



The lateral Habenula: Role in Chronic Pain and Depression

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Abstract

Pain and depression are highly prevalent and debilitating disorders that seriously affect certain individuals' quality of life. Clinical observations have long recognized the co-occurrence and interaction of pain and depression, and these disorders have been estimated to coexist in up to two-thirds of cases. However, the mechanisms underlying the comorbidity of pain and depression remain uncharacterized. The habenula is a conserved structure in the posterior-medial aspect of the dorsal thalamus that plays a crucial role in modulating midbrain monoaminergic systems. This structure receives input from forebrain structures, and its efferents primarily project into the midbrain and hindbrain, reaching well-known pain-modulating regions such as the periaqueductal gray matter and raphe nuclei as well as depression-modulating regions such as the dopaminergic ventral tegmental area and serotonergic dorsal raphe nucleus. Recently, numerous studies have indicated that the lateral habenula (LHb) is an important pain-processing region where external stimuli are received, evaluated, and redirected to motivate behavioral responses to pain. Furthermore, altered activity of the LHb is associated with depressive symptoms such as behavioral despair and anhedonia. Thus, increased activity of the LHb might play a key role in pain-depression comorbidity. Here, we review the interaction between pain and depression, describe the role of the habenula in each, and present evidence that the LHb is involved in the comorbidity of pain and depression.

Keywords

Lateral Habenula; Comorbidity; Chronic pain; Depression

Introduction

Chronic pain is defined as any pain lasting more than 3 months. In addition to physical reactions, chronic pain is often accompanied by negative emotions such as depression and anxiety, which seriously affect patients' quality of life [1-4]. Depression is one of the most common psychiatric disorders and is characterized by low mood and lack of pleasure. Additionally, the symptoms of depression usually include physical symptoms such as pain, insomnia, and fatigue [5-6]. Studies have shown that 30% to 100% of patients with chronic pain have depression, and 51.8% to 59.1% of patients with

depression also report pain symptoms [7-9]. The comorbidity of pain and depression has long been recognized in the clinic, and the two conditions together are more difficult to treat than either condition alone. Antidepressants have been used to treat chronic pain since the 1960s, and analgesic treatments can alleviate the manifestation of depression in patients with pain symptoms [10,11].

Pain and depression share common neuroanatomical underpinnings, and the brain area affected by depression is also involved in the perception and processing of pain. The brain areas affected by both pain and depression include the insular cortex, medial prefrontal cortex, anterior cingulate cortex, hippocampus, habenula, amygdala, and thalamus [12-14]. The habenula is an evolutionarily ancient and centrally located nucleus that participates in a series of important biological processes [15]. The neural circuit composed of the habenula, periaqueductal gray, ventral tegmental area (VTA), and dorsal raphe nucleus (DRN) regulates norepinephrine (NE), serotonin (5-HT), dopamine (DA), and other neurotransmitter systems that are closely related to pain and depression [16-18]. Recent studies have suggested that the activation of the habenula and the subsequent changes in neurotransmitter activity caused by chronic pain are an important explanation for the promotion of depression-like behavior, and the activation of the habenula might also be a key factor causing pain sensitivity under conditions of depression [19,20]. As a core brain region that transmits information from the forebrain limbic system to the midbrain monoaminergic and dopaminergic neurons, the habenula might be an important region in the pathogenesis of pain-depression comorbidity and might also serve as a therapeutic target. Thus, this article summarizes the structural and functional changes in the habenula in chronic pain and depression, both individually and together, and explores the mechanism of habenular involvement in pain-depression comorbidity.

Comorbidity of Chronic Pain and Depression

Pain and depression are two highly prevalent disorders with significant socioeconomic impact. Studies have shown that the prevalence of chronic pain in adults is approximately 10%-30% [21-23], and depression is one of the most common mental disorders in the world, with a morbidity rate of approximately 17% [24]. Patients with chronic pain often develop depression-like behaviors such as decreased personal coping ability, reduced interest, and insomnia. All types of depression, especially major depressive disorder (MDD), are often accompanied by unexplained pain symptoms [6]. Clinical studies have shown a significant correlation between the degree of pain and the severity of depression. People with depression have higher pain scores than those without depression, and an increase in the degree of pain increases the negative emotions and behaviors of these patients [25,26]. A cross-sectional survey showed that nearly half of patients with MDD had at least one chronic pain symptom, and this rate was four times higher than the rate in the normal population [27]. A retrospective analysis showed that the average prevalence of pain symptoms in patients with depressive disorder was 65% [28]. A total of 77% of American outpatients with depression meet the criteria for pain diagnosis [29]. Previous studies showed that approximately 34% of patients with neuropathic pain suffer from depression [30], and approximately 22-26% of patients with fibromyalgia show depressive symptoms [31]. Gormsen et al. found that, compared with a healthy control group, patients with fibromyalgia and neuropathic pain had significantly increased depression and anxiety scores [32]. Additionally, recent studies have shown that patients with higher postoperative persistent pain scores have higher anxiety and depression scores [33].

The comorbidity of pain and depression is also well reflected in animal models. Animal models of pain can induce depression-like behavior, which is characterized by prolonged immobility time during forced swimming and reduced sucrose preference. Suzuki et al. [34] found that mice subjected to spinal nerve ligation showed mechanical allodynia 2 days after surgery and increased immobility time on the forced swimming test 15 days after surgery. Depression-like behavior occurred 2 to 4 weeks after chronic constriction injury (CCI) of the sciatic nerve in rats [35,36]. Increased immobility time in the FST occurred 5 weeks after spared nerve injury in rats [37,38]. Kim et al. found that the mechanical and thermal pain thresholds of rats were significantly decreased 2 weeks after a complete Freund's adjuvant (CFA) injection, and this change was accompanied by a significant increase in immobility time [39]. Borges et al. found that rats showed significant depression-like behaviors 28 days after CFA injection [40]. Previous stud-

ies found that animal models of both acute and chronic depression showed hyperalgesia and allodynia [41-44]. In another study, an acute depression rat model subjected to forced swimming showed increased hyperalgesia compared to the control group on the formalin test [41]. Suarez-Roca et al. showed that continuous forced swimming can lead to a reduction in the thermal pain threshold [42]. In an animal model of chronic depression caused by social defeat stress, both the chemical and mechanical pain thresholds were significantly reduced [43,44].

Previous studies have suggested that multiple brain regions (the cortex, hippocampus, amygdala, thalamus, VTA, DRN, etc.) and multiple molecular mechanisms (neuroendocrine dysfunction, hypofunction of monoaminergic systems, decreased neuronal regeneration, increased neuroinflammatory response and synaptic transmission dysfunction) are involved in the occurrence of pain-depression comorbidity [45-48]; however, the mechanism of this comorbidity has not been clearly elucidated.

The Habenula and its Afferent and Efferent Connections

The habenula (Hb) is a small bilateral structure located on the dorsal side of the diencephalon and on both sides of the third ventricle. This structure is divided into medial (MHb) and lateral (LHb) components, which differ in their neurochemical characteristics and connectivity. The habenula is an important hub that connects the limbic forebrain and midbrain, and it participates in the regulation of various physiological activities, including pain, depression, sleep, rhythm, learning, cognition, and reward [49-53]. The Hb is evolutionarily conserved from lower animals to higher animals, including humans, which indicates the importance of its role. Previous studies have shown that Hb is involved in a number of behavioral functions, including reward, emotional regulation, pain, reproduction, nutrition, sleep, stress, and cognition [54,55]. However, studies into the function of the MHb are limited. In recent years, the LHb has attracted great attention due to its important role in the pathogenesis of depression and pain.

The LHb receives and integrates inputs from the forebrain limbic system, including the prefrontal cortex, septum, globus pallidus (GP), bed nucleus of the stria terminalis (BNST), lateral preoptic area (LPO), diagonal band of Broca's area (DBB), lateral hypothalamus (LH), and basilar nucleus. The LHb sends projections to the serotonergic DRN and median raphe nucleus (MRN), the dopaminergic VTA and substantia nigra pars compacta (SNc), the GABAergic rostromedial tegmental nucleus (RMTg), and the periaqueductal gray (PAG) [49-53]. Neurons of the LHb also project to DA neurons of the VTA and SNc and 5-HT neurons of the DRN through the RMTg, resulting in an indirect inhibitory effect on

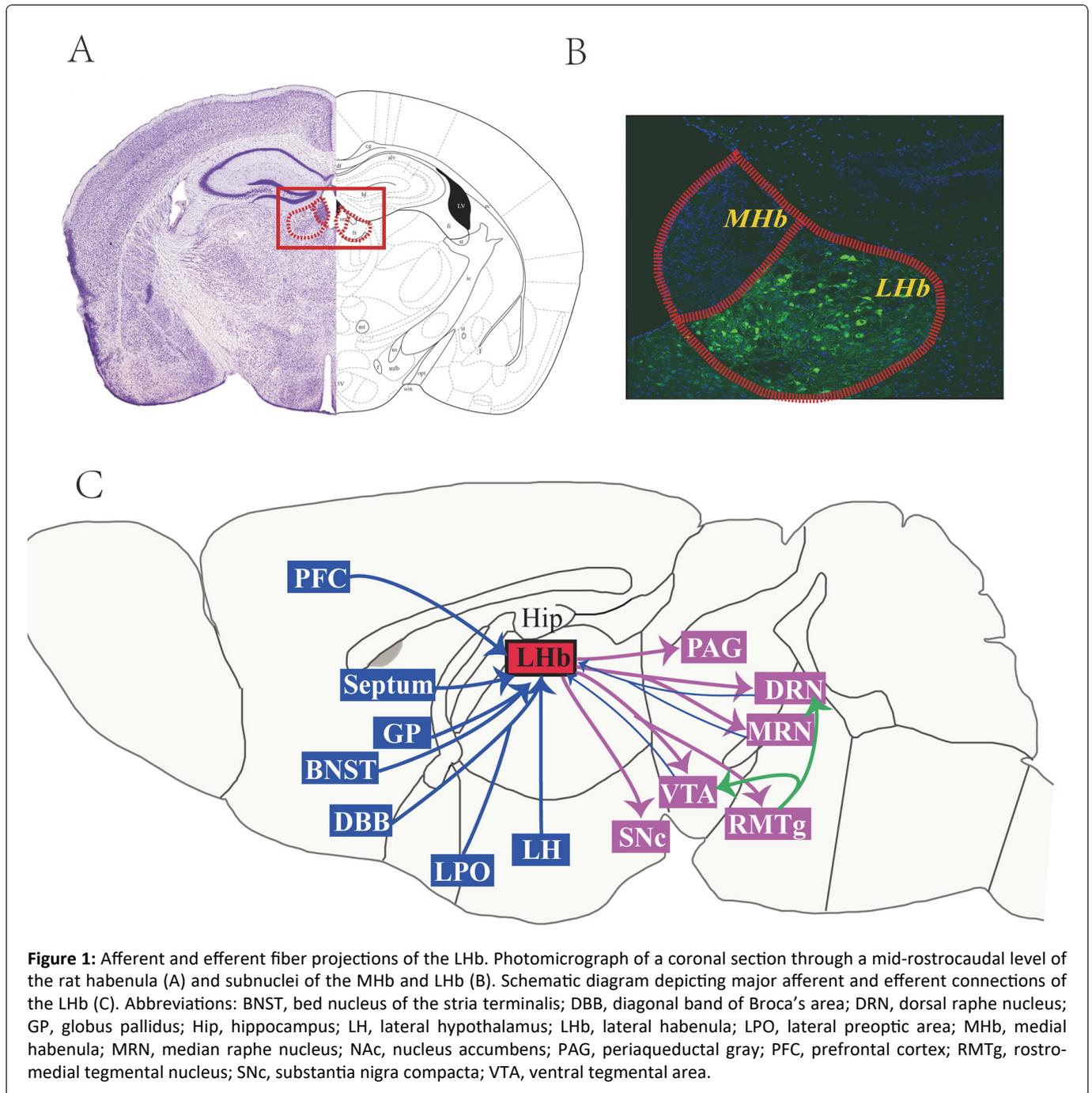


Figure 1: Afferent and efferent fiber projections of the LHB. Photomicrograph of a coronal section through a mid-rostrocaudal level of the rat habenula (A) and subnuclei of the MHB and LHB (B). Schematic diagram depicting major afferent and efferent connections of the LHB (C). Abbreviations: BNST, bed nucleus of the stria terminalis; DBB, diagonal band of Broca's area; DRN, dorsal raphe nucleus; GP, globus pallidus; Hip, hippocampus; LH, lateral hypothalamus; LHB, lateral habenula; LPO, lateral preoptic area; MHB, medial habenula; MRN, median raphe nucleus; NAc, nucleus accumbens; PAG, periaqueductal gray; PFC, prefrontal cortex; RMTg, rostro-medial tegmental nucleus; SNc, substantia nigra compacta; VTA, ventral tegmental area.

midbrain DA and 5-HT cell activity [56,57]. Some of the dopaminergic neurons in the VTA and some of the serotonergic neurons in the DRN also project back to the LHB, forming a feedback loop. Figure 1 illustrates the afferent and efferent fiber projections of the LHB.

The Role of the Habenula in Pain

Shelton et al. conducted MRI studies of healthy volunteers and found that noxious thermal stimulation significantly enhanced habenula activity [58]. Studies based on resting-state fMRI suggest that the association between the habenula and the forebrain is significantly abnormal in children with complex regional pain syndrome. Basic research using animal models of chronic pain has shown a marked increase in blood flow to the

habenula of rats [59,60]. Injecting morphine into the rat habenula relieves the acute inflammatory pain and trigeminal neuralgia caused by formalin [61-63]. Electrical stimulation of the habenula can be used to effectively treat the acute inflammatory pain caused by formalin [64]. After nociceptive stimulation, the expression of c-fos protein in the habenula increased significantly, which suggests that pain activates habenular neurons [19,65]. A previous result showed that the activity of the habenula was significantly enhanced after spinal cord injury using the ^{99m}Tc -hexamethylpropyleneamine oxime (^{99m}Tc -HMPAO) method to label neurons [66].

The habenula accepts both direct and indirect forms of ascending pain-transmitting fiber projection: direct transmission from lamina I of the spinal dorsal horn

and the trigeminal nucleus and indirect transmission through the afferent fibers of the LH to the habenula. The habenula participates in the downward modulation of pain by regulating the functions of the PAG and DRN. The PAG is an important structure in the endogenous pain modulation system. Ma et al. showed that the habenular injection of naloxone blocked the analgesic effect of a PAG injection of morphine [67]. The DRN can participate in pain regulation by modulating the 5-HT system. A previous study has shown that the activation of the DRN region produces analgesic effects [68]. Hyperactivation of the Lhb may inhibit the 5-HT neurons of the DRN through γ -aminobutyric acid (GABA) neurons in the RMTg to participate in pain.

The Role of the Habenular in Depression

The activation of the habenula is significantly increased in patients with depression and in various animal models of depression. Morris et al. [69] conducted PET imaging studies of patients with depression and found that when these patients developed depression symptoms, their habenula activity increased significantly. After deep brain stimulation (DBS) of the habenula to reduce the activity of the habenular neurons in clinical practice, the symptoms of some patients with treatment-resistant depression were greatly alleviated [70]. Caldecott-Hazard et al. [71] used ¹⁴C-labeled deoxyglucose to indicate the metabolic rates of different brain regions and found that the metabolism of the Lhb was significantly increased in several animal models of depression. Shumake and Gonzalez-Lima [72] found that the cytochrome oxidase activity of the Lhb was significantly upregulated in depressive animals. In 2013, Hu's research group found that the upregulation of β CaMKII in the Lhb of animals with learned helplessness promotes the excessive excitability of the habenula by increasing the membrane GluR1, thereby enhancing the inhibition of the VTA and the DRN, which leads to the core symptoms of depression (e.g., anhedonia and behavioral despair) [18]. In that study, antidepressant therapy downregulated β CaMKII and improved depressive symptoms [18]. In 2018, this research group published two papers in the same issue of *Nature*. They found that under external stress stimulation, the expression of the Kir4.1 ion channel of a glial cell in the Lhb was upregulated, decreasing the extracellular potassium ion concentration of neurons, promoting the conversion of neurons from a single to a clustered discharge pattern, and resulting in the excessive inhibition of downstream reward centers (including the VTA and DRN), thereby leading to depression [73,74]. The new antidepressant ketamine was able to exert a rapid antidepressant effect by blocking the bursting discharge of the Lhb [73,74]. Li et al. [75] found that the state of learned helplessness enhances the discharge of Lhb neurons in rats, and DBS selectively depletes glutamate from the Lhb

neurons projecting to the VTA dopaminergic neurons, significantly reducing learned helplessness. Injection of the GABAA receptor agonist muscimol in the Lhb also ameliorates depression-like behavior in rats [76], and inhibiting the excitatory pathways of Lhb neurons can be used to treat depression.

The habenula may participate in the pathological process of depression by enhancing the inhibition of DRN neurons and reducing 5-HT release. The basal level of 5-HT release by the raphe nucleus is low in depressed rats, and the metabolism and conversion rate of 5-HT can be improved by lesioning the Lhb to alleviate depressive symptoms [77]. The above evidence indicates that the activity of the habenula is significantly increased in both patients with depression and animal models of depression; conversely, the inhibition of habenula activity can alleviate depressive symptoms.

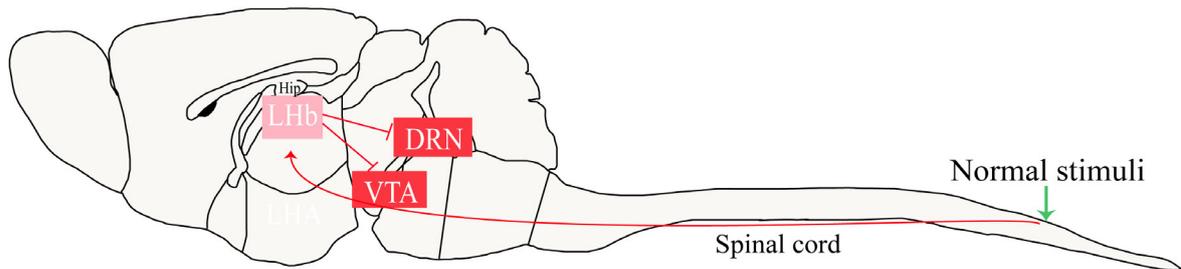
The Role of the Habenula in Pain-Depression Comorbidity

Recent studies have found that the discharge activity of the habenula is increased, along with the number of c-fos-positive cells in that region, in rat models (i.e., inflammatory pain + chronic unpredictable mild stress) of pain and depression comorbidity. Moreover, habenular damage can reduce pain-depression comorbidity [19]. In the CCI rat model, depressive symptoms occurred 28 days after hyperalgesia and were accompanied by an increase in habenular activity and a decrease in the 5-HT level in the DRN. Moreover, habenular damage may simultaneously improve the pain and depression caused by CCI [20]. Recently, Zhang's research group confirmed that SOM^{CeA} neurons mainly innervate Glu^{Lhb} neurons through glutamatergic projections using a viral tracing method, and their findings indicated that in mice with chronic pain and depressive-like symptoms, Glu^{Lhb} neuronal activity is stimulated by increased SOM^{CeA} glutamatergic inputs [78].

According to the pain-induced depression model, although hyperalgesia developed rapidly after tissue injury, depression-like manifestations usually appeared more slowly, following pain by 3 to 5 weeks [79]. It is unclear why depression takes this long to develop after hyperalgesia; however, the time-dependent relationship between hyperalgesia and depression is important for understanding the neuropathological mechanisms through which chronic pain causes depression.

Does a time-dependent change occur in the habenula and its downstream projection targets after tissue injury to mediate the time difference between the aforementioned symptoms? Studies of persistent noxious stimulation have shown that the Lhb initially acts as a relay station for nociceptive transmission and modulation; when this region receives nociceptive information from the spinal cord, voltage-dependent calcium

A Normal state



B Comorbidity of pain and depression

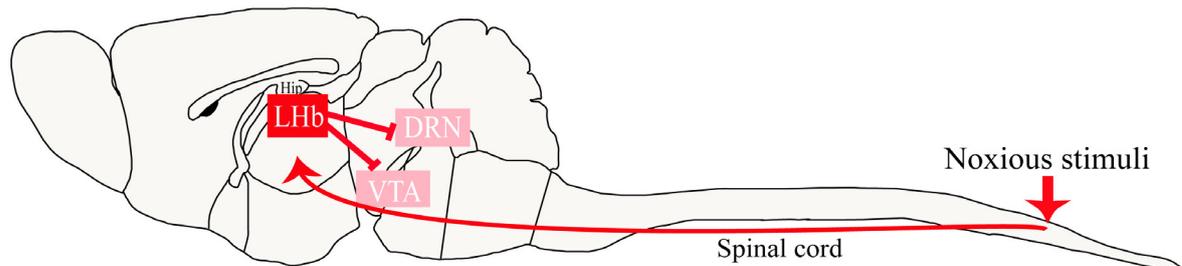


Figure 2: The role of the habenula in pain-induced depression. Under normal circumstances, the LHb provides a low level of inhibition to the VTA and DRN (A). In a state of pain-induced depression, noxious stimulation continues to activate the habenula, resulting in a significant increase in the excitability of the LHb neurons (B). The high excitability of the LHb enhances the inhibition of the VTA and DRN, leading to manifestations of depression such as anhedonia and behavioral despair.

channels open, increasing the intracellular calcium ion concentration [2,19]. Calcium ions act as a second messenger to promote the synthesis and release of many neuropeptides closely related to pain. Under the condition of acute pain, activity increases in the habenula and all associated circuits, which is a homeostatic response to a reversible physiological stimulus. Under the condition of chronic pain, the continuously activated spinal cord-habenula connection disrupts the related nerve projections and the homeostasis of the circuits. Eventually, the neural circuits associated with the reward responses of the VTA and DRN are suppressed, leading to a decrease in the release of 5-HT and DA, which causes depressive symptoms to appear [2]. Figure 2 illustrates the role of the habenula in pain-induced depression. Likewise, the activity of the habenula is increased in depression, and it modulates pain by regulating the functions of the PAG and DRN, leading to hyperalgesia.

The expression of the β CaMKII is significantly up-regulated in the LHb of animal in depressed state and β CaMKII overexpression in the LHb can increase miniature excitatory postsynaptic currents in the LHb and induce depression-like behaviors in rats [18]. Li et al. demonstrates that β CaMKII expression in the LHb is increased in pain-associated depression rats model [20]. These results suggest that β CaMKII may be an important molecule involved pain-depression comorbidity. Some studies also indicates that the dopamine receptors, melatonin receptors, and p11 are strongly linked

to LHb hyperactivation and maybe associated with pain-depression comorbidity [80-82].

Conclusions

Previous researches on chronic pain have primarily focused on the upstream nociceptive transmission pathways (e.g., the dorsal root ganglia and tractus spinothalamicus) and the downstream nociceptive regulation systems of spinal dorsal horn, the medulla oblongata, and midbrain. However, chronic pain is often accompanied by negative emotions such as depression; thus, the study of emotion-related brain regions has received increasing research attention in relation to the pain-depression comorbidity. Previous studies have suggested that the cortex, hippocampus, amygdala, thalamus, VTA, and DRN are involved in the pathogenesis of pain and depression. As an important relay station linking the forebrain and midbrain, the LHb receives projections from many brain regions involved in the pain-related stimuli, and sends outputs to well-known depression-modulating regions such as the dopaminergic VTA and serotonergic DRN. The important anatomical location of the habenula and its regulation of various neurotransmitter systems suggest that it is closely related to pain-depression comorbidity. LHb neurons are activated under conditions of both pain and depression, and these conditions can be relieved after inhibiting or destroying the habenula. The complex changes of LHb neural circuits may involve in pain-depression comorbidity. However, the cellular and molecular mechanisms

linking the habenula to pain-depression comorbidity remain unclear, and researches in this area remain in the initial stage, calling for further exploration. Researches on the changes in the habenula for pain-depression comorbidity might provide new ideas with regard to the mechanisms as well as scientific treatment guidance for this comorbidity in clinical practice.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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