions often exemplify differently directed disorders in the system of the organism's adaptive response to psychotraumatic events. In our opinion, comprehensive comparative study of the pathogenetic mechanisms of these states could facilitate development of objective methods for their differential diagnosis, creation of selective therapeutic approaches, identification of the role of individual and hereditary predisposition and its targeted correction.

Abbreviations: 5-HT1A, 1A-type serotonin receptors; ACC, anterior cingulate cortex; BDNF, brain-derived neurotrophic factor; CRH, corticotropin-releasing hormone; DMN, default mode network; dlPFC, dorsolateral prefrontal cortex; GR, glucocorticoid receptors; HPA axis, hypothalamus-pituitary-adrenocortical axis; MDD, major depressive disorder; mPFC, medial prefrontal cortex; PFC, prefrontal cortex; PTSD, post-traumatic stress disorder; SSRI, selective serotonin reuptake inhibitor; vmPFC, ventromedial prefrontal cortex.

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BRAIN STRUCTURES INVOLVED IN PATHOGENETIC CONTOURS IN PTSD AND DEPRESSIVE DISORDER

The cortico-limbic network and the default mode network (DMN) are the major neural networks investigated in the framework of MDD and PTSD pathogenesis. DMN includes ventromedial PFC (vmPFC) and dorsolateral PFC (dlPFC), lateral parietal cortex, and cingulate cortex with posterior cingulate gyrus and adjacent precuneus regions.

Connections between the brain structures in DMN, which combines orbitofrontal cortex with hypothalamus, amygdala, and hippocampus are changed in patients with MDD [3]. Pronounced microstructural changes are observed in the medial PFC and hippocampus of the patients with MDD, even in the remission state, as well as increase in the number of fibers connecting amygdala with other brain regions [4-6]. In addition to the decrease in the hippocampus volume, its activity was found to be asymmetric in the MDD patients, and increase in the blood flow in the region of amygdala nuclei was observed [7].

In the cortico-limbic networks the observed changes are associated not only with the grey matter, but also with the density of glial cells that is characteristic for MDD [8]. Increase in the number of connections between the amygdala, hippocampus, and basal nuclei could explain selective improvement of the memory about negative events in the patients with MDD in comparison with the healthy individuals not exhibiting such changes [9]. In patients with PTSD the described alterations specific for MDD were not observed in functioning of the cortico-limbic network and of DMN, however, a disorder was observed in the connections of the posterior cingulate cortex and precuneus with other DMN parts [10].

The PFC involvement in pathogenesis of the considered post-stress disorders was also confirmed by the data that the blood flow and glucose metabolism in patients with MDD were increased in the ventromedial PFC associated with regulation of emotions, whereas opposite changes were found in the dorsolateral PFC [11]. The importance of vmPFC in the MDD development was confirmed by the finding that the patients with damaged vmPFC got fewer points on the scale of the severity of depression symptoms than the patients with lesions in other parts of the brain [12]. In contrast to the patients with MDD, the patients with PTSD exhibited decreased blood flow in the vmPFC [13]. There are also data on the effect of dlPFC activity on manifestation of the PTSD symptoms: increased activity of dlPFC is associated with less pronounced symptoms of this disorder [14]. The results obtained in the experiments on animals demonstrated inhibitory effect of the prefrontal cortex neurons on the amygdala nuclei [15], which was in a good agreement with the data on changes in the activity of these structures PTSD.

Increase in the blood flow and glucose metabolism has been observed in the anterior cingulate cortex (ACC) of patients with MDD [16]. These data are in agreement with the studies on experimental animals. Thus, Barthas et al. [17] demonstrated involvement of ACC in the development of pathology in the model of chronic pain-induced depression [17]. In this case, chronic optogenetic stimulation of the ACC neurons led to formation of the depression-like behavior in intact animals. On the contrary, the blood flow intensity in the ACC was reduced in the patients with PTSD [18]. Thus, multidirectional changes were observed at the level of the cortex structures in these mental disorders: increase in the depressive disorders and decrease in PTSD.

Although the same neural networks and brain parts are associated with pathogenesis of MDD and PTSD, the observed changes in them are different in these pathologies, and, moreover, these changes are of opposite directions in some considered brain structures.

REARRANGEMENTS OF HYPOTHALAMIC- PITUITARY-ADRENOCORTICAL AXIS IN DEPRESSION AND PTSD, AND THEIR ASSOCIATION WITH NEUROPLASTICITY AND INFLAMMATION

Normally, glucocorticoid hormones bind to mineralocorticoid receptors (MR) at low concentrations, whereas at high concentrations (e.g., at stress response) they bind to glucocorticoid receptors (GR) through which the strength of the hypothalamic-pituitary-adrenocortical axis (HPA axis) reaction is regulated under stress conditions by the negative feedback mechanism. Glucocorticoids decrease secretion of corticotropin-releasing hormone (CRH) and adrenocorticotrophic hormone (ACTH) and thus decrease their own level via the negative feedback on levels of pituitary gland, hypothalamus periventricular nucleus, and hippocampus [19].

Multilevel changes are observed in the functioning of HPA axis of the MDD and PTSD patients, which are specific and can be reproduced in animal models of these disorders. Furthermore, the patients with MDD display an increased level of cortisol in blood [20] and of CRH in hypothalamus [21], whereas the patients with PTSD can have both normal [22] and decreased basal levels of blood glucocorticoids [23]. Such changes can be caused by different sensitivities of the negative feedback mechanisms: they are considered sensitized in PTSD [24] and desensitized in MDD [25].

Changes in the density of glucocorticoid receptors in the brain structures involved in pathogenesis of MDD were found in the post-mortem study of the patients' brains in the amygdala [26] and hippocampus [27]. Reduced level of glucocorticoid receptors in animal models of depression was observed in the hippocampus, PFC,

and hypothalamus [28]. The observed decrease in the number of GRs on the background of increased level of glucocorticoids and CRH reflects the down-regulation phenomenon.

The chronically increased level of glucocorticoids in MDD can explain the previously mentioned decrease in the volume of hippocampus, where neurons are thought to be harmed by high concentrations of glucocorticoids [29]. It is likely that precisely the decrease of the inhibitory effect of hippocampus on CRH secretion in the hypothalamus paraventricular nucleus caused by this leads to the detected desensitization of the HPA axis. Development of the depression-like pathology observed in animals subjected to chronic injections of glucocorticoids speaks in favor of the pathogenetic role of hypercortisolemia in depression [30].

Glucocorticoids have a pronounced effect on neuroplasticity and neurogenesis; they decrease expression of the brain-derived neurotrophic factor (BDNF) [31], content of which decreases significantly in different brain section under the action of chronic stress and is reported for MDD and PTSD [32]. Such changes became a basis for the neuroplastic theory of depression development, and the antidepressive effect of serotonergic preparations is now believed to be BDNF-mediated [32, 33].

In addition to the effect on the CNS functioning, such long-term high levels of glucocorticoids lead to the changes in immunity shifting the balance to chronic inflammation with high level of pro-inflammatory cytokines and neuroinflammation (which is especially important) accompanying the course of depressive disorder [34]. Introduction of proinflammatory cytokines leads to the development of depression-like symptoms [35], and exposure to lipopolysaccharides is used to induce depression in animal models [36]. Similarly to glucocorticoids, the cytokine IL-1 β also decreases the BDNF expression [37]. As with other changes observed in depression, when it is difficult to find out whether they are the cause or consequence of the disease, this phenomenon became the basis for the inflammatory theory of depression development [38]. However, regardless of the secondary or primary nature of these changes, they undoubtedly have strong effect on the HPA axis functioning and the course of depression, respectively.

In patients with PTSD with decreased or unchanged basal level of cortisol in blood, the level of CRH in the cerebrospinal fluid is increased [39]. We also demonstrated hyperproduction of the hypothalamus-derived CRH in the rat PTSD model [40]. At the same time up-regulation of the number of glucocorticoid receptors was detected in the medial PFC [41] and hippocampus in PTSD models, while their number in the amygdala nuclei was unchanged [42].

Thus, it can be stated that modifications of the HPA axis functions in MDD and PTSD exhibit complex bidirectional interactions, that makes it difficult to separate

them into conditionally primary (pathogenetic) and secondary due to subsequent rearrangements of the whole system via the feedback mechanisms. It seems that depression and to the lesser degree PTSD, as a disease with more heterogenous manifestations, also have heterogenous neuroendocrine disorders accompanying them.

MODIFICATIONS OF ACTIVITY OF THE BRAIN MONOAMINOERGIC SYSTEMS

The monoamine theory of MDD is the oldest among the existent theories of this disorder pathogenesis [43]. In the literature a great amount of data is accumulated on changes in the serotonergic neuron functioning in MDD in humans [44], as well as in the models of depression-like conditions in rodents with a decreased level of serotonin found in the PFC and hippocampus [45]. This decrease was accompanied by a compensatory increase in the expression of serotonin receptors in these structures [46, 47]. Changes in the dopaminergic system in MDD include decrease in the levels of dopamine and its metabolites in the cerebrospinal fluid [48] and decrease in the density of dopamine receptors in the nucleus accumbens [49]. Concurrently, increase in the dopamine level in the ventral cover was shown in the rat model of chronic pain-induced depression [50]. The studies on the depression-like syndrome in experimental animals revealed increase in the expression of D2-receptors of dopamine in the prefrontal cortex [51] and decrease in the expression of D2-dopamine receptors in the nucleus accumbens [52]. Furthermore, the deficiency of D2-receptors observed in the limbic system structures of the models in the depression-like state is alleviated following long-term administration of the tricyclic antidepressant imipramine [53].

The increased anxiety of rats in the PTSD model is accompanied by the increased level of dopamine in the PFC. It is known that dopaminergic fibers in this brain area are involved in realization of the fear-associated behavior [54], as well as in the emergence of emotionally colored memory [55], which is in agreement with the appearance of specific behavior symptoms in PTSD. Moreover, there are data on the anxiolytic effect of the dopamine D3-receptors antagonists in the rat PTSD models [56].

Changes in the serotonergic synapses detected in the patients and in PTSD models are more heterogenous. In particular, increase in the density of serotonin 1A-type receptors in the hippocampus (5-HT_{1A}) [57] and in the density of serotonin 2C-type receptors in the amygdala (5-HT_{2C}) was shown [58]. At the same time, decrease in the expression of 5-HT_{1A} receptors in the cingulate gyrus and suture nuclei was reported [59]. No changes were observed in the density of 5-HT_{1A} receptors [57]. Despite some inconsistency of the available data, in gen-

eral, excessive activation of serotonergic synapses was observed in PTSD in the subcortical formations in response to stress conditions [60].

Decrease in the norepinephrine levels in the medial PFC and the nucleus accumbens was shown in the experimental animal model of depression, and substances facilitating increase in the norepinephrine level led to disappearance of the depression-like behavior [61]. Thus, the depressive disorder is characterized by the pronounced decrease in the activity of adrenergic neurons, whereas PTSD is characterized by activation of this system of the brain: this is associated with the increase in the norepinephrine level under conditions of chronic and acute stress in the PFC, hippocampus, and amygdala [60, 62]. Increased levels of norepinephrine and its metabolites in the amygdala were detected also in the rat PTSD models [63].

Based on the monoamine theory of depression several groups of antidepressants were developed, which affected the level of monoamines. These antidepressants are used up to now, however, therapeutic effect of these preparations is manifested several weeks after the beginning of the therapy, despite the immediate effect on the monoamine neurotransmission. Moreover, not all pharmaceuticals increasing the monoamine level in the synaptic cleft are antidepressants, such as stimulants [64]. Such findings suggest more complex and delayed mechanisms of the antidepressive effect based on the changes in neuroplasticity and reorganization of pathological neuronal bonds, but not on elimination of the neurotransmitters disbalance, as suggested in the monoamine theory of depression. Moreover, the observed changes in the functioning of the monoamine neurotransmission in MDD could be of the secondary nature.

CHANGES IN ACTIVITY OF THE BRAIN GLUTAMATERGIC SYSTEM

Enough data have been accumulated to date on changes in the glutamatergic system that emerge in the depressive and post-traumatic disorders, however, as in the case of other neurotransmitters systems, it is rather difficult to identify whether the observed changes are of primary or secondary nature.

Administration of ketamine, an NMDA receptor antagonist, rapidly leads to manifestation of antidepressive effect in humans with MDD [65], glutamate deficit was detected in the medial PFC [66], ACC [67], and the amygdala nuclei [68], and it was also accompanied by the increase in expression of the NMDA-receptors in the amygdala nuclei [69]. Decrease in the density of metabotropic receptors and of NMDA-receptors in the medial PFC has been reported recently for the patients with depression [70]. The antidepressive effect of ketamine could indicate involvement of the glutamate trans-

mission disorder in the pathobiochemical mechanisms of MDD. Transient increase in the concentration of glutamate following ketamine injection could lead to the release of BDNF, which in its turn affects neuroplasticity disturbed in MDD [71].

Studies with PTSD patients revealed increase in the glutamate level in blood plasma [72], in the occipital-parietal areas of the cerebral cortex [73], and in the right hippocampus [74]. Decreased level of glutamate was found in the ventromedial PFC, which is characterized by the decreased activity in PTSD [75]. Increase in the density of the type-5 metabotropic receptors (mGluR5) was observed in the hyperactivated dorsolateral PFC [76].

Hence, in depression the glutamatergic system is suppressed in the prefrontal cortex, amygdala, and hippocampus, whereas the changes observed in the PTSD patients are more pronounced in the prefrontal cortex structures and characterized by sensitization of the neurons in this area to glutamate action.

PHARMACOTHERAPY OF MDD AND PTSD

The first choice of MDD treatment in the majority of cases are selective serotonin reuptake inhibitors (SSRIs) and/or of norepinephrine re-uptake. The second and third choices include non-selective inhibitors of monoamine reuptake and inhibitors of monoamine oxidase. However, the efficiency of antidepressants remains low and frequently is different from that of placebo only in the cases of severe depression [77]. To affect neuroplasticity more selectively and without side effects inherent for the existent monoamine antidepressants, a new class of therapeutics, "psychoplastogens", is being developed [78].

To date the PTSD pharmacotherapy is mainly symptomatic, most often the SSRI-antidepressants are prescribed, but their efficiency remains questionable [79]. Some researchers believe that administration of SSRI in PTSD in the absence of a comorbid depressive disorder has not been justified [80]. Using of adrenoblockers in PTSD, even those with a preferentially peripheral action, such as prazosin [81] is reasonable for eliminating the biological positive feedback, which underlies development of panic attacks in the patients with anxiety disorders (table).

CONCLUSIONS

In the present review we attempted to generalize and provide comparative analysis of the accumulated data on mechanisms of MDD and PTSD pathogenesis. Wide variety of the involved neurotransmitters and neuroendocrine systems and of the brain contours along with abundance of different modality connections between

Changes detected in depression and PTSD

Effects	Major depression	Animal models of depression	PTSD	Animal models of PTSD
Changes in the DMN functioning	pronounced [3]	pronounced [3]	partial [10]	—
Changes in the work of cortico-limbic network	pronounced [8, 9]	pronounced [8, 9]	partial [10]	—
Change in the hippocampus volume	decrease [6]	decrease [6]	—	—
Activity of the HPA axis	desensitization [25]	desensitization [25]	sensitization [24]	sensitization [24]
Glucocorticoid receptors in the hippocampus and PFC	decrease [26, 27]	decrease [28]	increase [41]	increase [41]
Neuroinflammation	pronounced [34]	pronounced [35, 36]	—	—
Activity of serotonergic system	decrease [44]	decrease [45]	increase [57-59]	increase [60]
Activities of the norepinephrine- and dopaminergic systems	decrease [48, 61]	decrease [50-52, 61]	increase [54, 55, 60]	increase [56, 63]
Change in the activity of the glutamatergic system	pronounced [66-68]	—	sensitization [72-74]	—
BDNF and neuroplasticity	decrease [32, 33, 71]	decrease [37]	—	—

Notes. Designations: BDNF, brain-derived neurotrophic factor; DMN, default mode network; HPA axis, hypothalamic-pituitary-adrenocortical axis; PFC, prefrontal cortex.

them makes generalization of the pathological changes a really difficult problem. In total, it may be concluded that these mental disorders have many common features (from etiological factors to neurotransmitter and hormonal systems involved in pathogenesis of these conditions). However, it is obvious that based on the nature of the majority of pathogenetic changes considered in the review, these states can be opposed to each other, which makes application of similar pharmacotherapeutic treatment strategies of these different disorders unreasonable. Obviously, MDD and PTSD are examples of differently directed disorders in the stress-adaptation mechanisms and require development of different approaches to their treatment.

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