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Annals of Psychiatry and Mental Health

Review Article

Depression: Abnormality in Neural Circuits

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Submitted: 08 August 2017

Accepted: 18 September 2017

Published: 19 September 2017

ISSN: 2374-0124

OPEN ACCESS

Keywords

- Depression
- Mental illness
- Pathophysiology

Abstract

Depression as a kind of mental illness affects huge number of population worldwide and is ranked as the fourth leading cause of disability worldwide, and is predicted to increase to the second place by 2020. Depression leads to great social burden because of its substantial impairment and disability in everyday activities. Though great efforts in previous decades have been made to understand this mental disease, to date, much still remains to be known about its pathophysiology, especially for the underlying neural circuit mechanisms. To better improve the diagnosis, treatment and prevention of this mental disorder, it is imperative and also very important to make more clarifications on the underlying neural circuitry mechanisms responsible for the occurrence of depression. Accordingly, here we briefly summarized some key studies pertaining to the neural circuits responsible for depression, and hopefully to shed some lights on the future studies concerning this annoying mental disorder.

INTRODUCTION

Depression as a kind of mental illness affects around 20% of the world's population [1]. It is ranked the fourth leading cause of disability worldwide, and is predicted to increase to the second place by 2020 [2]. Depression causes great social burden because of its substantial impairment and disability in everyday activities, which makes imperative investigations on the mechanisms underlying its pathophysiology so as to improve the diagnosis, treatment and prevention of this mental disorder. A growing body of studies emerges aiming to make a better understanding of depression [3-11]. Our recent work demonstrates that alterations of motor cortical neural microcircuits contribute greatly to the depressive-like behaviors in a light-deprivation induced mouse model of depression [8], which emphasizes the potentially robust changes in neural circuits during the occurrence of depression. Generally, neural circuits between distinct brain areas are responsible for the depressive-like phenotypes [9, 12-14]. The occurrence of depression is potentially associated with abnormalities of these specific neural circuits in/among distinct brain regions [15]. Here, we concisely summarized some key literatures pertaining to the neural circuits responsible for depression, hopefully to provide some insights into the future studies concerning this annoying mental disorder.

Multiple lines of evidence implicated the important role of the ventral pallidum (VP) in depression because of its special anatomical location at the interface of the motivational and reward circuitry [16-18]. A recent study indicated that neural circuits between the ventral pallidum (VP) and lateral habenula (LHb) as well as ventral tegmental area (VTA) mediated separate core symptoms of depression [9]. The VP parvalbumin-positive (PV) neurons projecting to LHb subserve the behavioral despair and those projecting to VTA contribute the social withdrawal of depressive behaviors. This work by Knowland et al. established a systematic approach that could be taken to explore how distinct neural circuits may subserve the heterogeneous symptoms seen in depression. It also implies that VP neural circuits endowed with distinct components could contribute to related, yet different depressive-like phenotypes in mice, which provides some insights into symptom-specific treatments of depression.

The amygdala is another key brain structure closely associated with depression [19-22]. A new clinical study documented that maternal depressive symptoms during pregnancy were closely related to the amygdala hyper responsivity in their children [23]. Moreover, a historic study has reported a critical role of amygdala-cingulate feedback circuit in depression [21]. Using the functional connectivity density (FCD) mapping method, It was found a decreased FCD in the mid-cingulate cortex (MCC)

while an increased FCD in the occipital cortex (OCC) in patients with depression [13]. In addition, evidence from functional magnetic resonance imaging (fMRI) showed that the amygdala-left rostral PFC (rPFC) functional connectivity was decreased in response to negative emotional stimuli in medication-naive subjects with major depressive disorder (MDD) [22], suggesting that abnormalities in neural circuitry between the amygdale and left rPFC potentially play a key role in the pathophysiology of MDD. A recently work by Young et al. found that the increased amygdala hemodynamic response to positive memories dependent on the real-time functional MRI neurofeedback (rtfMRI-nf) training could dramatically decreased depressive symptoms of patients. In addition, using the resting-state fMRI, another recent study reported that the resting-state amygdala-cortical functional connectivity with the prefrontal-cingulate-temporal circuit is abnormal chronic tinnitus patients with depressive mood [24]. Collectively, it suggests that abnormalities of neural circuits between amygdala and other brain areas are potentially responsible for the core symptoms of depression, and the amygdala as a potential target for the treatment depression should be paid more attention.

In a chronic mild stress (CMS) rat model of depression, it was found that the dopamine DA neuron population activity was remarkably decreased, which could be restored by attenuating the activity of either the VP or the basolateral nucleus of the amygdala (BLA). It highlighted that the CMS rat depression model was closely related to the BLA-VP-VTA inhibition of dopamine neuron activity, and shed some lights on the important role of neural circuits of the BLA-VP-VTA in depression [25]. In fact, VTA is also a very important brain area closely associated with depression [5, 26], and the inhibition of VTA dopaminergic neurons could lead to several depression-like phenotypes in mice [27]. The optogenetic stimulation of VTA projecting dopamine neurons in the nucleus accumbens (NAc) could greatly change the neural encoding of depression-related behaviors of freely moving rodents [27], which underscored the crucial role of the VTA-NAc neural circuitry in depression. The importance of the VTA-NAc neural circuitry in depression has been strengthened by a recent study depending on the chronic bilateral high frequency deep brain stimulation (DBS) of the medial forebrain bundle (MFB) [28]. It was documented that the lesion of VTA dopamine neurons could lead to the dopamine depletion in the NAc and, in the end, produced depressive-like behaviors in the rats, which was, to some extent, reversed by MFB-DBS. This study also highlights the DBS as a potentially efficient way in relieving depressive symptoms especially resulting from abnormalities of VTA-NAc neural circuitry.

In summary, future studies should make much more room for the important roles of neural circuits in depression [29], which will definitely supply some informative evidence for the clinical treatment of depression. Though the crucial roles of neural circuitry between the VP and LHb as well as VTA, the amygdale and PFC, the BLA-VP-VTA, and also the VTA-NAc, we should keep in mind that some other local neural microcircuits mentioned elsewhere also should not been neglected [29]. From this point, much more efforts in future studies should be made for the search of new potential brain regions and neural circuits related to depression. The rapid development of optogenetics makes it more convenient for the analysis of the role of specific neural circuits in specific behaviors in living animals [30,31], including depression-like behaviors, which subserves the investigations of new potential brain regions and neural circuits responsible for depression.

ACKNOWLEDGEMENTS

This study was supported by the grants from the Wenzhou Science and Technology Plans (No.Y20140139), the Foundation of School of Ophthalmology & Optometry, The Eye Hospital, Wenzhou Medical University (YNCX201311), the Natural Science Foundation of Zhejiang Province of China (No. LQ14H120003) and the National Natural Science Foundation for Young Scientists of China (No. 81301117).

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Cite this article

Lu C, Li YY, Lin HZ, Zhang YF (2017) Depression: Abnormality in Neural Circuits. Ann Psychiatry Ment Health 5(5): 1115.