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A Short Glance at the Neural Circuitry Mechanism Underlying Depression

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Abstract

Depression leads to a large social burden because of its substantial impairment and disability in everyday activities. The prevalence and considerable impact of this disorder call for a better understanding of its pathophysiology to improve the diagnosis, treatment and prevention. Though productive animal models and pathophysiological theories have been documented, it is still very far to uncover the complex array of symptoms caused by depression. Moreover, the neural circuitry mechanism underlying behavioral changes in some depression-like behavior animals is still limited. Changes in the neural circuitry of amygdala, dorsal raphe nucleus, ventral tegmental area, hippocampus, locus coeruleus and nucleus accumbens are related to depression. However, the interactions between individual neural circuitry of different brain areas, have not yet been fully elucidated. The purpose of the present review is to examine and summarize the current evidence for the pathophysiological mechanism of depression, with a focus on the neural circuitry, and emphasize the necessity and importance of integrating individual neural circuitry in different brain regions to understand depression.

Keywords

Pathophysiology, Depression-Like Behavior, Neural Circuitry

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1. Introduction

Depression is a heterogeneous symptom complex, characterized by an overwhelming sense of fatigue, neuropsychiatric and vegetative symptoms, neuroimmunological disturbances [1], neuroendocrine abnormalities, and some other somatic complaints [2]. Depression leads to a large social burden because of its substantial impairment and disability in everyday activities. The World Health Organization ranks depression as the fourth leading cause of disability worldwide and predicts that it will increase to the second place by 2020 [3]. The prevalence of depression transcends race, ethnicity, socioeconomic class, gender, and age. The prevalence and considerable impact of depression call for a better understanding of its pathophysiology to improve the diagnosis, treatment and prevention of this mental disorder. The official diagnosis of depression is subjective and relies on the documentation of limited symptoms that significantly impair functioning for a certain duration [4]. In addition, available techniques to document the pathophysiology usually depend on post-mortem studies, which have great limitations, or neuroimaging techniques, which base on detecting changes in neuronal activity by using indirect markers of activation [5]. Though these methods have provided important insights into candidate brain regions, simple changes in regional brain activity are probably insufficient to uncover the complex array of symptoms caused by depression.

The susceptibility to depression is attributed to interactions between heterogeneous genetic and environmental factors, which complexified the pathophysiology of depression. The pathophysiological theories of depression are manifold, mainly including the monoamine model, the HPA model and the neurotrophic model [6]. A great number of animal models emerged, accompanied with the imperative of deciphering the pathophysiological mechanism underlying depression [7]. Nevertheless, there are still important challenges to how information gained from these models should be interpreted, and the differences in behavioral characteristics between humans and these models are unknown. Previous work has demonstrated that depression is associated with decreased function in the noradrenergic (NA) locus coeruleus (LC), serotoninergic dorsal raphe (DR) and median raphe (MnR), and dopaminergic ventral tegmental area (VTA) systems in animal studies [8]-[11]. Increased apoptotic markers and the loss of cortical NA fibers/boutons in these areas were associated with behavioral indices of depression such as enhanced immobility time and decreased climbing time during the forced swimming test (FST) [11]. The depressive behavioral phenotype of mice is characterized by increased immobility and decreased activity in the FST and tail suspension test [11] [12]. These depression-like behaviors are considered to be mediated via the fundamental changes of complex neural circuits in the nervous system [13] [14]. However, the neural circuitry mechanism of the depression-like behavioral changes in rats still remains much to be known. In addition, knowledge about the neural circuitry mechanism underlying depression, especially for the interactions between individual neural circuitry in different brain areas, has not yet been fully elucidated.

Our ongoing study suggested that the neural circuitry in both intrinsic electrophysiological and synaptic connection properties of pyramidal neurons changed significantly in the depression-like behavior mouse model. However, the neural circuitry mechanism of the changes in depression-like behavior is still poorly understood because it is relatively difficult to analyze the neural circuits in living animals using the whole-cell patch clamp recording. Here, we examine and summarize the current evidence for the pathophysiological mechanism of depression, with a focus on the neural circuitry, and underscore the necessity and importance of integrating individual neural circuitry in different brain regions to understand depression.

2. Characteristics of Neuronal Activity and Neural Circuitry in the Amygdala under a Depression Condition

The amygdala is a key brain structure involving in the integration of emotions and stress. It has been confirmed that the dopaminergic abnormalities in this region were associated with depression [10]. The function of serotonin (5-hydroxytryptamine, (5-HT)) in the amygdala affects fear and pathological anxiety in both animal models and clinical studies. A functional polymorphism of the human serotonin transporter gene (*SLC6A4*) led to differential excitability of the amygdala neurons to emotional stimuli, which may contribute to the increased fear and anxiety behaviors [15]. This suggests that the increased amygdala neuronal activity is probably related to the occurrence of depression. On the other hand, one study has documented that the greater amygdala neuron activation to emotional facial expressions could predict the improvements in major depression [16]. This is supported by a finding that the amygdala did not change its activity from patients who were in remission [17]. However, Stuhrmann *et al.* observed that some inconsistencies were existed between amydala and prefrontal

cortex (PFC) for sad facial expressions [18], which is probably caused by heterogeneities in paradigms and patient samples. Depression is a heterogeneous symptom complex, and the occurrence of it can be attributed to either or both heterogeneous genetic and environmental factors. Therefore, distinct effects of the amygdala neuronal activity on depression could be, in part, due to varied responses to both inner (genetic factors) and outer stimuli (environmental factors).

There is a crucial role of long-distance neural circuitry between the amygdala and the anterior cingulate cortex in depression. It has been shown that the rate of uncoupling between the amygdala and the anterior cingulate predicted almost 30% of the variation in temperamental anxiety, as measured by a predictor of depression [19]. The functional connectivity density (FCD) mapping is a data-driven method to determine the regional density of functional connections and to identify the major cortical and subcortical FC hubs. Using this method, the role of neural circuitry between amygdala and other cerebral cortex areas has been identified an abnormal connectivity for each voxel in the whole brain of patients with depression. Patients showed a decreased FCD in the mid-cingulate cortex (MCC) and an increased FCD in the occipital cortex (OCC) [20]. Moreover, global changes in FCD were driven by the changes in abnormal local connectivity, the reduction of the functional connectivity (FC) toward the left amygdala for MCC and the increase in FC towards the right supplementary motor area for OCC. It has also been observed that medication-naive subjects with major depressive disorder (MDD) exhibited a decreased amygdala-left rostral PFC (rPFC) functional connectivity in response to negative emotional stimuli using functional magnetic resonance imaging (fMRI) [21]. This implies that abnormalities in amygdala-left rPFC neural circuitry responses to the negative emotional stimuli may play a crucial role in the pathophysiology of MDD.

Taken together, it implies that the amygdala neuronal activity is closely associated with depression. Moreover, it suggests that the occurrence of depression is not only because of the abnormal neural circuitry of amygdala, but also because of the dysfunctional neural circuitry between amygdala and specific cerebral cortex regions.

3. Characteristics of Neural Firing Property and Neural Circuitry in the Dorsal Raphe Nucleus under a Depression Condition

Recent work has examined the disturbed network connections in the dorsal raphe nucleus functionally and structurally in a clinically relevant fashion. It has been confirmed that very slow, low frequency oscillations in raphe connectivity are diminished by acute tryptophan depletion, which is associated with mood relapse in remitted depressives [22]. There is evidence showing that patients with weakened raphe-frontal tracts are less likely to respond to selective serotonin reuptake inhibitors (SSRIs) [23], suggesting that intact slowly oscillating modulatory inputs from the raphe are necessary for remission, and they are not improved by SSRIs in the presence of physical damage to the tracts. Together, it indicates that modulatory effects from the dorsal raphe nucleus are critical in achieving “normal mood”.

The dorsal raphe nucleus (DRN) harbors serotonergic neurons projecting throughout the brain, which endows the DRN with potential connections with the other brain regions. A possible role of the mPFC-DRN neural circuitry in depression has been confirmed by the fact that the stimulation of axons of the medial prefrontal cortex (mPFC) neurons in the DRN increased swimming behavior during the FST [24]. The important role of DRN neural circuitry in depression could be strengthened by the indirect impacts on the amygdala. The DRN serotonergic neurons could innervate the anterior cingulate by the fibers target to this area. Moreover, the anterior cingulate harbors subfields involved in negative feedback to the amygdale [6]. This suggests that the DRN serotonergic neurons may alter the cortico-amygdala coupling indirectly through the innervation to the anterior cingulate.

The firing properties of the DRN serotonergic neurons are also associated with depression. Evidence shows that the DRN serotonergic neurons inhibited firing rate in animal models of depression [25] [26]. The firing rate of the DRN serotonergic neurons could modulate the emotional state of an organism since there is an association between the temporal kinetics of the DRN firing and the onset of antidepressant efficacy [27]. In addition, the relationship between the DRN firing and depression has been highlighted by the inhibitory effect of some antidepressants on the firing rate of DRN serotonergic neurons [6] [25]. The disruption of firing properties of individual neurons or synaptic plasticity caused by antidepressants will consequently affect neural circuitry related to depression [28]. Collectively, it implies that both the intrinsic electrophysiological properties of the DRN serotonergic neurons and the neural circuitry formed between DRN and other brain areas are involved in depression.

4. Features of Neural Firing Pattern and Neural Circuitry in the Ventral Tegmental Area under a Depression Condition

The inhibition of VTA dopaminergic neurons in mice resulted in multiple depression-like behaviors [29]. The VTA dopamine neurons projected to multiple regions, including the nucleus accumbens (NAc) of the brain [30]. Depression may involve in the alterations of the neural encoding in the limbic circuitry. It has been shown that the optogenetic recruitment of these VTA projecting dopamine neurons in the NAc greatly changed the neural encoding of depression-related behaviors of freely moving rodents [29]. This underscores the crucial role of the VTA-NAc neural circuitry in depression. In addition, optogenetic induction of phasic firing, but not tonic firing, VTA dopaminergic neurons of mice experienced sub-threshold social defeat stress rapidly induced depression-like phenotypes [31]. Such discrepancy is possibly due to different firing patterns of the VTA dopaminergic neurons varying the responsive sensitivity and consequently affecting the VTA neural circuitry and resulting in depression-like behaviors. Therefore, although depression is likely attributed to the complex interactions of heterogeneous genetic and environmental factors, the variety of this mental disease may also be due to the different neurobiological mechanisms.

The activity of phasic firing dopaminergic neurons is regulated by cholinergic activity in the VTA. Addy *et al.* recently found that physostigmine (the acetylcholinesterase inhibitor) administration into the VTA increased the duration of immobility in the FST. However, the infusion of scopolamine (the muscarinic acetylcholine receptor (AChR) antagonist) and mecamylamine (the nicotinic AChR antagonist) into the VTA decreased the duration of immobility, exhibiting an antidepressant-like effect [32]. Distinct effects on depression-related behaviors could be owing to the VTA dopaminergic neurons having different sensitivities to the cholinergic inhibitor or antagonist. Nevertheless, there is evidence supporting that the neural circuitry in the VTA influenced by its dopaminergic neurons activity is closely associated with depression-related behaviors. In addition, it has been confirmed that the cholinergic neuron activity could exert powerful modulation on the neural circuitry activity [33]. Thus, though VTA dopaminergic neurons show firing pattern specific effects on depression-like behaviors and affect depression-related behaviors indirectly depending on the regulation by cholinergic activity, the crucial role of VTA neural circuitry in depression still needs further investigation.

5. The Role of Neural Circuitry in Other Brain Regions under a Depression Condition

Besides the brain regions aforementioned, the neural circuitry in other brain areas is also closely associated with depression. A previous study indicated that altered white matter integrity, especially in the cortical-subcortical neural circuit, may contribute to the pathophysiology of major depressive disorder [34]. It also provided new evidence that microstructural abnormalities in white matter may occur early during depression. Moreover, changes in the neural circuitry of the hippocampus, LC and NAc are also involved in depression. Hippocampus not only plays a central role in emotional processing and formation and retrieval of memories [35], but also is likely to play a more general role in the regulation of behaviors by the impact on neural information processing [36]. It has been suggested that the stress-induced decrease in hippocampal neuronal plasticity was one possible primary pathophysiological mechanism of depression [37]-[39]. One study confirmed that the functional connectivity of the hippocampus to the prefrontal and cuneus cortices decreased substantially in older adults with sub-threshold depression. Besides, the strength of hippocampus-cuneus connectivity was correlated with self-reported depressive symptoms [40]. This indicates that dysfunctional integration within the hippocampus and the cortical regions may involve in the occurrence of depression. A recent work also demonstrated that optogenetically direct reactivating dentate gyrus engram cells associated with a positive memory could suppress depression-like behaviors in mice [41]. This finding not only offers a potential therapeutic node for alleviating a subset of depression-related behaviors, but also suggests that direct activation of the endogenous neuronal processes may be an effective means to treat depression and some other maladaptive behaviors.

Previous evidence showed that intense stress damaged cortical LC axon terminals [42] accompanied depression-like behaviors in animal models [43] [44]. The dysregulation of the LC projection activities may produce abnormalities of both serotonergic and dopaminergic neurotransmission [9], which affects the neural circuitry in the LC. The occurrence of depression-like behaviors probably results from the abnormality of LC axon and consequently influences the synaptic connections between LC noradrenergic neurons and with their target sites. The relationship between the LC neural circuitry and depression was highlighted by the finding that the dys-

function of LC noradrenergic neurons in light-deprivation rats made cognitive impairment which was a hallmark of depression [11]. The NAc is also a critical brain region with neuronal circuits that are responsible for mood [45]. It has been documented that the accumbal cholinergic neuronal activity could regulate depression-like behaviors, suggesting that the activity of these neurons is crucial for the regulation of mood and motivation [46]. The accumbal neurons receive a highly compressed input from different brain areas, including the amygdala, the hippocampus, the cingulate gyrus, and the prefrontal cortex [47] [48], it can be speculated that integrating the NAc neural circuits with other brain regions will be a better way to understand the underlying neural circuitry mechanism of depression.

6. Perspectives

Our ongoing study suggested that the neural circuitry in both intrinsic electrophysiological and synaptic connection properties of pyramidal neurons changed significantly in the depression-like behavior mice. However, the neural circuitry mechanism of depression-like behavior in living animals still remains much to be understood. The development of optogenetics enables the analysis of the role of specific neural circuits in specific behaviors in living animals [49], and the relationship between the stimulation of a cohort of neurons with varied firing patterns and behavioral consequences [31]. This new technology will allow us to analyze the potential neural circuitry which is responsible for depression more conveniently.

Individual neural circuitry in specific brain regions as aforementioned plays crucial roles in depression. However, brain regions related to depression usually interact complexly, and more attention should be paid to the elaborate interactions between the individual neural circuitry. A recent study showed that a deep brain electrical high-frequency stimulation in different brain regions of rat models of depression exhibited varied antidepressant effects, with the ventromedial prefrontal cortex (vmPFC) producing the most profound antidepressant efficacy [50]. The high-frequency stimulation in the vmPFC modulated a brain circuit linked to the DRN and thus evoked a specific modulation of the serotonergic neurons in the DRN. Moreover, it suggested that DRN serotonergic neurons may alter the cortico-amygdala coupling through the innervation of the anterior cingulate [6]. Evidence also shows that alterations in anatomy and function of amygdala-cingulate feedback circuit were critical for the emotion regulation, implicating a developmental, systems-level mechanism underlying genetic susceptibility for depression [19]. Such intricate modulations among these brain areas highlight the necessary to embrace complex interactions between individual neural circuitry when understanding depression.

Recent studies documented that the dysfunction of the neural circuits between the prefrontal and bilateral parietal cortex was associated with cognitive impairment in depression [51] [52]. The role of individual neural circuitry between different brain regions in depression was further emphasized by the relationship between the strength of hippocampus-cuneus connectivity and self-reported depressive symptoms in elderly individuals with sub-threshold depression [40]. These studies indicate the neural circuitry mechanism of depression is likely due to the elaborate interactions between the individual neural circuitry in different brain regions, even in the whole brain networks [53]. This also highlights the necessity and importance of integrating individual neural circuitry in different brain regions (including new potential regions) to understand depression.

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Abbreviations

AChR, acetylcholine receptor;
DR, dorsal raphe;
DRN, dorsal raphe nucleus;
FCD, functional connectivity density;
fMRI, functional magnetic resonance imaging;
FST, forced swimming test;
5-HT, 5-hydroxytryptamine;
LC, locus coeruleus;
MCC, mid-cingulate cortex;
MDD, major depressive disorder;
MnR, median raphe;
NA, noradrenergic;
NAc, nucleus accumbens;
OCC, occipital cortex;
PFC, prefrontal cortex;
SSRIs, selective serotonin reuptake inhibitors;
VTA ,ventral tegmental area.