The Effects of Psychological Stress on Depression

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Abstract: Major depressive disorder is a serious mental disorder that profoundly affects an individual's quality of life. Although the aetiologies underlying this disorder remain unclear, an increasing attention has been focused on the influence imposed by psychological stress over depression. Despite limited animal models of psychological stress, significant progress has been made as to be explicated in this review to elucidate the physiopathology underlying depression and to treat depressive symptoms. Therefore, we will review classical models along with new methods that will enrich our knowledge of this disorder.

Keywords: Brain-derived neurotrophic factor, depression, glial cell-derived neurotrophic factor, hippocampus, nucleus accumbens, prefrontal cortex, psychological stress, ventral tegmental area.

INTRODUCTION

As the commonest cause of disability affecting nearly 16% of the global population [1], major depressive disorder (MDD) attracts increasing attention while the underlying mechanism of this disorder is largely uncharacterized. In accordance with published reports from the World Health Organizaton (WHO), MDD is projected to be a major reason for disability in the world by 2030 [2]. In the United States, about 10% of the whole population (that is 14 million people) at any time is afflicted with depression [1].

The cardinal symptoms of MDD include depressed mood (reduced motivation or hopelessness), anhedonia (diminished ability to experience pleasurable activity such as food, sex and social interactions), anergia, irritability, difficulty in concentrating, disrupted sleep, appetite and cognition and tendency to suicide [3]. Depression is not only highly comorbid with anxiety disorders [4], but is also closely associated with dementia [5], type 2 diabetes, coronary artery disease [6], Parkinson’s disease, epilepsy, pain, cancers [7], aging [8], osteoporosis [9] and irritable bowel syndrome [10]. Unfortunately, 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 [11].

Although much attention has been focused on this multifactorial and heterogeneous disorder, the aetiologies of depression remain hitherto poorly understood. 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 [11, 12]. Even so, genetic factors (about 40% [11]), 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 [11, 13]. The environmental risk factors associated with depression include endocrine abnormalities (hyper- or hypo-thyroidism), cancers (for example, pancreatic adenocarcinoma and breast cancers), adverse effects of drugs (such as recombinant interferons [14] and isotretinion [11]), and stressful events [11] and other factors will be detailed further in this review.

Stressful life events could induce a series of psychological and physiological changes including activation of hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system [15], 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.

PSYCHOLOGICAL STRESS

Psychological stress has been increasingly featured in scientific works as well as in popular media such as internet, newspapers and TV due to terrorism, war [16], divorce and unemployment [17]. Psychological stress which is an adaptation to the fight-or-flight response during evolution, can induce a constellation of physiological responses (including nervous, endocrine and immune systems) which otherwise could be harmful under some conditions [17]. Among those responses, hyperactivity of HPA axis is one of the commonest neurobiological changes in depressive patients (dysfunction of HPA axis is manifested in about...
70% patients of depression [18]) as is revealed by researches over the last 40 years [19].

According to the duration of stress, psychological stresses may be divided into two classes: acute psychological stress (surgical operation and examination, for example) and chronic psychological stress (such as anxiety about children, financial problems and periodic headaches) which could be subdivided into disconnected and persistent psychological stress [20].

Animal models are useful tools for investigating the neurobiology of psychological stress as well as mental diseases such as depression and anxiety [21]. Several animal models of psychological stress are listed in Table 1.

In response to psychological stress, impulses stemming from the higher cortical areas of the brain are transmitted to the hypothalamus through the limbic system [29]. Neurotransmitters such as serotonin, norepinephrine (NE), and acetylcholine are released, and certain cells of paraventricular nucleus (PVN) at the hypothalamus are activated to synthesize and secrete corticotrophin releasing factor (CRF) [3, 12, 29]. Subsequently, CRF enters the hypothalamic portal venous system and stimulates the corticotrophs located at the anterior pituitary gland to synthesize proopiomelanocortin (POMC) [19, 29]. Just as proinsulin cleaves to produce insulin and C-peptide, the polyprotein POMC subsequently splits to produce adrenocorticotropic hormone (ACTH) and alpha melanocyte-stimulating hormone (α-MSH) [29]. CRF from parvocellular neurons also stimulates the release of arginine vasopressin (AVP) from PVN which together with CRF synergistically stimulates the release of ACTH [3, 30]. ACTH stimulates the zone fasciculate and reticularis of the adrenal cortex to produce and release glucocorticoids (GCs, cortisol and corticosterone in human and rodent, respectively) [19, 29, 30], which together with catecholamine released by sympathetic nervous system (SNS) are the main stress hormones [20c, 29]. GCs exert their effects on the multiple aspects of the brain function, such as survival of neurons, neurogenesis, hippocampal size and emotional events, and the peripheral functions including metabolism and immunity [3, 19]. By binding to glucocorticoid receptors (GRs) in the hypothalamus, the pituitary and the medial prefrontal cortex (mPFC), which will result in a decrease in CRF secretion and subsequent reduced release of ACTH from the pituitary, these GCs inhibit activity of HPA axis through negative feedback mechanism to sustain homeostasis [3, 13b, 19, 20b, 21a, 31].

**BRAIN REGIONS INVOLVED IN DEPRESSION**

Signals from environmental stressors such as danger to life, social stressors and responses to injuries in the body are firstly transduced by sensory nervous systems, and then the sequent information is processed by so-called emotional circuits in the brain [16]. Although so far we have no clear understanding of the neural loops underlying the pathology of depression, the diverse symptoms of depression imply that many brain regions could be involved in the affection disorders [12]. Human brain imaging researches have demonstrated alterations of hemorheology and related parameters in brain regions such as amygdala, thalamus, striatum, hippocampus, prefrontal and cingulate cortex and

### Table 1. Animal models and involved factors discussed in brief.

| Model                   | Triggers                        | Involved Symptoms       | Related Factors                          | Acute /Chronic | Ref. |
|-------------------------|---------------------------------|-------------------------|------------------------------------------|----------------|------|
| Forced swimming test    | Waters immersion                | Behavioral desparation   | HPA axis, corticosterone                 | Acute          | [21a]|
| Learned helplessness test| Inescapable foot shock          | Behavioral desparation   | LHB, VTA, serotonin, dorsal raphe nucleus, CRF | Chronic        | [21b, 22]|
| Social defeat stress    | Aggressive counterpart          | Social avoidance         | BDNF, VTA, mPFC, AFosB                   | Chronic        | [21b, 23]|
| Reward based tests      | Food (sucrose), sex, drugs      | Anhedonia                | VTA, NAc, PFC, amygdala, Hippocampus,    | Chronic        | [24] |
| Tail-suspension test    | Restraints                      | Behavioral desparation   | HPA axis                                 | Acute          | [21a]|
| Early life stress       | Maternal separation, prenatal stress | Social relationship disruption | HPA axis, Hippocampus, serotonin       | Chronic        | [25] |
| Olfactory bulbectomy    | Lesion                          | Irritability             | IL-1β, TNF-α, HPA axis, hippocampus      | Chronic        | [26] |
| Hyponephagia            | Novel environment               | Reduced appetite          | Hippocampus                              | Chronic        | [27] |
| Chronic unpredictable stress | Unpredictable physical factors | Anergia, anhedonia       | HPA axis, SNS, Lipid peroxidation        | Chronic        | [28] |

Abbreviation in the table: AFosB, a highly stable isoform of FosB which is a component of transcription factor-activator protein-1 (AP-1); BDNF, brain-derived neurotrophic factor; CRF, corticotrophin releasing factor; HPA, hypothalamic-pituitary-adrenal; IL-1β, interleukin-1β; IL-6, interleukin-6; LHB, lateral hebenula; mPFC, medial prefrontal cortex; PFC, prefrontal cortex; SNS, sympathetic nervous system; TNF-α, tumor necrosis factor-α; VTA, ventral segmental area.
so on, and many abnormalities in those regions have been evidenced by studies on brains of depressive patients on autopsy [12].

The most frequently reported findings obtained by brain-imaging technology are diminished grey-matter volumes and reduced glial densities of hippocampus and prefrontal cortex (PFC) in depressive patients [11], while it is still inconclusive whether these alterations in hippocampus and PFC represent a precipitating factor or are just a result of major depression [32].

Prefrontal Cortex

Reduced neuronal activity of medial PFC (mPFC) is found in social defeat-induced depression mice models despite its unclear pro-depressant mechanism [21b]. Degeneration of astrocytes in the PFC of rat induced depressive symptoms [33] and glial loss in PFC could effectively generate behaviors similar to depression [34]. The activity of ERK1/2 MAPK pathway as well as levels of mRNA expression and protein of ERK1/2 significantly declined in the PFC of depressive people who committed suicide [35]. The antidepressant action of ATP was evidenced to be modulated by P2X2 receptors in PFC [36].

Recent studies showed that transcription factor ΔFosB in mPFC, the prelimbic area in particular, regulates the vulnerability to stressful events and its overexpression exerts an enhancing effect on vulnerability to stress, in part via suppressing activity of cholecystokinin (CCK)-B-receptor [21b]. Blocking CCKB receptor in mice generates a pliable phenotype while the ligand CCK administered into mPFC in mice produces depressive symptoms similar to those induced by social defeat stress [21b].

These results suggest that CCKB and ΔFosB may be novel potent targets for preventing and/or curing depression [21b]. However, optogenetic stimulation of mPFC projections to basolateral amygdala or nucleus accumbens (NAc) after CCK infusion in mPFC can block the anxiogenic effect of CCK but no other antidepressant-like effect was observed in social defeat stress models [21b], which indicates that more detailed underpinnings of those effects need to be mapped out.

Ventral Tegmental Area

Dopamine neurons in ventral tegmental area (VTA) determine vulnerability versus resilience to social defeat stress, while vulnerable phenotype will manifest depressive behaviors [23a]. Induction of phasic rather than tonic firing by optogenetic methods in VTA dopamine neurons (projecting to NAc rather than to mPFC) of mice which experienced a social defeat stress beneath the threshold, caused a rapid vulnerable phenotype evidenced by increased social avoidance and reduced sucrose preference [24]. Optogenetic induction of VTA phasic firing also transformed resilient mice that underwent repeated social defeat stress previously into a vulnerable phenotype. Optogenetic suppression of the VTA-NAc dopamine projections generated resilience while suppression of VTA-mPFC dopamine projection induced vulnerability [24]. These projection-specific and fire-pattern-specific findings improve our understanding regarding roles of VTA dopamine neurons in susceptibility to stress and in pathology of depression [24].

Hippocampus

Structural and neurochemical changes of the hippocampus such as hippocampal neurons atrophy [37] and decreased ERK1/2 MAP kinase activity (detected in the post-mortem hippocampus of depressed persons [35]) are among the characteristics of major depression. Chronic stress exposure induces reduced hippocampal volume and diminished expression of neurotrophic factors and inhibits neurogenesis occurring in dentate gyrus in the adult brain [38]. Those alterations could be reversed by antidepressants [38c]. In psychological stress induced rat model of depression, levels of total zinc and mRNA expression of zinc transporting-associated proteins decreased in the hippocampus, while zinc functioned as cofactor for enzymes which are critical for biochemical processes especially in the brain [39]. Supplements with zinc or treatment with antidepressants could reverse the changes that are mentioned above [39]. Both drugs (such as resveratrol) and antidepressants (fluoxetine for example) could enhance the levels of BDNF mRNA and protein in the hippocampus and the mPFC [21a]. The ATP abundance in interstitial fluid derived from the hippocampus and PFC of the mice vulnerable to chronic social defeat stress was lower than that from the resilient mice [36]. The phospholipidomic profile (such as catalase, superoxide dismutase (SOD) and glutathione reductase) in the hippocampus was changed in mice exposed to chronic unpredictable stress [28a]. Micro-RNAs in the hippocampus such as miR-16 and miR-598-5p could be targeted to generate antidepressant behavior effects [40]. All those studies corroborate that the hippocampus may play diverse roles in the psychopathology of depression and much more details need to be further explored.

ENDOCRINE SYSTEM AND DEPRESSION

Glucocorticoids

Upon activation of HPA axis by the psychological stress, more GCs are released into the blood. Elevated concentrations of cortisol in the blood, saliva and urine, as well as bigger size and increased activity of adrenal gland, are found in a large part of depressive patients [41]. Hypercortisolemia can cause excitotoxicity to pyramidal neurons in the hippocampus and can lead to spine loss and atrophy of dendrites, as well as inhibition of neurogenesis in the dentate gyrus of the hippocampus [12]. Redundant GCs may also reduce the volume of hippocampus [42] thus affecting the function of brain areas related to emotion and reward circuitry. Many of these alterations could be rescued by antidepressant drugs [12]. Under normal conditions, GCs contribute to the termination of the stressful reaction via complicated feedback loops which involve the participation of hippocampus and paraventricular nucleus [12, 19]. However, the dysregulation of GC-mediated feedback loops, such as decreased function of glucocorticoid receptor (GR) in HPA axis, peripheral blood mononuclear cells (PBMC) and skin cells, was identified in depressive patients by a series of studies [19, 26a].
The abnormalities in GR may explain the hyperactivity of HPA axis in depression, and antagonists of GR (such as mifepristone) and GC synthesis inhibitors (for example, metyrapone) exhibit some therapeutic efficacy on depressive symptoms [43]. However, different effects of GCs and GR on depressive symptoms remain to be further explored.

Corticotrophin Releasing Factor

Evidence for the important role played by CRF in depression increased over the past decade. Acting as a neurotransmitter in the central nucleus of amygdala and bed nucleus of stria terminalis, concentrations of CRF in those areas, as well as the number of CRF-secreting neurons in the hypothalamus and locus coeruleus, were found elevated in patients with depression [12, 31, 44]. CRF overexpression in transgenic mice induced depressive behaviors and histonic signatures such as hypercortisolemia, anorexia, weight loss and decreased libido, which could also be achieved by infusion of CRF into CNS [31].

CRF exerts its physiological function by binding to its G-protein coupled receptors, CRF₁ and CRF₂, to activate the downstream cAMP signaling [31, 45]. CRF₁ receptors are highly expressed in the pituitary and the limbic areas where they modulate the activity of HPA axis [46]. Selective deletion of CRF₁ receptors in limbic areas leads to antidepressant-like behaviors in mice subjected to stress while antagonists of CRF₁ receptors could attenuate a series of depressive behaviors generated by withdrawal of drugs of abuse, but inconsistent results still exist [12, 31]. A major frustration about developing antagonists of CRF₁ receptors as antidepressants is the pharmacokinetic issue as well as hepatotoxicity [12]. The major function of CRF₂ receptors might be keeping the HPA axis response, rather than activating the HPA axis when exposed to stress, by functioning as auto-receptors on some neurons in paraventricular nucleus (PVN) [47]. Genetic deletion of CRF₂ receptors induces anxiety-like symptoms in mice and antagonists exhibit anxiolytic effects, and some antagonists even exhibit antidepressant effects in chronic mild stress model [12]. With less side effects compared to antagonists of CRF₁ receptors, exploring antagonists of CRF₂ receptors is of great interest to treat depression even though there are much more efforts to be made [12, 31, 47]. For more detailed knowledge about CRF, please see Reference 31.

Vasopressin

Synthesized in and secreted from paraventricular and supraoptic hypothalamic nuclei, this neuropeptide along with CRF stimulates the release of ACTH from corticotropes located at anterior pituitary and thus tunes the activity of the HPA axis when exposed to stress [12, 13b]. After binding to vasopressin V₁a and V₁b receptors which are also GPCRs [48], the activated complex exerts its influence throughout the limbic brain system, especially in the amygdala and bed nucleus of the stria terminalis [12]. The physiological effects of vasopressin include regulating water balance, blood pressure stress and anxiety among others [48, 49]. Vasopressin exerts driving influence on HPA axis related to chronic psychological stress by interacting with its V₁b receptors which are widely distributed in the limbic brain regions [48, 50]. Concentrations of vasopressin were elevated in depressive patients which might conduce to the hyperactivity of the HPA axis in those patients, while SSRI drugs treatment reverses this kind of alterations [48, 51]. The quantities of V₁b receptor-expressing neurons in depressive patients are larger than those of the healthy ones [48]. Antagonists of vasopressin V₁b receptors of non-peptide property exhibit antidepressant action while conflicting results about the antidepressant effects of genetic deletion of V₁b receptor gene in mice have been found [48, 52]. These confusing results need more detailed explanation by more well-designed experiments.

Glutamate

As a major excitatory neurotransmitter in the central nervous system, glutamate functions by binding metabotropic glutamate receptors (mGluR) and ionotropic glutamate receptors (iGluR) localized on both neurons and non-neuronal cells to produce rapid synapses-crossing transmission [53]. The levels of glutamate (or glutamine) in patients with depression were found elevated in the brain, cerebrospinal fluid and plasma [33, 54]. Exposure to stress leads to the release of glutamate from presynaptic neurons, which subsequently binds to iGluRs (such as N-methyl-D-aspartate (NMDA) receptors, kainite receptors and α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMP A) receptors on the postsynaptic neurons), as well as mGluRs located on both presynaptic and postsynaptic cells, and activates the downstream signaling pathways [54, 55].

NMDA Receptors

Two NR1 subunits, combined with either two NR2 subunits (the NR2 subunits could be subdivided into NR2A to NR2D subunits) or two NR3 subunits (NR3A to NR3B, less common), form the tetrameric NMDA receptors [54, 56]. They play important roles in learning and cognition and are closely associated with depression [57] while NMDA receptor antagonists are attractive drug candidates for refractory depression therapy [58].

Despite the fact that supportive results from clinical trials for the use of NMDA receptor antagonists remain weak, the diminished function of the receptors still shows antidepressant-like activity in the animal models [12]. The low status of NMDA receptor function could also prevent the morphological changes in hippocampal neurons induced by psychological stress and NMDA receptors expression could also be repressed by the marketed antidepressants [12]. By inhibiting glutamate activity, antagonists of NMDA receptors such as ketamine exhibited rapid antidepressant properties in both animal models and depressive patients [59]. However, ketamine could risk a series of side effects which set a limit to its use [33]. But another non-competitive and low-affinity antagonist of NMDA receptor, memantine, failed to produce rapid antidepressant-like responses until a high dose [54], which imply the complicated mechanism underlying the pathology of depression. Genetic deletion of NMDA receptor ε4 subunit (GluRε4, also named as NR2D) could generate antidepressant-like effects in mice [60]. The specific antagonists of NMDA receptors containing NR2B subunits may present good candidates considering that the
NR2B subunits are mainly localized in the depression-associated brain regions such as the hippocampus [54] but there are also results showing that NR2B and NR2A levels are reduced in the PFC of depressive patients [56], which is confusing. However, the identified X-ray crystal structure of NMDA will shed more light on the depression treatments based on NMDA receptors [61].

**AMPA Receptors**

After binding with glutamate, the activated APMA receptors elevate the expression of BDNF in the hippocampus leading to fast neurogenesis and sprouting of hippocampal neurons [12]. Positive allosteric modulators (such as piracetam, aniracetam and cyclothiazide [54]) exhibit antidepressant profiles alike to tricyclic drugs and SSRIs in several animal paradigms without fast desensitization of AMPA receptors which are often observed with full agonists [54]. In forced swim and tail suspension paradigms of mice, inhibitors of AMPA receptors may suppress the antidepressant-like behaviors induced by ICV administration of lithium, which could also elevate the protein level of glutamate receptor 1 (GluR1) and GluR2 in the mice hippocampus [62]. There is also an evidence proving that antidepressant drugs may be attributed to the biological effects of AMPA receptors [12].

**Metabotropic Glutamate Receptors**

Adverse effects of NMDA receptor antagonists resulting from direct suppression of glutamatergic function turned our focus to metabotropic glutamate receptors (mGluR, class C G-protein-coupled receptors (GPCR)) [33]. Highly expressed in the hippocampus, cortex, striatum, caudate nucleus and NAc, mGluR5 are mainly localized on postsynaptic membrane [33] and drugs targeted at this receptor to cure depression, anxiety and fragile X syndrome are experiencing clinical trials [53b]. Antagonists of group II metabotropic glutamate (mGlu2/3) receptor exhibit acute and sustained antidepressant-like actions in tail suspension and novelty-suppressed feeding paradigms [63]. Antidepressant effects in behavior could also be induced by mGluR5 antagonists such as MTEP [33]. The structure of mGluR5 transmembrane domain helps greatly in understanding the pathologies of neuropsychiatric disorders [53b].

**Gamma-aminobutyric Acid (GABA)**

It is postulated that the imbalance between glutamate and GABA with glutamatergic hyperactivity is involved in the neurobiology of major depression disorder [33]. GABA is the major inhibitory transmitter in the central nervous system and some brain regions (such as PFC, hippocampus, NAc, amygdala, VTA and hypothalamus) closely related to depression have GABAergic neuronal projections [12]. Therefore, there is a hypothesis that the activation of the GABA receptors may produce antidepressant effects [33]. The α2/α3 GABA<sub>A</sub> receptor modulators are supposed to probably serve as novel antidepressant candidates [64]. However, GABA receptor antagonist bicuculline can reverse the depression-like behaviors generated by ICV administered neuronostatin [65]. The resolved three-dimensional structure of GABA<sub>A</sub> receptor will further explore our understanding of depression and the design of potential drugs [66].

**Serotonin**

Serotonin and its receptors are among the major targets for depression therapeutic drugs such as tricyclics, selective serotonin re-uptake inhibitors (SSRIs) and serotonin and noradrenaline re-uptake inhibitors (SNRIs) [12]. Serotonin from the dorsal raphe (DR) located in the periaqueductal grey area and other raphe nucleus innervates many brain areas involved in depression such as the amygdala, the NAc and the PFC [67]. Elevated levels of serotonin contribute to the antidepressant effect [68]. By binding to serotonin receptors, serotonin activates a series of signaling pathways including AMP-PKA-CREB pathway to generate antidepressant effects [55]. The X-ray structure of 5-HT<sub>3</sub> receptor in complex with stabilizing nanobodies [69] may help us understand the antidepressant effects of drugs at the molecular level and reasonably design drugs targeted at this receptors with less side effects.

These structures of transmitters receptors involved in the pathology of depression will help us to study the antidepressant molecular mechanism and to design more rational chemical drugs with specific target sites.

**Brain-derived Neurotrophic Factor**

Neurotrophic factors play important roles in the regulation of neurogenesis, synaptic and structural plasticity, which are involved in the pathology of depression [37, 70].

Stressful exposure could induce reduced hippocampal neurogenesis and lower expression of brain-derived neurotrophic factor (BDNF) in limbic structures [70] and declined BDNF concentration in serum, the source of which is still disputed [11]. Neurotrophic factors such as BDNF (one member of nerve growth factor (NGF) family) play central roles in the survival, function and neuronal plasticity of the brain of adults as well as in the development of nervous system [55]. The binding of BDNF with its receptor tropomyosin-related kinase B (TrkB, a membrane-spanning protein with tyrosine kinase site at the cytoplasmic side) activates a series of downstream signaling pathways including phosphatidyl inositol-3 kinase (PI3K)-Akt (protein kinase B or serine threonine kinase) pathway, Ras-mitogen activated protein kinase (MAPK) pathway and phospholipase Cγ (PLCγ)-Ca<sup>2+</sup> pathway (which splits afterwards into 1,4,5-triphosphate inositol (IP3)-Ca<sup>2+</sup>/calmodulin-dependent protein kinase (CAMK) signaling and diacylglycerol (DAG)-PKC signaling) [55]. The NMDA receptor antagonist 7-chlorokynurenic acid could generate fast antidepressant effects such as elevated sucrose preference via alterations in expressions of microRNA that are involved in TrkB-ERK/Akt signaling in a chronic mild stress model of mice [40]. The activation of these pathways convergently promotes the survival, growth, synaptic plasticity and/or differentiation [55].

Consistent with the decreased BDNF in the hippocampus and prefrontal cortex (PFC) caused by stress, protein levels of the PI3K-Akt and Ras-MAPK signaling pathways decline, and this effect could be reversed by antidepressant
treatments [71]. Meanwhile, the rapid antidepressant action of NMDA receptor antagonist 7-chlorokynurenic acid could be blocked by the MAPK/Akt inhibitors in the animal models [40]. Antidepressant drug ketamine (another NMDA receptor antagonist) could increase the level of BDNF, and BDNF conditional deletion in mice could block the antidepressant action of ketamine [72]. The fact that BDNF could effectively generate antidepressant-like behaviors in the animal paradigms of depression and antidepressant effects of drugs could be blocked by genetic deletion of BDNF [37] leads to the thought that BDNF and downstream elements of BDNF signaling may render some therapeutic targets different from those targeted by monoamine re-uptake inhibitors.

However, the fact that genetic deletion of BDNF in rodent models is insufficient to cause depressive symptoms [55], suggests that BDNF is not the main cause for depression or maybe there is an alternative unknown factor leading to depression in parallel with BDNF and probably components downstream of BDNF are better targets [55].

Although blockade of IP3 receptors in PFC of stressed mice could improve the cognitive function involved in depression [73], the pervasive expression of such signaling pathways hinders the research and application of potential drugs (for example, activation of MAP kinase in cingular cortex and paraventricular hypothalamus generated different effects [74]), which is probably the leading cause of few literatures about depression and the aforementioned signaling pathways downstream of BDNF.

**Glial Cell-derived Neurotrophic Factor**

Exposure to chronic stress reduced the mRNA transcription and protein synthesis of glial cell-derived neurotrophic factor (GDNF) in NAc in stress-susceptible BALB/c (BALB) mice strain but increased those in stress-resistant C57BL/6 (B6) mice [75], but sequences of the GDNF promoters between the two strains showed no differences [13a, 76]. This led to the finding that chronic ultra-mild stress (CUMS) enhances DNA methylation at the CpG site 2 and the binding level of methyl-CpG binding protein 2 (MeCP2) to the CpG2 site 2 [13a]. The complex together with histone deacetylase2 (HDAC2) represses acetylation of Histone 3 (H3) and subsequently inhibits the GDNF transcription and finally results in depression-vulnerable phenotype in BALB mice [13a]. While in B6 mice subjected to CUMS, although enhanced methylation and binding status of MeCP2 were also detected in NAc, the levels of GDNF expression and H3 acetylation were higher [13a]. These demonstrated that MeCP2-cyclic AMP response element binding protein (CREB) complex binds to methylated site on GDNF promoters in resilient B6 mice [13a].

These results suggest that different epigenetic signatures may affect the adaptive ability to stress [13a, 76]. It is interesting that in depressive patients, GDNF levels in serum are lower [77] while elevated GDNF levels are reported in drug-resistant depressive patients after electroconvulsive therapy [78]. This may be of prognostic importance to individuals from families historically involved in depression.

**IMMUNE SYSTEM IN DEPRESSION**

Increasing studies suggest that psychological stress has an important effect on the immune system [17, 79], while researches showing that components of immune system such as interleukin-1β (IL-1β), IL-6, soluble IL-2 receptors and tumor necrosis factor-alpha (TNF-α) were elevated in depressive patients [80] indicate that the immune system is closely associated with depression. Peripheral inducers of immune cytokines may generate symptoms of depression [81] and in the brain, these inducers may decrease monoamine levels [82] that most current antidepressants aim to increase.

As an important regulator of brain-body interaction, immune mediators such as cytokines affect diverse central nervous system (CNS) functions involved in depression such as cognition, sleep and reward [83].

Expressed in the hypothalamus (mainly), hippocampus, cerebral cortex and thalamus, IL-1β (derived from microglia, astrocytes and neurons [84]) functions through interaction with its receptor, IL-1R1, which is expressed in several areas of the brain with more prominent expression in the hippocampus [85]. The binding of IL-1β to IL-1R1 activates a triad of signaling pathways including nuclear factor (NF)-κB, MAPK and JNK to function as host defenders [84]. Exposure to psychological stress will increase IL-1β in the hypothalamus and hippocampus while the administration of IL-1β will induce effects similar to stress response including activation of HPA axis, suppression of hippocampal long-term potentiation and down-regulated expression of BDNF [86]. Blockade of IL-1β signaling by administration of IL-1β receptor antagonists reversed stress-like symptoms induced by IL-1β at both cellular and behavioral levels [86]. IL-1β can also regulate the expression of the serotonin transporter gene [87], which is involved in the treatment of depression. This implicates the potential of IL-1β antagonists as a new candidate for depression therapy.

Although IL-1β plays a necessary and sufficient role in the cytostatic effect of stress on hippocampal progenitor cells, IL-6 may also conduce to the inhibition of proliferation [86]. This may be consistent with the hypothesis that hippocampal neurogenesis is necessary for the treatment of depression [38a]. Furthermore, mice with IL-6 gene deleted manifested resistance to the development of depressive symptoms induced by stress [88], which could be adopted as a tool to study the mechanism underlying the pathology of depression and to screen potential antidepressant drugs.

TNF-α could activate HPA axis [89] and directly activate indoleamine-2,3-dioxygenase, which is expressed in macrophages and dendritic cells in the brain and could through kynurenine pathway catabolize tryptophan which is the substrate for serotonin synthesis [90]. Succeeding studies identified that via p38 MAPK signaling, TNF-α, as well as IL-1β, promotes the serotonin uptake in mice midbrain and striatal synaptosomes by activating serotonin transporters [68]. This kind of serotonin-decreasing effect of TNF-α may suggests that blocking the TNF-α signaling may contribute to ameliorate the depressive symptoms, which have the same target as the selective serotonin reuptake inhibitors (SSRIs):...
to inhibit the re-uptake of serotonin [68]. Studies showing that genetic deletion of either TNF-α receptor 1 (TNFR1) or TNFR2 generates a series of antidepressant-like behaviors in several animal models [91] while administration of TNF-α induced depression-like behaviors which could be prevented by antidepressant drug such as fluoxetine [89] corroborate the thought above.

The existence of those cytokines in both central nervous system and peripheral organs may explain, at least partly, the concomitance of mental and somatic symptoms in depressive patients [3, 12]. Future researches about relationship between depression and cytokines may focus on the largely undiscovered neural circuits underlying the somatic and behavioral effects and the more detailed interaction among cells in brain.

NEW APPROACHES

Voltage-sensitive dyes (VSD) can be incorporated into cytoplasmic membranes and thus reflect the alteration of membrane potential [92]. With the help of suitable VSD, macrosopes and high-frequency cameras connected to computers, VSD imaging (VSDI) provides a quantitative method to quickly analyze neuronal activity involved in psychiatric diseases such as depression and anxiety at millisecond level, with a micrometer-level spatial resolution and a range spanning whole brain network [92, 93]. This method is useful for investigating the dynamics of neuronal networks, especially in the animal models of stress [93b]. However, this technology could only investigate the exposed areas which do not include deep brain regions. Other methods such as two-photon microendoscopy, will make up for that limitation [92].

3D anatomical and phenotypical maps are important for us to understand the relationships between structures and functions at cellular, circuit and organic levels [94]. Clearing tissues are the basis for the imaging of the whole body or whole organ, which is required for the identification and analysis of neuronal circuits in the brain [94, 95]. Using passive clarity technique (PACT) followed by perfusion associated agent release in situ (PARS) method, optical access into intact tissues could be easily obtained, so the target tissues labeled with fluorescent probes could be readily detected in the premise of preserving tissue morphology [94]. With cellular and subcellular resolution, this kind of improved CLARITY technology, could make the study of intercellular spatial relationship and neuronal connectivity in the brain much easier, and thus improve the animal models of depression [94, 96]. The CUBIC (clear, unobstructedbrain imaging cocktails and computational analysis) method could also be used to generate whole-brain image with single-cell resolution quickly, and in combination with other protocols, this method could also be utilized to visualizes and quantify the neuronal activities induced by ambient stimulation [95]. Those whole-body clearing technologies will provide insights into the neuronal circuits underlying the pathophysiology of depression.

As an outstanding example for the combination of genetics and optical methods, optical stimulation plus genetic engineering (optogenetics) could rapidly and precisely control specific function (gain or loss) of precisely defined biological processes in living tissues, especially in the central nervous system [97]. This kind of effect is based on light-activated ion channels and pumps (mainly channelrhodopsin 2, ChR2) which could be expressed in neurons and used to manipulate the firing rate and duration of neurons [24, 98]. Using this technology, stimulation imposed upon cells can be manipulated at the speed of millisecond scale with precision of cell type level (such as stimulating or suppressing dopamine neurons in VTA projecting to NAc [97]). The well-designed manipulations could be made upon specific neural circuits in awake and freely moving animals and present us precise results with good repeatability, compared to other approaches in neuroscience such as lesions and pharmacological interventions [97, 99]. Moreover, optogenetics could be used for behavioral controlling for a long period, which is important for identifying new neural loops involved in chronic stress [99]. Although optogenetic manipulations have been performed on the ex vivo retina (one kind of living human neural tissue), the major influence of this technology on human health comes from using it as a tool to gain insights into complex tissue function in diseases such as depression and Parkinson’s disease [97].

Magnetite nanoparticles could be used to generate heat under an alternating magnetic field, and heat could induce expression of some genes. When the heat-induced genes and magnetic nanoparticles are introduced into tumor xenografts, the expression of these genes could be controlled in a temporally and spatially selective manner, by altering the magnetic field [100]. The remote control of gene expression without lesions is very useful in animal models, especially models of mental diseases such as depression. With the improvement of this method, more insights into genes in neuronal circuits underlying the pathophysiology of depression will be obtained, although there is still much to do to achieve this purpose.

CONCLUSION

Although more and more focus has been laid on the brain research, especially the “BRAIN Project” launched by the national institutes of health (NIH) which will invest more money and energy into this area, our understanding about how the brain deals with the external information and how mental diseases especially depression and schizophrenia occur, remains to be further explored. However, the VSDI, optogenetic, CLARITY, PACT-PARS and CUBIC technologies will shed more light on our researches on the pathology of depression, or even more diseases such as cancer.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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