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Lateral habenula in the pathophysiology of depression

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Depression is a devastating disorder with a combination of diverse symptoms such as low self-esteem, lack of motivation, anhedonia, loss of appetite, low energy, and discomfort without a clear cause. Depression has been suggested to be the result of maladaptive changes in specific brain circuits. Recently, the lateral habenula (LHb) has emerged as a key brain region in the pathophysiology of depression. Increasing evidence from rodent, non-human primate and human studies indicates that the aberrant activity of the LHb is associated with depressive symptoms such as helplessness, anhedonia, and excessive negative focus. Revealing the molecular, cellular and circuit properties of the LHb will help explain how abnormalities in LHb activity are linked to depressive disorders, and shed light on developing novel strategies for depression treatment.

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Introduction

The lateral habenula (LHb) is a phylogenetically well-preserved brain structure [1] and has long been recognized as a key region mediating communication between the forebrain and monoaminergic systems in the midbrain and hindbrain [2,3]. Many functions are subject to LHb regulation, including pain, behavioral flexibility, maternal behavior, circadian rhythm, sleep, addiction, anxiety, and depression [4–11]. Recently, several important findings have proposed that the LHb participates in the processing of negative-valence information [11–14]. Mounting evidence from animal and human studies also suggests that aberrant LHb activity is associated with depressive symptoms such as helplessness [15,16] and lack of pleasure (anhedonia) [17]. Circuitry-wise, the LHb acts as a relay station that interconnects the limbic forebrain with depression-related monoaminergic centers including the ventral tegmental area (VTA) and raphe [4,11,18]. In this article, we review the output regions downstream of the LHb, as well as the source of inputs into the LHb, which may mediate different negative symptoms of depression. We also summarize major findings addressing the molecular and cellular mechanisms by which the LHb neurons become aberrantly overactive and how that may lead to depression.

Activity of LHb neurons in normal and depressive conditions

The ability to predict reward and punishment and to adjust behavior accordingly is essential for animal survival [11]. The LHb is believed to play a central role in encoding negative-valence signals and promoting behavioral aversion. Recordings in macaque monkeys show that LHb neurons encode negative reward prediction error (RPE), whereby they increase firing when animals fail to receive an expected reward ('disappointed') or receive a cue predicting aversive stimuli [12,14]. Moreover, the LHb is activated by different stressors and negative emotional stimuli [19], suggesting that it may mediate behavioral responses underlying stress and aversion under normal physiological conditions. However, aberrant LHb activity may lead to detrimental consequences, such as depression, as evidenced below.

The LHb shows higher metabolic activity in various animal models of depression [20–23]. In both acute learned helplessness (aLH) and congenital learned helplessness (cLH) rats, VTA-projecting habenula neurons demonstrate enhanced synaptic activity [15]. Interestingly, such elevated LHb firing and depressive behaviors can be reversed following antidepressant treatment [15].

Because of the small size of the LHb, human functional imaging is challenging and still inadequate; however, several studies have provided evidence for habenula hyperactivity in depressed human subjects [24,25]. Tryptophan-depletion treatment, which usually deteriorates symptoms in depressive patients, increases the cerebral blood flow in the habenular region [25]. Moreover, depressive patients show abnormal phasic habenular responses elicited by cues that predict upcoming punishment [26].

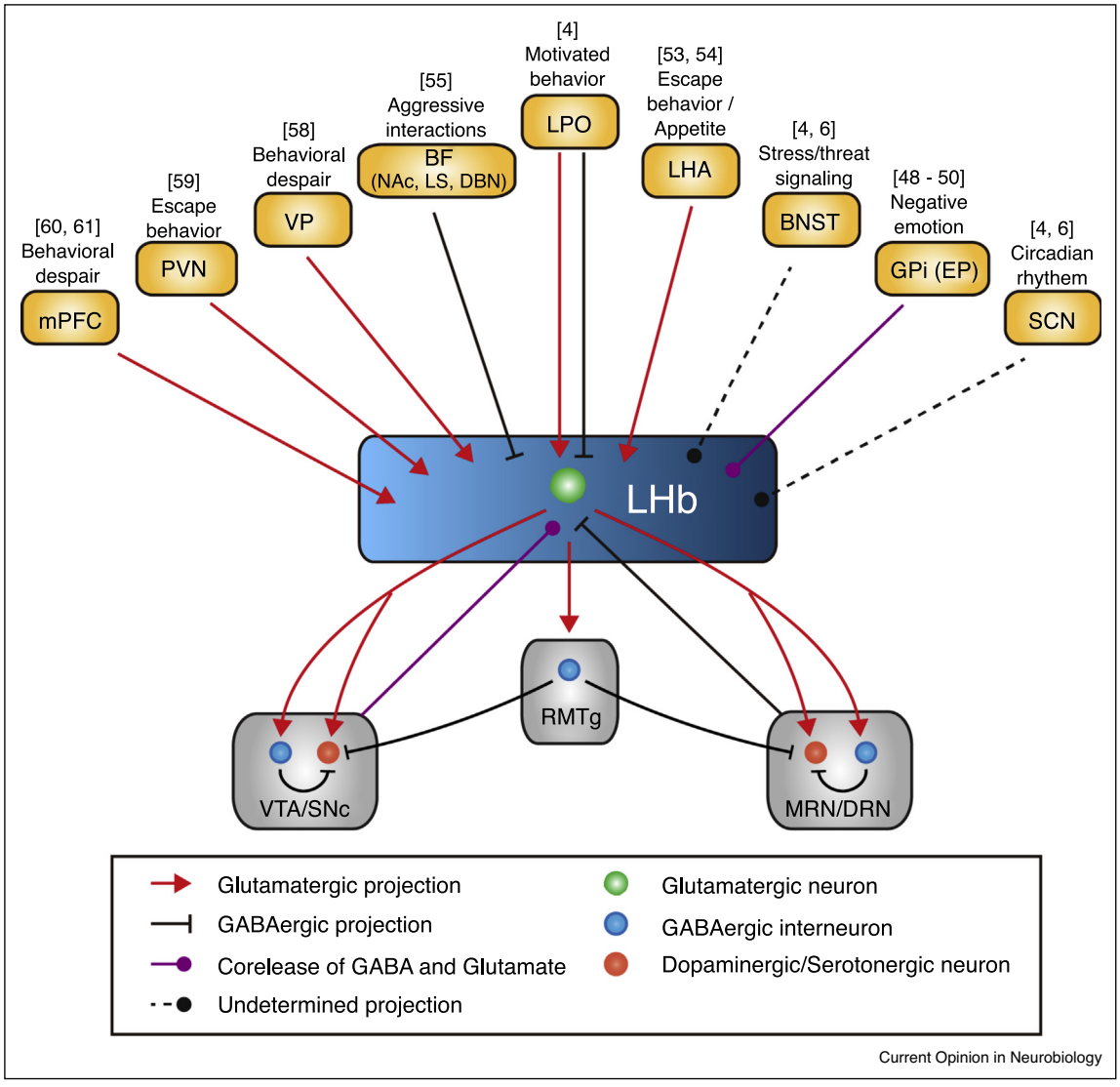
Taken together, increasing evidence from both animal and human studies suggests that LHb hyperactivity is associated with symptoms of depression.

Output regions of the LHb

The primary output regions from the lateral habenula are midbrain aminergic centers, which include the dopaminergic (DA) VTA and substantia nigra pars compacta (SNc), serotonergic (5-HT) dorsal and median raphe (DRN, MRN), and GABAergic rostromedial tegmental nucleus (RMTg, also known as tail-VTA).

The 'amine hypothesis of depression' postulates that depression results from a deficiency of the monoamine neurotransmitters [27]. Consistent with this hypothesis, the LHb is known to exert a powerful inhibitory influence over the midbrain DA and 5-HT neurons [12,13,28–32]. As the main output neurons of the LHb are glutamatergic [15,28,33,34], this inhibition over midbrain monoaminergic neurons may be achieved either through relay at the GABAergic RMTg [13,28,35] or local interneurons [36] (Figure 1). Ultrastructural analysis shows that within the VTA, LHb axons target GABAergic and dopaminergic neurons to a comparable extent (52% and 45%,

Figure 1



Summary of the input and output circuitry of the LHb. Projections to the lateral habenula (LHb), shown in brown, include the paraventricular nucleus (PVN), basal forebrain (BF, including the nucleus accumbens (NAc), lateral septum, and diagonal band nuclei (DBN)), lateral hypothalamic area (LHA), lateral preoptic area (LPO), ventral pallidum (VP), globus pallidus (GPi), medial prefrontal cortex (mPFC), suprachiasmatic nucleus (SCN), and bed nucleus of the stria terminalis (BNST). Potential functional role of each input pathway is noted. The references are indicated on the top of the figure. The main output of the LHb, shown in red, is glutamatergic. The LHb neurons preferentially form synapses on GABAergic or dopaminergic neurons in the VTA and substantia nigra pars compacta (SNc) [30,37], GABAergic or serotoninergic neurons in the dorsal raphe nucleus (DRN) and median raphe nucleus (MSN) [35,36], as well as GABAergic neurons in the rostromedial tegmental nucleus (RMTg) [38–40]. The GABAergic RMTg inhibits DA and 5HT neurons [38–40]. The VTA and DRN/MSN also send reciprocal feedback inputs into the LHb [43–47].

respectively) [37], suggesting that the robust inhibition of DA cells by the LHb is unlikely to be fully accounted for by selective innervation of VTA GABA neurons. The RMTg is a region that receives dense projections from the LHb and sends strong GABAergic projections to midbrain monoaminergic nuclei [38,39]. Axon-sparing lesions of the RMTg and recordings of DA neuron firing have shown that the robust inhibition of DA cells evoked by the LHb is mainly through the RMTg [40]. At the behavioral level, optogenetic activation of the LHb-VTA or LHb-RMTg pathway produces conditioned place avoidance [28,34].

The DRN receives a moderate direct projection from the medial part of the LHb (LHbM) and a robust projection from the RMTg [35]. The glutamatergic inputs from the LHb target both 5-HT and GABAergic neurons in the DR, which provide feedforward inhibition to 5-HT neurons [36].

Collectively, the circuit configuration downstream of the LHb suggests that during depression, hyperactivation of the LHb may suppress DA and 5-HT neurons through the GABAergic RMTg neurons and local interneurons.

Presynaptic inputs controlling LHb activity

The primary regions sending input into the LHb are the various limbic and basal ganglion structures, which include the internal segment of the globus pallidus (GPi), lateral hypothalamic area (LHA), basal forebrain, ventral pallidum (VP), paraventricular nucleus (PVN), and lateral preoptic area (LPO) [4,41] (Figure 1). These pathways contain both glutamatergic and GABAergic axons and sometimes cholinergic axons [42]. In addition, another major input comes as a reciprocal feedback from the monoaminergic centers, including the VTA [34,43–46] and raphe [47]. These various presynaptic partners of the LHb convey different components of positive or negative emotional state to regulate LHb activity and modulate normal and depressive behaviors.

The GPi, as well as its non-primate homologue, the entopeduncular nucleus (EPN), is a major output station of basal ganglia and sends a direct projection to the LHb [48••,49]. Habenula-projecting globus pallidus (GPh) neurons are important for the evaluation of action outcome, encoding whether an outcome is better or worse than expected [50]. Optical stimulation of the terminal of the EPN (GPh)→LHb pathway is aversive [49]. Although outputs from the EPN are mainly GABAergic, the efferents to the LHb co-release both GABA and glutamate [48••]. Interestingly, at the EPN-LHb synapses, the ratio of GABA/glutamate neurotransmission is reduced in animal models of depression and increased by antidepressant treatment [48••]. Thus, tipping the balance of this co-transmission at the EPN-LHb synapses may be important for regulating LHb activity and mood.

The co-transmission of GABA and glutamate also exists in the VTA-LHb projections [43,45,46]. Single axons from the mesohabenular neurons co-express vesicular GABA transporter (VGaT) and vesicular glutamate transporter 2 (VGluT2), and form both symmetric and asymmetric synapses on the same LHb neurons [43]. *In vivo* light stimulation of the mesohabenular terminals can either inhibit or excite LHb neurons, possibly dependent on the activity pattern or membrane potential of individual postsynaptic LHb neurons [43]. The LHb-targeting VTA neurons include a tyrosine hydroxylase (TH)-positive population. Although it is not clear whether this population releases dopamine or not [51•,52•], it is clear that they release GABA and suppress LHb output [44]. *In vivo* activation of this pathway prompts reward-related phenotypes dependent on intra-LHb GABA-A receptor signaling [44]. These findings reveal that neurotransmissions from the VTA to the LHb are highly heterogeneous. It will be of interest to examine whether these co-release mechanisms can be a target for the treatment of depression, as in the case of EPN-LHb synapses.

Loss of appetite is a common symptom of depression. A direct projection from the LHA to the LHb is suggested to negatively regulate food consumption [53]. Optogenetic activation of LHA-LHb glutamatergic fibers results in an increase in the firing of most LHb neurons as well as avoidance behavior, whereas optogenetic inhibition of this pathway produces a real-time place preference and an acute increase in the consumption of liquid caloric reward [53]. The same LHA-LHb circuit has also been shown to mediate foot-shock-driven escape behavior [54].

Abnormality in social behavior is another hallmark of depression. A GABAergic input from the basal forebrain (BF, including the nucleus accumbens (NAc), lateral septum, and diagonal band nuclei (DBN)) to the LHb can bidirectionally control the valence of aggressive interactions [55•]. Optical silencing the GABAergic BF-LHb terminals of aggressors leads to an increase in LHb neuronal firing and abolishes conditioned place preference (CPP) to the intruder-paired context. Conversely, activation of the terminals of non-aggressors decreases LHb neuronal firing and promotes CPP to the intruder-paired context. These results reveal a critical role of the BF-LHb circuit in modulating aggression reward during social behaviors [55•].

The VP is an important convergent region within the motivational and reward circuitry, and has been implicated in depression [56,57]. In social-defeat-stress-induced depressive mice, activity of parvalbumin (PV) neurons in the VP is significantly increased and can be reversed by antidepressant treatment [58••]. Both optogenetic and chemogenetic silencing of PV^{VP-LHb} neurons attenuates behavioral despair, whereas the same manipulation of PV^{VP-VTA} neurons rescues social

withdrawal. Therefore, distinct VP-PV neuronal projections to the LHb and VTA may contribute to different aspects of depressive-like behaviors [58••].

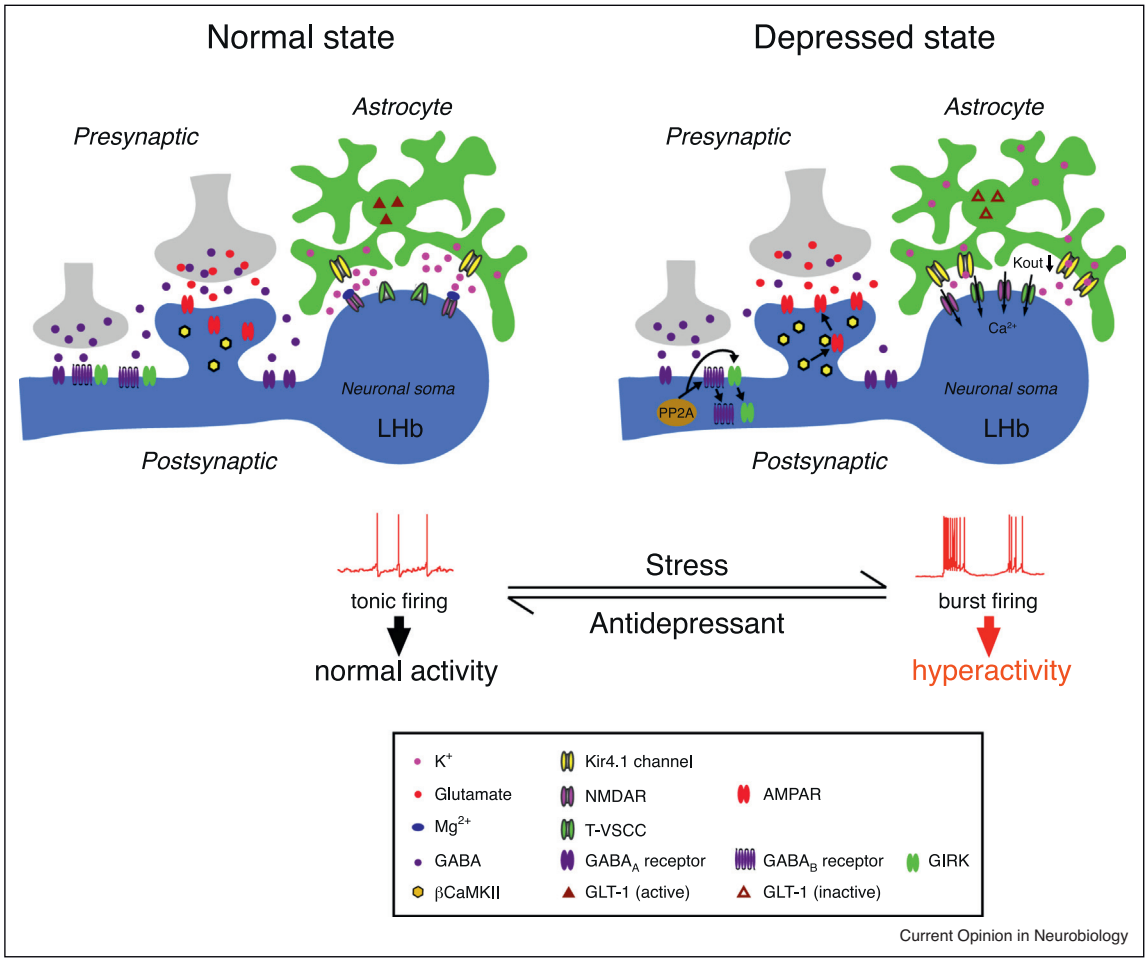
A group of vasopressin-expressing neurons in the PVN of the hypothalamus also sends glutamatergic input into the LHb, targeting the medial LHb (LHbM). Water deprivation suppresses LHb output through this pathway, leading to decreased freezing during innate fear and immobility in behavioral despair assessment [59].

Circuit tracing studies also show inputs from the medial prefrontal cortex (mPFC) [60,61], suprachiasmatic nucleus (SCN), and bed nucleus of the stria terminalis (BNST) into the LHb [4]. However, the functions of these pathways need further research.

Molecular and cellular mechanism of LHb hyperactivation during depression

In order to search for the molecular mechanism underlying habenular hyperactivity, Li *et al.* (2013) initiated an unbiased high-throughput proteomic screen and identified several proteins showing altered expression in the LHb of cLH rats [17]. Among these, the β form of calcium/calmodulin-dependent protein kinase II (β-CaMKII) is significantly upregulated in animal models of depression and downregulated by an antidepressant [17]. Increasing β-, but not α-, CaMKII in the LHb enhances the synaptic efficacy of LHb neurons, possibly by facilitating the synaptic delivery of glutamate receptor GluR1, and produces profound depressive-like behaviors. Notably, loss-of-function manipulations of β-CaMKII are antidepressant (Figure 2) [17].

Figure 2



Summary of the molecular mechanism underlying aberrant activity of LHb neurons during depression. Major molecular changes at several subcellular locations have been suggested to account for LHb hyperactivity in depression. At presynaptic sites, GABA/glutamate at the EPN-LHb synapse is shifted toward reduced GABA [48••]. At the postsynaptic sites of excitatory synapses, upregulation of βCaMKII by stress can lead to increased membrane trafficking of AMPAR and increased synaptic efficacy [17]. At the postsynaptic sites of inhibitory synapses, activation of PP2A by stress triggers internalization of GABAB1 and GIRK2, causing an increase in neuronal excitability [62••]. At the interface between neuronal soma and astrocytic endfeet, upregulation of astrocytic Kir4.1 causes enhanced K^+ buffering, decreased extracellular potassium concentration (Kout), and increased NMDAR- and T-VSCC-dependent burst firing of LHb neurons (Cui *et al.* and Hu, unpublished data). Blockade of NMDARs by ketamine stops burst firing and relieves depression (Yang *et al.* and Hu, unpublished data).

Apart from excitatory glutamatergic synapses, the inhibitory GABAergic transmission at the LHb also undergoes changes after aversive experience. Salvatore *et al.* found that foot-shock exposure upregulates the activity of protein phosphatase 2A (PP2A), which then triggers GABAB receptor (GABABR) and G protein-gated inwardly rectifying potassium (GIRK) channel internalization, leading to rapid and persistent weakening of GABAB-activated GIRK-mediated (GABAB-GIRK) currents [62••]. Accordingly, pharmacological inhibition of PP2A restores both GABAB-GIRK signaling and neuronal excitability, and ameliorates depressive-like symptoms [62••].

In addition to these postsynaptic mechanisms, presynaptic changes have also been reported, which include increased release probability of glutamatergic synapses onto LHb neurons [15] and an altered GABA/glutamate ratio at EPN-LHb synapses [48••].

At the cellular level, several synaptic plasticity mechanisms have been described in the LHb. mGluR-dependent long-term depression (LTD) at the excitatory (eLTD) and inhibitory (iLTD) synapses both exist and can bidirectionally tune LHb output [63•]. mGluR-eLTD occurs presynaptically through a cannabinoid receptor 1 (CB1R)-dependent decrease in glutamate release, whereas mGluR-iLTD occurs postsynaptically through a PKC-dependent reduction of b2-containing GABAA-R function [63•]. Effects of stress on bidirectional synaptic plasticity of long-term potentiation (LTP) and LTD at the LHb have also been reported [64,65•]. Acute stress exposure facilitates LTP by lowering the induction threshold [64], while impairing CB1R-dependent LTD [65•] in the LHb. Thus, stress disturbs the balance of LTP and LTD in the LHb neurons, leading to further potentiation of LHb activity.

The above studies have focused on aberrant synaptic plasticity and synaptic transmission of the LHb in depression etiology. Several recent studies further revealed a critical contribution of LHb neuronal firing pattern, regulated by neural-glial interactions, to depression and the rapid antidepressant effects of ketamine. When characterizing additional candidates from the proteomic screen [14], Cui *et al.*, discovered an astrocyte-specific potassium channel, Kir4.1, which is upregulated in the LHb and causes increased burst firing of LHb neurons in depressive-like animals (Cui *et al.* and Hu, unpublished data). This NMDAR-dependent bursting of LHb neurons turns out to be a potent target of ketamine (Yang *et al.* and Hu, unpublished data). Another glial protein, glial glutamate transporter GLT-1, when inhibited in the LHb, was found to increase neuronal excitability and cause depressive-like phenotypes [66].

Collectively, it is likely that neurons and glia, synaptic inputs and intrinsic membrane properties of LHb neurons interact intimately to give rise to enhanced LHb output in depression.

Conclusions and perspective

The last ten years have witnessed explosive growth in our understanding of the function of the LHb and its role in depression. According to current evidence, the hyperactivity of the LHb plays a critical role in depression etiology, and its suppression may relieve depressive symptoms. On the basis of such evidence, deep brain stimulation has already been applied to suppress neural activity of the LHb in treatment-resistant patients and has induced remission of depressive symptoms [67,68]. In the future, continuous efforts are needed to understand how the LHb becomes hyperactive in depression. Specifically, what kind of plasticity mechanisms lead to prolonged alteration of LHb neural activity in depression? How do stress and neuromodulators regulate the burst firing patterns of LHb? What molecular substrates can be targeted for selective suppression of this hyperactivity? Understanding these questions will help design effective pharmacological and interventional treatment for depression.

Conflict of interest statement

Nothing declared.

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