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The Role of Lateral Habenula in Depression: What We Know and What We Don't Yet Know

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Abstract

Depression is a serious neuropsychiatric disorder and affects a large number of populations worldwide, and results in great social and economic burden. The lateral habenula (LHb), as one main subnucleus of the habenula which is part of the epithalamus, could decode aversive signals in the brain. The LHb showed some innervations to the dorsal raphe nucleus and the locus coeruleus that had closely relationship with depression. A plethora of evidence including both animal models and clinical studies has confirmed the involvement of LHb in the pathophysiology of depression. The LHb generally exhibited hyperactivity under the depressed state, which may, to some extent, be due to the aberrant regulation or dysfunctions of certain specific molecules in the LHb, for example, the β form of calcium/calmodulin-dependent protein kinase type II and p11 as well as protein phosphatase 2A. Though great efforts on the study of the role of the LHb in depression and great advances had been made, far more remains to be addressed concerning functional role of LHb in anxiety and the interactions of LHb with other brain systems related to stress which acts as a crucial factor inducing depressive-like symptoms. Accordingly, in the present mini-review we took a brief glance at some key findings pertaining to the role of LHb in depression and tried to inspire some hints on the unresolved aspects concerning this specific brain area in the pathogenesis of depression, and hopefully to provide some insights into future studies on the potentially crucial role of LHb in depression.

Keywords: Depression; Lateral habenula; β form of calcium/calmodulin-dependent protein kinase type II; p11; Protein phosphatase 2A

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Introduction

Depression as one kind of serious neruropsychiatric disorder has made great social and economic burden [1,2]. A great number of studies emerging aimed to decipher the pathogenesis of depression [1-11]. Dysfunctions of various brain areas including the lateral habenula (LHb) were involved in the occurrence of depression [12-15]. A fruitful of studies emerged in recent years lay the foundation of unveiling the association between the LHb and depression [14-19], however, much more still remains to be known especially about the mysterious role of LHb in depression. Here in the current min-review, we briefly summarized some key findings pertaining to the role of LHb in depression and potentially intended to inspire some hints on the unresolved aspects concerning this specific brain area in depression, and hopefully to provide some insights into the future research on the underestimated important role of LHb in depression.

The medial and the lateral habenula (LHb) are two main sub-nuclei of the habenula which is part of the epithalamus [20]. Generally, the LHb could be activated by stimuli related to negative experiences and participated in decoding aversive signals. In recent years the LHb has emerged as a crucial brain region involved in the pathophysiology of depression. Evidence from functional magnetic resonance imaging studies revealed that patients exhibiting psychiatric disorders showed hyperactivity of LHb neurons accompanied with depressive phenotypes [16]. In a rat model of depression induced by the congenital learned helplessness, it was documented that gamma-aminobutyric acid (GABA) agonist muscimol could inhibit LHb activity, which eventually produced antidepressant effects in this treatment resistant animal model of depression [17-23].

Moreover, clinical evidence showed that functional inhibition of the LHb depending on deep brain stimulation exhibited antidepressant effects on patients with depression [23], which was possibly due to the innervation of LHb to the dorsal raphe nucleus and the locus coeruleus. This evidence implies that the inhibition of LHb activity could be considered as a potential therapeutic target for the treatment of depression. On the one hand, it has been summarized that the complicated interactions of the LHb and dorsal raphe nucleus contributed to the regulation of physiological mechanism underlying depression, and the disruption of these normal interactions were responsible for the pathogenesis of depression. On the other hand, the antidepressant effects of antidepressants were generally relied on its influence on the serotonergic and noradrenergic systems. Serotonergic fibers and noradrenergic fibers are originated from the dorsal raphe nucleus and the locus coeruleus, respectively. Both the dorsal raphe nucleus and the locus coeruleus are, at least to some extent, innervated by the habenular complex, suggesting that the LHb may also exert its modulatory role during the pathogenesis of depression through an indirect way depending on the innervation of the dorsal raphe nucleus and the locus coeruleus [23].

Several lines of evidence have identified enhanced habenula activity in the depressed state [24-26]. Scientists worldwide recently have made great efforts on clarifying the molecular mechanism of the LHB hyper-activation in inducing depressive-like phenotypes [27]. It has been demonstrated that the β form of calcium/calmodulin-dependent protein kinase type II (βCaMKII) was remarkably increased in the LHb of animal models of depression and was significantly decreased by antidepressants. Also, the increase of βCaMKII was sufficient to induce conspicuous depressive-like symptoms. On the other hand, the decrease of βCaMKII could reverse the depressive symptoms. These findings indicated that βCaMKII was a key mediator in maintaining normal functions of LHb neuron and a crucial molecular determinant of depression. A new recent study pertaining to the role of LHb in depression documented that the elevation of p11 in LHb neurons could mediate depression-like behaviour in mice. It was demonstrated that p11 was remarkably increased in LHb neurons in the chronic restraint stress-induced mice exhibiting depressive-like phenotypes. The knockdown of p11 expression in LHb ameliorated the stress-induced depressive-like phenotypes and the over-expression of p11 in LHb neurons with dopamine D2 receptor expressed of control mice led to depression-like behaviours.

Conclusion

This study highlighted that p11 in LHb was a crucial molecular determinant in regulating negative emotions, and provided some insights into the understanding of the molecular and cellular basis of depression. Another recent study also provided some evidence concerning the cellular mechanisms underlying LHb hyperactivity which potentially led to the depressive-like phenotypes. It was reported that foot-shock exposure as an aversive experience could result in LHb hyperactivity and depressive-like symptoms in mice [27]. It was found that foot-shock exposure could increase the activity of protein phosphatase 2A (PP2A), which in further persistently weakened the GABAB receptor (GABABR)-activated G protein-gated inwardly rectifying potassium (GIRK)-mediated currents. The inhibition of PP2A could restore both GABAB-GIRK function and also alleviated the depression-like behaviours. This interesting research actually supplied a new therapeutic method to ameliorate depressive-like symptoms in disorders typical of the LHb hyperactivity. Collectively, the aforementioned evidence underscores the crucial role of LHb in the pathogenesis of depression.

Great efforts on the study of the role of LHb in depression and great advances had been made in the past decades, however, far more remains to be addressed concerning the functional role of LHb in anxiety and the interactions of LHb with other brain systems related to stress. It is well known that stress exposure could lead to depression in both animal models and humans [28]. In addition, the exposure to stress could alter the synaptic plasticity through lowering the threshold for long term potentiation induction in LHb [28], which may further disturb both the local neural microcircuits and long projection properties in LHb and, in the end, subserved the depressive-like phenotypes. The LHb could relay neuronal information from limbic forebrain areas to a plethora of monoamine regions [29]. Historic research has demonstrated that LHb neurons could form synapses on dopamine neurons in the ventral tagmental area projecting to the medial prefrontal cortex (mPFC) [30]. Depending on the connections with dopamine neurons in the ventral tagmental area, LHb could form reciprocal interactions with mPFC, which has been confirmed having roles in regulating emotional and cognitive function in rodent, monkeys and humans [31-33]. In addition, LHb was also received GABAergic innervations which are probably from the ventral pallidum, ventral tegmental area and nucleus accumbens [34], however, implications for most of these functional connections so far remains largely unknown. Thus, the clarification of these functional projections between the LHb and the above mentioned brain areas will undoubtedly deepen our current understandings of the mysterious role of the LHb in the pathogenesis of depression.

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