Medica and Clinica Press

Publishing press
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Mini Review

Depression: Cortical circuit dysfunctions and beyond

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Received: *December 16th, 2017*
Accepted: *December 21st, 2017*
Published: *December 26th, 2017*

Citation
Lu C, Li YY, Lin HZ, Zhang YF. Depression: Cortical circuit dysfunctions and beyond. *Mec Clin Press*. 2017; 1(1): 56-58. doi: 10.28964/ClinPress-1-111

Depression as one serious neuropsychiatric disorder affects great number of population worldwide[1] and is ranked as the fourth leading cause of disability.[2] A plethora of studies have advanced the understanding of the pathogenesis of this mental disease.[3-11] Our recent study depending on a depressive-like mouse model induced by light deprivation indicated that aberrant motor cortical microcircuit was a potential causal factor leading to depressive-like phenotypes in mice. At both single neuron and synaptic connection levels, our study, to some extent, has shed some lights on the pathogenesis of depression. Here in the present short review, based on our recent findings we summarized what was implicated in the dysfunctions of motor cortical circuit underlying depression, and together with some other key researches on depression, aiming to provide some insights into the potential important role of cortical circuits during the pathogenesis of depression.

Dysfunctions in certain cerebral cortex have been implicated in depression. For example, it was demonstrated that abnormalities in the medial prefrontal cortex (mPFC) was closely associated with depressive-like phenotypes in a depression-like behavior mouse model induced by learned helplessness.[12] Our recent study showed that light deprivation could successfully induce the depression-like behavior in mice which was characterized by the significant increase in immobility during the forced swimming test and tail suspension test.[9] In addition, the depressive-like mice exhibited weakened static and dynamic locomotor abilities which were highlighted by the remarkable decrease in the duration of pole-climbing in the anti-static fatigue test and swimming time in the exhaustive swimming test. These abnormal behavioral changes in the depressive-like mice were confirmed to be closely associated with electrophysiological properties changes of single motor cortical layer 5 pyramidal neuron. Among the great number of layer 5 pyramidal neurons recorded, it was demonstrated that the percentage of bursting firing neurons was significantly decreased while the proportion of regular spike neurons was dramatically increased in mice with depression-like behavior. Moreover, it was revealed that neural excitability was significantly reduced in layer 5 pyramidal neurons from the depression-like behavior mice. These results suggest that even subtle changes in electrophysiological modalities of motor cortical layer 5 pyramidal neurons could be a potential causal factor resulting in the abnormal behaviors in the depressive-like mice.

More interestingly, we confirmed that obvious changes in motor cortical circuit were related to the depressive-like phenotypes in mice. The single synaptic connection probability among individual layer 5 pyramidal neurons was markedly decreased in the depressive-like mice. Also, great differences were found in the proportion of excitatory synaptic subtypes of layer 5 pyramidal neurons between the control and the depression-like behavior mice, which was highlighted by the loss of facilitated excitatory synapses and a slightly increase in the balanced excitatory synapses in the depressive-like mice. Besides, the depression-like behavior mice showed a reduced synaptic

transmitter release probability but an enhanced absolute synaptic strength among individual layer 5 pyramidal neurons in the motor cortex. Last but not the least, a simplified morphological complexity of basal and apical dendrites of layer 5 pyramidal neurons from the depression-like behavior mice was found, and such decreased structural complexity was implied to be closely associated with the great changes in the motor cortical circuit. Taken together, the decreased synaptic connection probability and synaptic transmitter release probability, the enhanced absolute synaptic strength, accompanied with the changes in excitatory synaptic subtypes and the simplified neural morphology of layer 5 pyramidal neurons, in the end, will definitely lead to great modifications on the motor cortical microcircuit. These abnormal changes/dysfunctions of motor cortical circuit will possibly influence the neural transmission in and between its projection targets in the brain, which together, in the end, produced depressive-like phenotypes in mice.

Some historic studies also strengthen the crucial role of some other cortical projections to certain brain areas. For example, it was confirmed that stimulation of the mPFC-amygdala circuit[13,14] or the projections from mPFC to lateral habenula[15-17] could produce depressive-like phenotypes. In contrast, it was suggested that the stimulation of the mPFC-dorsal raphe circuit has some antidepressant effects.[17] These meaningful studies together with our recent findings aforementioned above strengthen the crucial role of cortical circuits in the pathogenesis of depression, and will provide some insights into the clinical treatment of depression especially from a view of cortical circuit. The occurrence of depression usually accompanies with deficits in several aspects of reward and, during the past decades, great efforts were also made on deciphering the relationship between the brain reward circuitry and depression.[18] Thus, besides the brain cortical regions, other brain areas such as the ventral tegmental area and nucleus accumbens related to reward should also be seriously taken into consideration when decoding the mechanisms underlying depression in the future studies.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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