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REVIEW

Synaptic Microenvironment in Depressive Disorder: Insights from Synaptic Plasticity

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Abstract: Depression is a major disease that can affect both mental and physical health, limits psychosocial functioning and diminishes the quality of life. But its complex pathogenesis remains poorly understood. The dynamic changes of synaptic structure and function, known as synaptic plasticity, occur with the changes of different cellular microenvironment and are closely related to learning and memory function. Accumulating evidence implies that synaptic plasticity is integrally involved in the pathological changes of mood disorders, especially in depressive disorder. However, the complex dynamic process of synaptic plasticity is influenced by many factors. Here, we reviewed and discussed various factors affecting synaptic plasticity in depression, and proposed a specific framework named synaptic microenvironment, which may be critical for synaptic plasticity under pathological conditions. Based on this concept, we will show how we understand the balance between the synaptic microenvironment and the synaptic plasticity network in depression. Finally, we point out the clinical significance of the synaptic microenvironment in depression.

Keywords: depression, synaptic plasticity, synaptic microenvironment, glia, influence factors

Introduction

Depression is nowadays a major common mental illness in most societies worldwide and has become an important public health problem.[1] It will seriously affect physical and mental health.[2] The World Health Organization estimates that more than 350 million people worldwide suffer from depression.[3] According to the Global Burden of Disease Study 2017, depression was one of the leading level 3 causes of years lived with disability (YLDs) counts in 2017, whereas this was not the case in 1990.[4] China has 56.36 million people suffering from depression in 2017, accounting for 21.3% of total subjects in the world.[5] However, many patients with depression do not receive extensive diagnosis and treatment, which is possibly due to ambiguous and confusing concepts, stigma, multimorbidity, lack of effective therapies, inadequate mental-health resources and the absence of reliable and valid biomarkers.[6]

Synaptic plasticity refers to the capacity of pre-existing connections between two neurons to change their original strength with neural activity.[7] It has long been believed that synaptic plasticity in the adult brain represents the cellular mechanism of learning and memory.[8] However, with the growing knowledge of mental illness, synaptic plasticity has been gradually found to be one of the important neural mechanisms of depression.[9] Interestingly, mounting evidence suggests that synaptic

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plasticity is often influenced by the synaptic microenvironment, such as astrocytes and microglia.[10,11] Meanwhile, cytokines and their receptors can exert a regulatory effect of brain synaptic plasticity.[12] In addition, synaptic remodeling depends on the signaling between the serotonin receptor and extracellular matrix, which is deeply associated with synaptic plasticity.[13] In this review, we briefly evaluate the current studies on the role of synaptic plasticity in depression. More specifically, we discuss the role of immune signaling, oxidative stress, mitochondria, glia and neurotransmitter in synaptogenesis, and how these factors regulate synaptic plasticity as part of the synaptic microenvironment. Finally, we point out the clinical significance of the synaptic microenvironment in depression.

Role of Synaptic Plasticity in Depression

Synapses are the sites of contact and point-to-point information transmission between neurons and their partner cell.[14] Each synapse is mainly composed of presynaptic structure, synaptic gap, postsynaptic structure and supporting cells, which act as a specialized neural junction. Presynaptic cells assemble the secretion mechanism of the neurotransmitter, while postsynaptic cells assemble components to receive and integrate this signal.[15] During this dynamic process, the function and/or structure of synapses change, which is called synaptic plasticity and is also a key link in several neurological diseases.

Although considerable progress has been made in the pathophysiology of depression, there is no single mechanism that can explain all aspects of the disease satisfactorily so far.[16] At present, it is believed that the decline of monoamine hypothesis transmitters system, enhancement of the hypothalamic–pituitary–adrenal (HPA) axis, inflammatory activation, decreased neuroplasticity and neurogenesis, changes in brain structure and function, genes, environmental milieu and epigenetics are involved in the pathogenesis of depression.[17] In addition, synaptic plasticity may be another important aspect.

Existing studies have also shown that the occurrence of depression is closely related to changes in synaptic plasticity.[18] This possibility has been found in preclinical and clinical studies of stress, depression and antidepressants.

Firstly, as we all know, chronic stress has a crucial role in the development of psychiatric diseases, such as anxiety and depression, and stress differentially affects the DSM-5 depressive symptoms.[19,20] Even though none of the animal models developed so far perfectly reproduce the depression-like phenotype observed in humans, breakthroughs have still been found in rodents over the last few decades.[21] Chronic stress can lead to a wide range of behavioral deficits in rodents, including decreased sucrose preference, motivation for reward stimuli and sexual behaviors, along with increased aggression, anxiety-like behaviors and altered sleep patterns.[22] A preclinical study has shown that brain-derived neurotrophic factor (BDNF), which plays a key role in synaptic plasticity, is significantly reduced in the hippocampus tissue in chronic unpredictable stress (CUS) depressed model rats.[23] Meanwhile, a study focused on the effects of authentic stress and transmitted stress on nerve synapses found that both of them in mice primed paraventricular nucleus of the hypothalamus (PVN) corticotropin-releasing hormone (CRH) neurons, enabling the induction of metaplasticity at glutamate synapses.[24] Another basic study shows that exposure to stress alters spine morphology, function and plasticity and that antidepressants, particularly new rapid-acting agents, can reverse these effects.[25] Also, early life stress (ELS) has been proved to impair fear memory in 6-month-old mice and decreased hippocampal long-term potentiation (LTP) synaptic plasticity as well as the paired-pulse ratio (PPR), and this mechanism is related to the reduction of hippocampal GluN2B expression.[26]

Secondly, clinical studies demonstrate that the volume of hippocampus and medial prefrontal cortex in depression patients is significantly reduced, neurons and glial cells atrophy with loss in vulnerable brain regions, such as hippocampus and prefrontal cortex, and the number of synapses is significantly lower.[27] A prospective trial of 220 patients with major depressive disorder (MDD) who were non-responders to a previous antidepressant showed replicated expression of genes related to synaptic plasticity such as ZNF804A rs7603001, CREB1 rs2254137 and CHL1 rs2133402.[28] A study using anatomical brain magnetic resonance imaging in a randomized, double-blind, placebo-controlled trial (RCT) of antidepressant medication for 10 weeks' duration in patients with dysthymia found that, at baseline, patients had diffusely thicker cortices than did healthy participants, and patients who had thicker cortices had proportionately less severe symptoms; these findings provide in vivo evidence within an RCT for the presence of neuroanatomical plasticity in depression.[29]

In addition, most antidepressants can significantly affect the levels of monoamine neurotransmitters secreted by synapses predominantly, and modulate synaptic

transmission using the neurotransmitter glutamate,[30] showing that antidepressants can regulate synaptic plasticity. As a rising star in the field of antidepressants, ketamine can induce rapid and sustained antidepressant action by regulating downstream mechanisms of synaptic plasticity, including BDNF, eukaryotic elongation factor 2 (eEF2), mechanistic target of rapamycin (mTOR) and glycogen synthase kinase-3 (GSK-3).[31] Ketamine may act in a complementary manner to exert acute changes in synaptic plasticity in the CA3 subregion of the hippocampus,[32] resulting in sustained strengthening of excitatory synapses, which are necessary for antidepressant behavior. In addition, a basic study has found that the prefrontal circuit plays a critical role in sustaining specific antidepressant behavioral effects and maintaining long-term behavioral remission through repeated longitudinal imaging of medial prefrontal microcircuits in the living brain, and antidepressant-dose ketamine reversed these effects by selectively rescuing eliminated spines and restoring coordinated activity in multicellular ensembles that predict motivated escape behavior.[33] Also, a single injection of ketamine or its metabolite (2R, 6R)-hydroxynorketamine (2R, 6R)-HNK can induce enduring alterations in the function of AMPA receptors (AMPARs) and synaptic plasticity in brain regions involved in reward-related behaviors.[34]

Gender Differences in Depression and Synaptic Plasticity

Clinical studies have shown that women are more susceptible to depression than men.[35] Gender differences in depression have been associated with social, cultural, as well as biological factors.[36] One study indicated that neuroactive estrogenic and androgenic steroids influence synaptic transmission in both directions, finely modulating synaptic plasticity in several brain regions including the hippocampus CA1 region. While estrogens facilitate LTP, androgens are involved in the induction of long-term depression (LTD) and depotentiation (DP) of synaptic transmission.[37] Another study using a 64-channel multielectrode (MED64) system to record synaptic plasticity in the ACC of male and female adult mice found that LTD was greater in slices of ACC in male mice than in female mice.[38] In addition, synaptic-plasticity protein markers, including postsynaptic density 95, synaptophysin and growth-associated binding protein 43, had significantly lower expression levels in the maternal separation (MS) group than in the non-MS (NMS) group. Metabolomics analysis shows that the MS model caused adult Sprague-Dawley (SD) rats to be susceptible to depression, which may regulate synaptic plasticity through arginine and proline metabolism; pantothenate and CoA biosyntheses; glutathione metabolism; and phenylalanine, tyrosine and tryptophan biosyntheses. All these studies reflect the impact of gender differences on synaptic plasticity in depression.

In spite of extensive preclinical studies in animal models for depression that have been used for understanding the mechanisms of the disease as well as for new drug development, a substantive lack of attention to sex-specific phenotypes in depression might mask the effect of gender on the outcome, even on the recurrence.[39–41] So, a more systematic consideration of the influence for synaptic plasticity on biological gender as a variable in depression research will be essential in the discovery and development of pharmacotherapies that are effective for both men and women.

Role of Synaptic Microenvironment in Synaptic Plasticity in Depression

At a certain stage of neuron development, the differentiation of its chemical properties is plastic, and the formation of neurotransmitters and synapses will change accordingly. Of course, the differentiation of neurons and the changes of neuronal synaptic plasticity are not only affected by the transmission of information centers, but also closely related to the ion concentration of contact neurons and their surrounding cells, which we call the synaptic microenvironment.

The synaptic microenvironment refers to the neuron synapses and their surrounding environment at microscopic level. This concept usually needs to be understood from a holistic perspective, not only focusing on changes in the structure and function of synapses in diseases, but more importantly focusing on the impact of the surrounding environment on synapses, similar to the concept of the tumor microenvironment. Under this concept, changes in synaptic plasticity in depression not only focus on the remodeling of the synapse itself, but also focus on the influence of the environment around the synapse on the plasticity of the synapse. In such a microenvironment, the mechanism of interaction of many factors, and how to analyze it qualitatively and quantitatively, has always been an important proposition in neuropsychiatric research, and the same is true for depression research.

Structural Changes of Synaptic Microenvironment in Relation to Synaptic Plasticity

As the connection between neurons, synapses are closely related to their surrounding changes. We mainly focus on the extracellular matrix (ECM), neurovascular units and glial and other cells. These areas are briefly summarized and illustrated here.

Firstly, investigators have demonstrated that the ECM molecules, which are synthesized by neurons and glial and non-neuronal cells, form highly organized ECM structures around cell somata, axon initial segments and synapses and play a prominent role by regulating the closure of critical periods of synaptic plasticity.[42,43] These molecules includetenascin R (TNR), reelin, chondroitin sulphate proteoglycans (CSPGs), tenascin-C (TN-C) and integrins.[44–48] Also, the ECM plays a dual role, not only as an accelerator of structural and functional plasticity, but also as a biodegradable stabilizer of neural microcircuits, which is important for mental health.[49] A study mechanistically links a signaling pathway involving the serotonin 5-HT7 receptor (5-HT7R), matrix metalloproteinase 9 (MMP-9), the hyaluronan receptor CD44 and the small GTPase Cdc42, and found that 5-HT7R stimulation increases local MMP-9 activity, triggering dendritic spine remodeling, synaptic pruning and impairment of LTP.[50]

Secondly, the neurovascular plasticity of hippocampus is an important theory underlying major depression. Published research shows that the neurovascular unit, which includes neurons, astrocytes, pericytes and microglia as well as the blood vessels themselves, participates actively in neurostructural changes and mediates the bioavailability of cytokines and molecular mediators, and is fundamental for the synaptic plasticity.[51,52] A study investigating the structural plasticity of the hippocampus with ketamine found that neurovascular changes of the hippocampus could be one of the possible mechanisms underlying the sustained antidepressant effect of ketamine, by altering the number of the excitatory synapses as well as the neuronal number and length of the microvessels in the hippocampus.[53] This fully confirms our argument.

Thirdly, synaptic plasticity is obviously influenced by three main non-neuronal cells: astrocytes, microglia and oligodendrocytes. Recent studies indicate that glial cells, which include astrocytes and microglia, tightly and dynamically interact with the processing of synaptic information in depression.[54,55] A study identified that chordin-like 1 (Chrdl1), which is restricted to cortical astrocytes in vivo, is necessary and sufficient to induce mature GluA2-containing synapses to form. Astrocytes, via the release of Chrdl1, promote GluA2-dependent synapse maturation and thereby limit synaptic plasticity.[56] Another study expressed the Gq-coupled receptor hM3Dq in CA1 astrocytes, which can activate the astrocytes by a designer drug, and found that astrocytic activation is not only necessary for synaptic plasticity, but also sufficient to induce NMDA-dependent de novo LTP in the hippocampus that persisted after astrocytic activation ceased.[57] Studies also confirmed the molecular interaction between neurons and microglia that drives experience-dependent synapse remodeling in the hippocampus. The cytokine interleukin-33 (IL-33), which is expressed by adult hippocampal neurons, defines a neuronal subset primed for synaptic plasticity. Also, the neuronal IL-33 instructs microglial engulfment of the extracellular matrix (ECM), and its loss leads to impaired ECM engulfment and a concomitant accumulation of ECM proteins in contact with synapses.[58] Besides, NogoA is mainly expressed by oligodendrocytes, but also in the hippocampus where it is found at synaptic sites, which indicates that the oligodendrocytes also limited synaptic plasticity.[59] A study using fusion proteins to track synaptic vesicle localization and membrane fusion in zebrafish during developmental myelination also investigated expression and localization of PSD95, a dendritic post-synaptic protein, within oligodendrocytes.[60] This work raises the possibility that axon–glial communication contributes to myelin plasticity and is also part of synaptic plasticity. Studies have also shown that oligodendrocytes modulate neurotransmitter release at presynaptic terminals through secretion of BDNF. Oligodendrocyte-derived BDNF functions via presynaptic tropomyosin receptor kinase B (TrkB) to ensure fast, reliable neurotransmitter release and auditory transmission in the developing brain.[61]

In addition, the long-range interaction between immune cells and the central nervous system allows the immune system to engage the communication pathways of the nervous system, with immune cells and mediators playing a regulatory role in the nervous system, and also participating in the elimination and plasticity of synapses during development.[62] When the activation of the peripheral immune system continues unabated, the ensuing immune signaling to the brain can lead to the development of depression symptoms,[63] and the synapse acts as a bridge between immune cells and depression.

Functional Changes of Synaptic Microenvironment in Relation to Synaptic Plasticity

In addition to structural changes, variations of function are also an important aspect of the synaptic microenvironment, which affect synaptic plasticity in depression significantly, and, to some extent, functional diversity is also the result of structural modifications. Several proposed mechanisms are currently recognized as the causes of functional changes in the synaptic microenvironment in depression, such as abnormal immune signaling, excessive oxidative stress, mitochondrial dysfunction and cytokine changes.

Increasing amounts of data suggest that abnormal immune signaling plays an important role in the pathophysiology of depression.[64] The levels of factors associated with immune function, like pro-inflammatory factors, acute phase proteins, cellular adhesion molecules and chemokines, have been found to be higher in depressed patients than in others,[65] and these chemokines can elicit behavior change in animals that are homologous to depression. Moreover, it has been shown that pro-inflammatory factors interact with the pathophysiological domains of depression, including synaptic plasticity.[66] Abnormal immune signaling of the brain leads to elevated levels of factors associated with immune function and stimulates the activity of serotonin (5-HT) and dopamine (DA) neurons, thereby accelerating the reuptake of central monoamine neurotransmitters and reducing the synaptic neurotransmitter concentration, and influencing the synaptic microenvironment.[67]

Oxidative stress has historically been considered to be mainly related to neurodegenerative disorders, such as Alzheimer's disease, Huntington's disease and Parkinson's disease. But now, its involvement in neuropsychiatric diseases, including anxiety and depression, is beginning to be recognized.[68] As a consequence of the biological imbalance between reactive oxygen species (ROS) and antioxidants, oxidative stress can lead to the alteration of biomolecules and the loss of control of the intracellular redox-related signaling pathways. The failure of cells to adapt to the changes in redox homeostasis and the subsequent cell death, together with the damage caused by inflammatory mediators, has been considered as major causes of neuroprogression and hence MDD.[69] Meta-analysis also suggests that oxidative stress is increased in depression.[70] Another study predicates that oxidative stress is a major regulator of synaptic function and growth by the activation of Jun-N-terminal kinase (JNK) and its transcriptional effector AP-1 and autophagy.[71] Overall, the relationship between oxidative stress and the synaptic microenvironment deserves more attention.

Mitochondria are synthesized in nerve cells, transported along axons to nerve endings and aggregated and provide energy for the transmission and release of neurotransmitters in synapses through oxidative phosphorylation.[72] The reduction or dysfunction of mitochondria inside synapses resulting from various causes will change the state of energy supply in the local microenvironment of the synapse and affect the synapse function. One study using a super-resolution microscope to observe the mitochondria in the synapses of neurons revealed that dendritic mitochondria exist as stable compartments of single or multiple filaments. If these local mitochondrial compartments are depleted, both the plasticity and the stimulus-induced synaptic translation are abolished.[73] The mitochondrial ROS act as synaptic activity sentinels that can regulate the phenotypical consequences of forced synaptic inactivity.[74] Meanwhile, mitochondrial dysfunction can also be used as a trigger, leading to insufficient adenosine triphosphate production and a lack of energy in the external environment of the synapse. Such balance disruption will lead to the formation of multiple pathological products in the microenvironment and cause synaptic dysfunction.[75] One study using the isobaric tag for relative and absolute quantitation (iTRAQ)-based quantitative proteomics reported results that suggest synaptic mitochondrial dysfunction in the hippocampus of rats susceptible to chronic mild stress.[76] Results from another study imply that mitochondria play a critical role in synaptic plasticity accompanied by increased BDNF levels, with a significant positive correlation between BDNF levels and mitochondria and synapse numbers.[77]

In addition, neurotransmitter transmission is also affected by the synaptic microenvironment. It has been confirmed that under different conditions the release ability and movement mode of synaptic vesicles containing neurotransmitters are greatly different.[78] A review summarized the three ways of neurotransmitter release – synchronous, asynchronous and spontaneous – and analyzed the similarities and differences in the mechanisms of these three release methods. The results show that the modes of these three ways of release have key fusion processes in common but may differ in the source of and necessity for

Ca(2+) to trigger release and in the identity of the Ca(2+) sensor for release.[79] However, mitochondria always act as sensors and regulators of calcium signaling,[80] therefore, the release of neurotransmitters is affected by mitochondria. In addition, neurotransmitter release from axon terminals is regulated by glial cells. One study found that glutamate release in the brain is impaired in mice lacking low-density lipoprotein receptor-related protein 4 (Lrp4), a protein that is critical for neuromuscular junction formation, and revealed compromised release probability in astrocyte-specific Lrp4 knockout mice.[81] Another study suggests that chronic mild stress impairs GABA release and uptake by upregulating miRNAs and downregulating mRNAs and proteins, which may constitute the subcellular and molecular mechanisms for the lowered GABA tone in major depression.[82] All these findings indicate that dynamic changes in synaptic microenvironment will result in abnormal intracellular transport of neurons and synaptic vesicle transport, which is related to depression.

Clinical Significance of Studying the Synaptic Microenvironment in Depression

Synaptic Microenvironment and Neural Plasticity

Neuroplasticity is one of the most important characteristics of the central nervous system (CNS) and encompasses the vast changes occurring in all of the constituents of the CNS throughout the life of an individual in response to stimuli.[83] Moreover, neuroplasticity is manifested as changes in brain memory and learning, body motor function and mental activity on the macro level, while on the micro level it refers to structural and functional alterations in neuronal synapses.[84] Various stimuli cause changes in plasticity of neurons, resulting in synaptic degeneration and loss, and leading to the remodeling of new synapses and the changes of the transmission efficiency between synapses; this can affect the occurrence and development of neurological diseases.[85]

However, synaptic plasticity is also an important aspect of neuroplasticity and is affected by the synaptic microenvironment. The synaptic microenvironment can be used as one of the targets of neuronal plasticity to improve the synaptic microenvironment, speed up the synaptic transmission efficiency, help the establishment of damaged neuron information and promote damage repair.

Biomarkers of the Synaptic Microenvironment

Biomarkers for depression are still controversial. Evidence from clinical research and animal models has long suggested that mechanisms and biomarkers associated with synaptic plasticity have always focused on Alzheimer's disease and cognitive decline.[86,87] As an important member of the neurotrophic family of secreted proteins, BDNF and its receptor participate in a variety of CNS functions, like neuronal growth and differentiation, synaptic plasticity[88] and its role in depression. Therefore, BDNF has become one of the biomarkers of synaptic plasticity.[89]

Regrettably, as the internal and external environment of synapses, the biological markers of the synaptic microenvironment have not yet been determined. Strengthening the research of biological indicators of the synaptic microenvironment for depression can provide references for rapid clinical diagnosis and treatment.

A Breakthrough in Molecular Imaging in Depression

Molecular imaging techniques such as magnetic resonance (MR) spectroscopy and positron emission computed tomography (PET) have been used to explore the molecular pathophysiology of depression and evaluate treatment response.[90]

However, due to the complexity and heterogeneity of depression, there are still major challenges for MR spectroscopy and PET, which are limited to examining a few metabolites or a single radioligand at a time.[91] In this case, the synaptic microenvironment can be used as a breakthrough in molecular imaging of depression. It can monitor the interaction between the synaptic microenvironment and its surroundings in real time, and analyze the relationship between them from multiple levels, so as to promote the dynamic visualization development of biological research.

Synaptic Microenvironment as Potential Drug Target in Antidepressant Treatment

Taking the synaptic microenvironment as the intervention target can provide new ideas for antidepressant treatment. As mentioned above, the synaptic microenvironment of depression is affected by abnormal immune signaling, oxidative stress, neurotransmitters, mitochondrial energy metabolism and other factors. However, most of the current research on depression disease focuses on a single

influencing factor,[92] while ignoring the interaction between various factors. The study of the synaptic microenvironment can open up a new window for solving this problem, and the comprehensive research of factors affecting synaptic structure and function can provide a target for establishing the overall level of synaptic.

Conclusion and Outlook

This is an exciting time for the study of the synaptic microenvironment and synaptic plasticity in depression. The changes induced by neuroplasticity in depression have been described in detail at different levels of the CNS, and all these aspects are strictly intertwined. Indeed, emerging study supports the view that even a small structural modification of one of the neuronal networks may cause alterations in synaptic function and affect the synaptic microenvironment of neurons. At the same time, in the pathological process of depression, the synaptic microenvironment is also affected by abnormal immune signaling, excessive oxidative stress, mitochondrial dysfunction and neurotransmitter deficiency. Unfortunately, the synaptic microenvironment has not yet attracted the attention of depression scholars, but it may have more clinical value.

The importance of the synaptic microenvironment for the maintenance of synaptic homeostasis and synaptic plasticity suggests that it may play a key role in the pathogenesis of depression. Further research on the role of the synaptic microenvironment and synaptic plasticity will shed new light onto potential mechanisms contributing to depressive disorders and provide targets for antidepressant treatment.

Disclosure

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