Review

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The glutamatergic system in the development of stress-induced depression

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Abstract

Major depression is one of the most prevalent neuropsychological disorders and affects millions worldwide. In response, the monoaminergic system has been proposed to be one of the major focuses for conventional drugs in the treatment of depression, such as selective serotonin reuptake inhibitor (SSRI). Meanwhile, accumulating evidence suggests a paradigm shift from the monoamine system towards the glutamatergic system (Gerard Sanacora, Giulia Treccani, and Maurizio Popoli 2012) due to the long onset of the monoamine system targeting anti-depressant drugs. Both clinical and pre-clinical data support that glutamatergic system dysfunction were involved in the development of depression. Furthermore, therapeutic approaches that manipulating neuronal activity and N-methyl-D-aspartic acid (NMDA) receptor antagonist were shown to have profound effects in the treatment of depression. Here, I systematically reviewed our current understanding of the involvement of glutamatergic system dysregulation in the development of depression, which potentially could provide the mechanistic basis for future treatment development.

Keywords: animal model, BDNF, glutamatergic neurons, ketamine, monoamine system, NMDA receptor

Introduction

Major depression is the most common disabling psychiatric disorder that has been estimated to affect 21% of the world's population[1–5]. In accordance with published reports from the WHO, MDD is projected to be a major reason for disability in the world by 2030. In the United States, about 10% of the whole population (that is 14 million people) at any time is inflicted with depression. Moreover, Depression is not only highly comorbid with anxiety disorders, but is also closely associated with dementia, type 2 diabetes, coronary artery disease, Parkinson's disease, epilepsy, pain, cancers, aging, osteoporosis and irritable bowel syndrome.

MDD is defined in DSM-IV (Diagnostic and Statistical Manual of Mental disorders-IV), as a condition characterized by loss of interest in usual activities and/or diminished ability to experience pleasurable activities (anhedonia)[6], together with a range of other features including anergia, changes in sleep and appetite, sadness, and suicidal tendency. Although meta-analyses from epidemiological studies indicate that depression is largely heritable, intense stress for long period has been attributed as one of the crucial components in the emergence of major depression[7–9]. Chronic stress activates peripheral and central immune systems accompanied with the release of inflammatory mediators. Activated immune system mediates the process of depression by means of its interaction with the nervous and neuroendocrine systems through regulating the synthesis,

HIGHLIGHTS

- Major depression as a prevalent neuropsychological disorder.
- Limitations of current monoaminergic treatments.
- The emerging importance of the glutamatergic system in depression treatment.
- Therapeutic approaches focusing on the glutamatergic system
- Mechanistic study of dysfunction of glutamatergic neurons in depressed animal models.
- The paper reviewed the monoaminergic system as one of the major focuses for conventional drugs in the treatment of stress-induced depression, such as selective serotonin reuptake inhibitor (SSRI). Meanwhile, the paper expands to the glutamatergic system due to the long onset of the monoamine system targeting anti-depressant drugs. Both clinical and pre-clinical data support that glutamatergic system dysfunction were involved in the development of depression. Furthermore, therapeutic approaches that manipulating neuronal activity and N-methyl-D-aspartic acid (NMDA) receptor antagonist were shown to have profound effects in the treatment of depression. Here, I systematically reviewed our current understanding of the involvement of glutamatergic system dysregulation in the development of depression, which potentially could provide the mechanistic basis for future treatment development.

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metabolism and reuptake of monoamines, over activation of hypothalamus-pituitary-adrenal (HPA) axis and by reducing neurogenesis.

As shown in the Figure 1, depression is a major research direction in the biomedical investigation. According to the newly published landscape of biomedical research, depression is one of the major topics, both in clinical and basic scientific research[10].

Although much attention has been focused on this multifactorial and heterogeneous disorder, the aetiologias of depression remain hitherto poorly understood. The chronic and debilitating nature of depression makes the prognosis of many chronic diseases complicated and aggravates the situation of disease and disability in the world. While risk loci for many other common diseases have been identified by genetic analysis, the true "depression genes" which are responsible for the onset and the cure of depression and could be manipulated to produce models of depression in rodents, have not been identified. At present, there are several types of classical anti-depressants in clinical practice, including tricyclic anti-depressants (TCA), monoamine oxidase inhibitors (MAOI), selective serotonin reuptake inhibitors (SSRI), noradrenergic reuptake inhibitors (NARI) and serotonin and noradrenaline reuptake inhibitors (SNRI). Nevertheless, there is no long-term cure for depression. Conventional behavioral and pharmacological treatments, though not a cure, have shown effectiveness in the alleviation of symptoms. However, dissatisfaction has arisen with psychopharmacological interventions due to their profound side effects, escalating prescription rates, and recent uncertainties on the effectiveness and long-term benefits.

Even so, genetic factors (about 40%), together with external environmental factors (stressful events in particular such as losing jobs and beloved ones), are considered to be involved in the onset of depression. Stressful life events could induce a series of psychological and physiological changes including activation of hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system, which could be referred to as psychological stress responses. Here, recent approaches and effects dedicated to uncovering the interconnections between psychological stress and depression will be briefly reviewed.

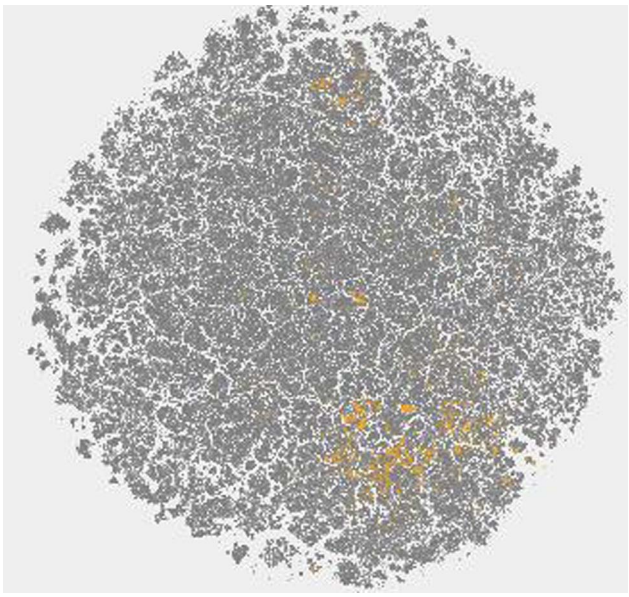

Figure 1. Distribution of "depression" related publications[10].

Medication targeting the monoamine system

Based on the monoamine deficiency hypothesis, the monoamine reuptake inhibitor has been developed as the anti-depressant drugs. Serotonin, including other monoaminergic system has been promising targeting in the treatment of depression. The SSRI is well-accepted as the first-line medication to treat depression. However, the SSRI would take at least 3 weeks to kick in. Moreover, it only works for part of the patients. Even after tremendous effort in improving the effect the monoaminergic system targeting drugs, they are still uncapable of producing a rapid and sustained anti-depressant effect[11].

Besides the monoaminergic system, glutamate is the major neurotransmitter in the central nervous system that mediates the communication between neurons. Several clinical approaches including electroconvulsive therapy, as well as the NMDA receptor antagonist (e.g. Ketamine) are becoming promising acute and effective approaches in the treatment of depression.

Clinical evidence about the dysfunction of glutamate in depression

It has been suggested that circulating glutamine down-regulation is causally linked to depression[12]. Using liquid chromatography-fluorescence method, it has been shown that the plasma and brain glutamine were significantly decreased[13]. In addition, mean glutamate levels in occipital cortex were significantly increased in depressed subjects[14]. It has been shown that mitochondrial energy production of glutamatergic neurons was reduced by 26% in MDD subjects. Paradoxically we found no difference in the rate of glutamate/glutamine cycle (Vcycle)[15].

Deep brain stimulation which directly manipulate neuronal activities could have anti-depressant effect

In the past two decades, clinical evidence has proved the importance of deep brain stimulation (DBS) in neurosciences. It has the capability of directly measuring pathological brain activity and delivering adjustable stimulation, which exhibits therapeutic effects in neurological and psychiatric disorders correlated with dysfunctional circuitry. However, there is still a crucial question remain, including the chosen of brain areas and patients[16].

Considering the limited therapeutic choice that treatment-resistant depression patient suffers from, DBS may appear to be a potential treatment. Based on the observation that the subgenual cingulate region (Brodmann area 25) is metabolically overactive in treatment-resistant depression. In 2005, Helen S Mayberg and her team disrupting focal pathological activity in limbic-cortical circuits using high-frequency electrical stimulation of the subgenual cingulate white matter (Cg25WM), they effectively reversed symptoms in treatment-resistant depression[17]. The patients with profound improvements showed decreases of neuronal activity in hypothalamus, anterior insula, and medial frontal cortex as well as increases in dorsolateral prefrontal, dorsal anterior and posterior cingulate, premotor, and parietal

regions, which were not seen in non-responders[17]. DBS utilize electric stimulation to directly manipulate neuronal activity and exhibit acute behavioral and clinical effects in depression treatment. The modulation of specific brain area activity suggested that neuronal activity malfunction could be the underlying mechanism for the development of depression. However, the brain regions with therapeutic potential require further exploration.

However, regarding the side effects of DBS, it is considered as a treatment only when the symptoms are disabling despite optimal medical therapy, especially in patients with hypertension. A study conducted by Xiaowu *et al*.[18] founded that the microelectrode trajectories used in DBS may increase the risk of intracranial hemorrhage. A study conducted by Schuepbach and colleagues concluded that depression was more frequent in the neurostimulation group than in medical therapy group. Also, DBS has been proven to be responsible for devices-related risks such as displacement caused by the dislocation of the stimulator, cable or lead can lead to reoperation[19]. DBS also shows a positive correlation with suicide and hospital readmission with worsening of mobility or infection after the therapy[20]. Tripoliti and colleagues studied the short-term and long-term speech response to subthalamic nucleus DBS patients and patients with medical therapy, and came with the conclusion that both surgical and medical factor contribute to the speech decline, and researchers explain that the dysarthria and dysphagia can be attributed to the stimulation of STN and its vicinity to the corticobulbar pathways[21,22]. the basis for the increased anger scores associated with sub-thalamic nucleus and Globus Pallidus Internus DBS is studied in Subhyadhom A *et al*.[23] study, that the connection of the sub-thalamic nucleus to the frontal cortex and basal ganglia structures forms a circuit.

Sertraline versus escitalopram in moderate to severe major depressive disorder

Sertraline and escitalopram are selective serotonin reuptake inhibitors (SSRIs). SSRIs exert their mechanism of action by binding to the sodium-dependent serotonin transporter protein (SERT) in the presynaptic neuron. SERT assist the reuptaking serotonin from the synaptic cleft into the presynaptic neuron. The action of mechanism of sertraline is exerted as serotonin uptake inhibitor, and cytochrome P450 2D6 Inhibitor. Escitalopram, the (S)-enantiomer of citalopram, inactivates SERT and results in an elevation in synaptic serotonin levels[24]. Sidra Raza and colleagues conducted an double-blinded research on 744 South Asian participants with moderate to severe major depression disorder whom were randomly assigned to receive either sertraline or escitalopram for 8 weeks. The effect of these two dosages are presented through the Montgomery-Åsberg Depression Rating Scale (MADRS) and the clinical global impression (CGI) scale, and also the frequency of adverse events in both groups. The result shows that sertraline is more efficacious than escitalopram in anti-depression symptoms, given the reducing depression rating scales in MADRS and CGI. Also, sertraline displays enhanced safety or tolerability as participants subjectively feel better in the sertraline group.[25] The conclusion reveals the advantage of sertraline, as it is reflected with milder side effects such as high levels of drowsiness, dizziness, weight increase, blurred vision that are frequently caused by other anti-depression drug.

Electroconvulsive therapy for depression

Besides deep brain stimulation, electroconvulsive therapy has also been used in the treatment of depression. Basically, the electroconvulsive therapy would apply direct current through the brain, and potentially could manipulate the glutamatergic transmission during this process.

The therapy was developed initially based on the observation that high fever caused symptomatic improvement in general paresis of the insane and infected syphilitic patients with malaria, Wagner–Jauregg suggested that the idea that a disease could be cured by inducing another disease. This theory was further developed in the late 1920s, when Meduna observed the over-occupation of spaces left by lost neurons by glial cell in the brains of epileptic patients. There is also an antagonism between epilepsy and schizophrenia. The rate of schizophrenia was significantly lower among patients with epilepsy than in the general population. Chemical seizure has been adopted but was proved to be unpredictable and with considerable interpersonal variance. Now that electroconvulsive therapy was done under general anesthesia and a small electric current will pass through the brain to trigger the brief seizure. Now many clinical investigations have approved that this type of therapy exhibit anti-depressant effect, especially for drug-resistant patients[26]. The mechanism for this therapy is largely unknown. Based on the electric stimulation, the glutamatergic system would potentially be activated, strongly. Meanwhile, the glutamatergic transmission could be depleted due to the synchronized release triggered by the electroconvulsive stimulation.

Pre-clinical models regarding the contribution of glutamate in the development of depression

Glutamate is the major neurotransmitter in the central nervous system that been used in the excitatory synaptic transmission. The action potential could trigger the release of glutamate. Partially, the neuronal activities of excitatory population could indicate the glutamate activity in the central nervous system. In the following section, we will discuss the contribution of different brain structures in the development of depression. LH rats is proved to experience up-regulations of glutamate transporter-1 and glutamine synthetase of astrocytes in the CA-1, CA-3, DG,mPF, and NAc and a down-regulation of GS in the amygdala[27]. Using gas chromatograph-mass spectrometer-based metabolomic analysis in chronic mild stress-induced depression animal, it has been shown that the glutamine-glutamate-GABA cycle in the striatum, hippocampus and the cerebellum could be disturbed[8]. Clinical studies suggested that the pathophysiology of depression is associated with dysfunction of glutamatergic system. Animal studies suggested that the environmental stressors could enhance glutamate transmission in limbic and cortical areas. It has been proposed that a paradigm shift from the monoamine hypothesis to the neuroplasticity hypothesis may help with the drug development[28].

Animal models used to mimic depressive-like status

The pre-clinical models have mostly been carried out using rodent[5]. The chronic body restrain, and the chronic mild stress

are the two most common protocols to induce depressive-like behaviors in animals.

Chronic body restrain model

One well-accepted model is the chronic immobilization stress protocol, which is been used to induce depression-like behavior in mice. To establish the animal model, the animals will be placed in a body-fit sized cylinder for 2 h per day for 2 weeks, which is sufficient to cause depressive-like behaviors with minimum pain in mice. After the chronic immobilization stress, the animals would have a lower sucrose preference and a high immobility time, when compared with control animals. Under restraint conditions, blood corticosterone levels are rapidly increased[7].

Chronic mild stress

In the chronic mild stress model, the animal will go through randomized mild stressors, including cage tilting, wet bedding, reversed lighting cycle, predator smell, noisy environment, novel environment. The animals were be exposed to one of these stressors for 2–3 h per day. After 3–8 weeks exposure, the animals will exhibit depressive-like behavior phenotype. For example, they will have dirty fur based on the coat status score; they would have a longer latency in the sucrose splash test; longer immobility time in the tail suspension test[9,13].

Social status loss model

In the social status loss mode, the animals with higher social ranking will experience a forced loss. As a results, the higher-ranking animal will exhibit a depressive-like behavioral phenotype[29]. In this experiment, a tube competition test will be used to measure the ranking of tested animals.

The behavior test used to verify the depressive-like behaviors in animal model

To test if the subjected animals exhibit any depressive-related behaviors, a battery of standardized tests will be carried out.

Tail suspension test

The tail suspension test is a behavioral test used in pre-clinical research to determine potential depressive-like phenotype, thus helping us to evaluate potential anti-depressant effects of drugs or other interventions in laboratory animals. As shown in the Figure 2, the test involves suspending a mouse by its tail, using adhesive tape, for a 5–10 min. During this time, the animal is unable to touch the ground or any other surface and is forced to rely on its forelimbs to maintain a balance or posture. In this test, animals with depression phenotype would tend to exhibit passive, immobile behavior during the test, while animals without depression would tend to exhibit more active struggling.

Sucrose preference test

The sucrose preference test is a behavioral test used to evaluate anhedonia, which is one of the core symptoms of depression. Anhedonia refers to the inability to experience pleasure or interest in enjoyable stimulation. As seen in the Figure 3, the test involves providing the laboratory animals with a choice between two bottles of liquid, one containing plain water and the other containing a dilute sucrose solution (2–5%). The animals will have free access to both bottles for a period of time (2 h). Their preference for the sucrose solution versus water is measured by calculating the ratio of sucrose to water consumed. Animals with depressive-like phenotype would exhibit decreased sucrose preference.

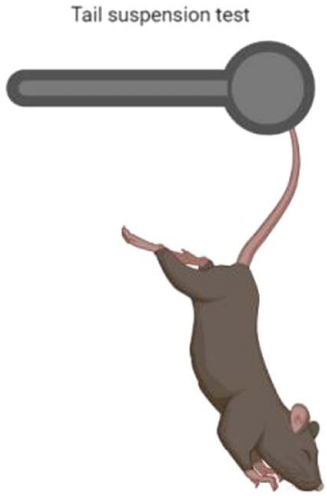

Figure 2. Schematic drawing of tail suspension test[30].

Forced swimming test

Forced swimming test is used to evaluate the helplessness in pre-clinical animal models, serving a similar function as the tail suspension test. The test involves placing the animal in a container of water for 5–10 min as demonstrated in Figure 4, and the immobility duration will be calculated. Animals with depressive-like phenotype would have increased immobility.

Dysfunction of glutamatergic neurons in depressed animal models

In the stress-induced animal models, single unit electrophysiological recording and observed the glutamatergic neuronal

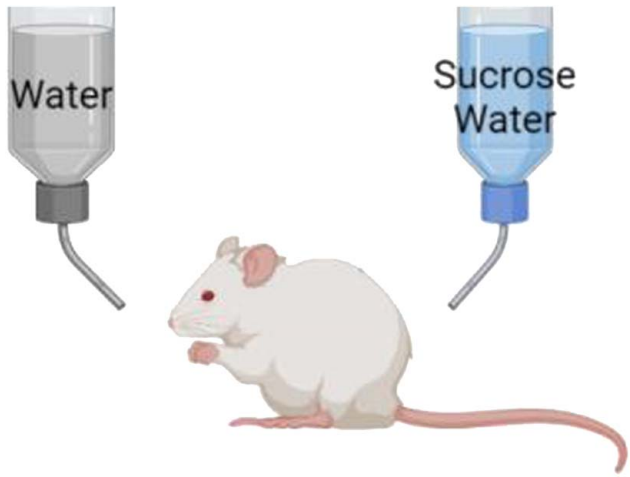

Figure 3. Schematic drawing of sucrose preference test[31].

Figure 4. Schematic drawing of force swimming test[32].

activity change. In the social status loss animal model, Fan *et al.*[29], observed that the neuronal activities in the lateral habenula increased a lot after the forced loss of social status.

We know that anxiety is always a strong prediction risk factor in the development of depression. Previous studies have demonstrated that glutamatergic neuronal activity will increase in exposure of anxiogenic stimulation. For example, the anxiogenic electric shock would activate the glutamatergic neurons in the medial preoptic area[33]. In the meantime, the activation of these neurons would put the animal in a very anxious status. These results suggested that the glutamatergic neuronal activity increase would potentially be a risk factor for the development of depression.

Dysfunction of glutamate in astrocytes

A metabolite shuttle known as the glutamate/GABA-glutamine cycle describes the release of neurotransmitter glutamate or GABA from neurons and subsequent uptake into astrocytes. In return, astrocytes release glutamine to be taken up into neurons for use as neurotransmitter precursor. Glutamine synthetase-expressing astrocytes are prominently involved in glutamate-related disturbances in major depression. GS immunoreactive oligodendroglial cells are unable to contribute to the glutamate–glutamine cycle due to the complete lack of amino acid transporters, which supports that GS-expressing oligodendrocytes play a minor (if any) role in mood disorder pathology[34]. In the glutamate–glutamine (Glu–Gln) cycle, glutamate and its amidated molecule glutamine is transported in the tripartite synapse in the brain. Once released from presynapses, extracellular Glu is transported to surrounding glial cells, including astrocytes, via (GLT-1). Glu is then amidated to Gln, a non-toxic neutral amino acid. A removal of Glu from extracellular space (ECS) by astrocytes maintains the homeostasis of glutamate in the tripartite synapse. If astrocytes do not function properly, the glutamate molecules accumulate in the ECS, leading to glutamate excitotoxicity. That is, the Glu–Gln cycle involving astrocytes may play a role in mediating depressive-like deficits when exposed to stress repeatedly. Animal studies show that dysfunction of glutamate transporter-1 (GLT-1) can induce some depressive-like behaviors, and drugs that upregulate GLT-1 ameliorate such deficits[35].

The effect of stress on the glutamatergic synaptic release

With regard to the glutamatergic synapse, stress can have either plasticity-enhancing effects that are associated with improved cognition and function or noxious effects that are associated with impaired function, depending on the type, intensity and duration of the event. And the presynaptic release of glutamate is rapidly increased by mineralocorticoid or glucocorticoid receptor-mediated effects on the machinery that regulates glutamate release[36].

NMDA receptor antagonists as anti-depressant drugs

In pre-clinical models, functional N-methyl-d-aspartate (NMDA) antagonists including competitive antagonists, glycine partial agonists, and use-dependent channel blockers have exhibited anti-depressant-like actions. Direct targeting of the NMDA receptor exhibits rapid anti-depressant effect, either alone or combined with traditional anti-depressant drugs[37].

Eliprodil, an NMDA antagonist acting at polyamine sites, has been tested to have anti-depressant effect. The study examined the effects of eliprodil (SL-82.0715), in behavioral and neurochemical tests predictive of anti-depressant activity. In the forced swim test, eliprodil produced a dose-dependent reduction in immobility; however, shows no effect in in the tail suspension test, which suggested that eliprodil may potentially have anti-depressant-like actions in pre-clinical tests[38].

MK-801, an non-competitive NMDA receptor antagonist, and the competitive NMDA receptor antagonist, CGP 37849 and CGP 40116, were studied in a chronic mild stress model of depression by Mariusz Papp and Elżbieta Moryl in 1994. They found that the stress-induced deficit in sucrose intake was gradually reversed by chronic treatment with MK-801, CGP 37849 and CGP, suggesting that antagonists of NMDA receptors may have anti-depressant properties[39]. Moreover, in the investigation carried out 1993, Domenico Meloni reported that, MK-801 completely antagonized the capacity of another anti-depressant drug imipramine (IMI) to prevent the development of the learned helplessness behavior in rats, suggesting a completed drug mechanism between different NMDA receptors antagonists[40]. Using the forced swimming test in rats, E. Przegalinski and colleagues examined the anti-depressant-like activity of ACPC and CGP 37849, competitive NMDA receptor antagonist. ACPC and CGP 37849, administered i.p., produced a dose-dependent and significant reduction of the immobility time in the forced swimming test. But no change in the exploratory activity of the rats in the open field test[41].

The activation of the NMDA receptors in the inescapable stress would inhibit the induction of LTP in the CA1 region of hippocampus, indicating that the NMDA receptor complex may be involved in the behavioral deficits induced by inescapable stress. Accordingly, the capability of reducing neurotransimission at the NMDA receptor complex presented by NMDA receptor may make it a potential new class of anti-depressant drug[42].

MK-801, also known as dizocilpine, is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist that has

been studied as a potential anti-depressant drug. However, despite promising pre-clinical results, MK-801 has not been approved as an anti-depressant for clinical use due to several reasons. In rat, a single does injection of MK801 could cause acute psychosis, and impaired spatial memory and synaptic plasticity[43]. These side effects can be severe and limit the drug's usefulness as an anti-depressant. Additionally, NMDA receptor antagonists have been associated with the development of neurotoxicity and neurodegenerative disorders[44], which is a concern for long-term use in patients with depression. Furthermore, while pre-clinical studies have shown that MK-801 can produce rapid and sustained anti-depressant effects in animal models of depression, these findings have not consistently translated to human studies.

In summary, while MK-801 has shown potential as an anti-depressant drug in pre-clinical studies, the significant side effects and concerns regarding neurotoxicity and neurodegeneration have prevented its approval for clinical use.

However, memantine, which is a partial antagonist of NMDA receptor, has been shown to be able to improve the cognitive function of the Alzheimer's disease patients without significant side effects. It is possible that the memantine could be used in the treatment of depression. Indeed, a recent study reviewed the anti-depressant effect of memantine in bipolar depression and observed a significant improvement[45], which further supported this possibility.

Anti-depressant effects of ketamine in depressed patients

In order to investigate the role that brain glutamate systems plays in the pathophysiology of major depression and the mechanism of action of anti-depressants, Berman and colleagues conducted the first placebo-controlled, double-blinded trial and assess the treatment effects of a single dose of an N-methyl-d-aspartate (NMDA) receptor antagonist in patients with depression. They tested ketamine hydrochloride, a potent NMDA antagonist. The purpose of Berman's study was to determine whether ketamine had anti-depressant effects in patients with depression. During the 2 test days, the seven subjects with major depression received intravenous treatment with ketamine hydrochloride or saline solutions under randomized, double-blind conditions. The results show that within 72 h after ketamine injection, the symptom of subjects significantly improved, indicated from the mean 25-item Hamilton Depression Rating Scale scores, which decreased by $14 \pm$ SD 10 points versus 0 ± 12 points, respectively during active and sham treatment, while this did not occur in placebo infusion group.

These results suggest a potential accessibility of NMDA receptor-modulating drugs in the treatment of depression[46].

The ketamine-mediated blockade of NMDAR at rest deactivates eukaryotic elongation factor 2 (eEF2) kinase, resulting in reduced eEF2 phosphorylation and de-suppression of translation of brain-derived neurotrophic factor. And inhibitors of eEF2 kinase induce fast-acting behavioral anti-depressant-like effects[47]. Bursting firing in the lateral habenula has been suggested to be involved in depression, local application of Ketamine into lateral habenula has been shown to be able to rescue stress-induced depression[48].

The changes in other neural transmitter or neural peptide systems

The changes in GABAergic system

It is shown that the overall amount of glutamic acid decarboxylase, the GABA synthesizing enzyme, immunoreactivity from medication-free MDD subjects was significantly lower (– 34%) compared to control subjects[49]. It has been revealed a hippocampal dysfunction in the GABAergic system in the chronic mild stress model of depression in rats, caused by a reduction in action potential-dependent GABA release[50]. Depressed subjects had significantly lower occipital cortex GABA concentrations[14].

The changes in BDNF

There is a growing body of evidence demonstrating that stress decreases the expression of brain-derived neurotrophic factor (BDNF) in limbic structures that control mood, which could contribute to the atrophy of certain limbic structures, including the hippocampus and prefrontal cortex that has been observed in depressed subjects[51].

Structural changes in depression

The hippocampus is intimately sensitive to stress hormones and responds to stress through changes in structure, neurochemistry, and excitability. Both acute and chronic stress can compromise the hippocampus: acute stress exacerbates hippocampal damage when combined with a metabolic challenge, while chronic stress directly produces hippocampal dendritic retraction[52]. Depressed subjects had significant reductions in the percentage of solid tissue and the percentage of white matter in the voxel were also observed in the occipital cortex[14].

NMDA receptor changes in depression

Glutamate is the prominent excitatory input to the noradrenergic locus coeruleus (LC). The LC is activated by stress in part through this glutamatergic input. Evidence has accrued demonstrating that the LC may be overactive in MDD, while treatment with traditional anti-depressants reduces LC activity. MDD subjects exhibited significantly higher expression levels of the NMDA receptor subunit genes, GRIN2B and GRIN2C, and the metabotropic receptor genes, GRM4 and GRM5, in LC neurons[53].

NMDA receptors are also observed to change in other mental disorders such as Alzheimer's (AD) disease and Down syndrome (DS). The cognitive impairment in such cases is determined by the synaptic loss, which can trace to Aβ oligomer deposits. Amyloid β peptide can cause the hyperphosphorylation of Tau. As the result, Tau loses its ability to bind to microtubules and setup a series of reactions by generating insoluble aggregates within the neuron, altering the axonal transport, which leads to neuronal death[54]. These oligomeric forms of Aβ bind with NMDA receptors from the glutamatergic system, up-regulates oxidative stress, and alters homeostasis of Ca^{2+} and excitotoxicity to interfere the glutamate homeostasis and eventually lead to loss of synapses[55]. Therefore, Aβ peptides and phosphorylated tau are measured to deduce the dementia onset and progression in DS patients as blood biomarkers. The positive correlation of these biomarkers expand in pre-clinical AD phase in DS patients, which suggests a pathological bridge between DS and AD[54].

Discussion

The limitation of using animal models to study the development of depression

Earlier studies have demonstrated the relevance between stress and MDD by presenting methods where depressive-like behavior is induced in animal models. Nevertheless, it may be difficult to perfectly simulate the pathway in which lead to the condition due to the heterogeneity of MDD. The capability of animal models to replicate human behaviors is still unclear. Animal models should be treated with caution. Studies of depression using animals largely focus either on behavioral tests such as stress responses, or on attempts to model and measure aspects of the disorder, such as helplessness or anhedonia[7].

CIS (chronic restraint stress) is an animal model that be broadly used due to higher efficiency and simplicity. Animals are placed in a body-fit sized cylinder for 1–8 hours per day for 2 or 4 weeks. Restraint stress conditions are applied in alternating pattern, which is sufficient to cause depressive behaviors with minimal pain in mice. Under restraint conditions, blood corticosterone levels were rapidly increased. However, the development of depressive-like behavior in CIS might be affected by several factors.

Firstly, the extent of stress response to CIS may vary depending on the animal strain.

Additionally, for female animals, the emotional and cognitive behaviors could be affected by the menstrual cycle, and female rodents are also relatively more susceptible to stress-related disorders, such as depression.

The length of period of habituation to the new circumstance should be treated with caution, and the experimenter should avoid adding new animals to the testing room during the experiment, in case the mice may sense new olfactory and ultrasonic cues during the experiment. In conclusion, despite the animal model did provide pee-clinical evidence for the pathological mechanism of major depression disorder, it remains a challenge of establishing a systematic mechanism of MDD.

The possibility of targeting glutamatergic system to treat depression

Abundant evidence, both clinical and pre-clinical, have suggested that glutamatergic system undergoes dramatical changes in depression patients or depression-related animals. More importantly, the success of the NMDA receptor antagonist, ketamine, in the treatment of depression suggest that glutamatergic system becomes a promising candidate in the treatment of major depressive disorder. However, due to the potential psychosis of Ketamine, further exploration of other drugs acting on the glutamatergic system will be needed. It worth noting that the glutamine and glutamate may exert divergent effect on the central nervous system. For example, the glutamate

Ethical approval

Ethics approval was not required for this review.

Consent

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X.W.: collecting data and analysis, reviewing papers, writing the paper.

Conflicts of interest disclosure

The authors declare no conflict of interest.

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Guarantor

Xinran Wei.

Data availability statement

Datasets analyzed during the current study are publicly available.

Provenance and peer review

Not applicable.

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