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Review

The role of lateral habenula–dorsal raphe nucleus circuits in higher brain functions and psychiatric illness

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HIGHLIGHTS

- Lateral habenula (LHb) and dorsal raphe nucleus have close anatomical connections.
- LHb-raphe circuits influence cognition, reward, pain, sleep and circadian rhythms.
- Abnormal LHb-raphe activity may disrupt these functions in psychiatric disorders.
- Increased LHb activity may contribute especially to the symptoms of depression.

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ABSTRACT

Serotonergic neurons in the dorsal raphe nucleus (DRN) play an important role in regulation of many physiological functions. The lateral nucleus of the habenular complex (LHb) is closely connected to the DRN both morphologically and functionally. The LHb is a key regulator of the activity of DRN serotonergic neurons, and it also receives reciprocal input from the DRN. The LHb is also a major way-station that receives limbic system input via the stria medullaris and provides output to the DRN and thereby indirectly connects a number of other brain regions to the DRN. The complex interactions of the LHb and DRN contribute to the regulation of numerous important behavioral and physiological mechanisms, including those regulating cognition, reward, pain sensitivity and patterns of sleep and waking. Disruption of these functions is characteristic of major psychiatric illnesses, so there has been a great deal of interest in how disturbed LHb–DRN interactions may contribute to the symptoms of these illnesses. This review summarizes recent research related to the roles of the LHb–DRN system in regulation of higher brain functions and the possible role of disturbed LHb–DRN function in the pathogenesis of psychiatric disorders, especially depression.

Contents

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1. Introduction

The habenula (Hb) is an evolutionarily conserved part of the epithalamus that is common to all vertebrate brains. The Hb is a complex structure, one division of which, the lateral habenula (LHb), has attracted a great deal of interest with respect to its important roles in regulation of behavior and its potential role in the pathogenesis of psychiatric disorders. Recent studies have demonstrated a role for the LHb in influencing a number of behaviorally important functions, including reward, emotional regulation, pain, stress, sleep and cognition [1].

Many of the functions attributed to the LHb relate to its several roles in regulating the activity of monoamine neurotransmitter systems [2]. Monoaminergic transmission has been implicated in both normal behavioral functions and in the genesis and treatment of psychiatric disorders, including depression. In particular, the LHb plays a key role in the regulation of serotonin (5-HT) neurotransmission, which is a frequent target for pharmacological treatments of depression [3]. The role of the LHb in the regulation of reward, sleep, cognition and pain may be related in large part to its influence via the dorsal raphe nucleus (DRN) on 5-HT neurotransmission. Because 5-HT activity is also linked to depression, and disruption of these behavioral functions is common in this condition, this review will discuss the possible contributions of the LHb to these symptoms and the potential for developing treatments based on its role.

2. Functional anatomy of the lateral habenula–dorsal raphe nucleus circuit

The habenular complex is a midline structure located on the dorsomedial surface of the caudal thalamus, adjacent to the third ventricle. In mammals, the habenular complex consists of two highly differentiated nuclei, the medial habenula (MHb) and the lateral habenula (LHb). Based on anatomical and immunocytochemical features, the MHb can be further subdivided into 5 sub-nuclei and the LHb into 10 sub-nuclei [4]. Although the MHb and LHb share some sources of afferent inputs and efferent targets, they are very distinct in terms of their anatomy, afferent and efferent connections and physiological functions [5–7].

Compared with the MHb, the LHb shows broader and less evolutionarily conserved connectivity. The LHb receives input via the stria medullaris from nuclei in the basal ganglia and limbic forebrain, including the entopeduncular nucleus (EP, the rodent homolog of the internal portion of the primate globus pallidus), the lateral hypothalamus, the lateral preoptic area, suprachiasmatic nucleus, the nucleus accumbens, septum and medial frontal cortex [8–14]. One functional illustration of the convergent nature of this connectivity is the finding that electrical stimulation of either the lateral preoptic area or the EP suppressed firing rates of a large proportion of LHb neurons, most of which responded to both inputs [11].

The LHb thus receives and integrates inputs from a number of limbic forebrain and motor systems involved in motivation and behavioral organization, and transmits information to many brainstem nuclei. The midbrain dorsal raphe nucleus (DRN), which synthesizes and releases 5-HT, is one of the most prominent targets of LHb efferents [15], and the two structures have close anatomical and functional connections [6,16]. Injections of the retrograde neuronal tracer horseradish peroxidase (HRP) in the DRN, for example, labeled more somata in the LHb than in any other brain region projecting to the DRN [17].

Projection neurons from the LHb are characterized by the presence of the excitatory neurotransmitter glutamate [18,19]. Functional anatomical studies using a combination of retrograde wheat germ agglutinin and D-[^{3}H]aspartate tracing confirmed that LHb afferents to the DRN use an excitatory amino acid [20]. Consistent with this conclusion is evidence that glutamate uptake in the DRN was reduced after ablation of the LHb [21]. The functional impact of activation of the LHb projection to the DRN and other structures is, nevertheless, strongly inhibitory. Electrical stimulation of the LHb inhibited firing rates of 5-HT neurons in DRN and thereby decreased release of 5-HT [22–24]. Consistent with this inhibitory role, ablation of the LHb increased levels of 5-HT in the DRN [25].

The inhibitory effect of LHb inputs on DRN neurons is likely mediated indirectly by activation of inhibitory interneurons in the DRN that release γ-aminobutyric acid (GABA) [26]. Consistent with this hypothesis, there is anatomical evidence for GABAergic innervation of 5-HT neurons in the DRN [27,28]. Electrophysiological studies also demonstrated that application of a GABA receptor antagonist to the DRN decreased the inhibition of 5-HT neurons elicited by electrical stimulation of the LHb [16,26].

GABAergic interneurons also mediate the inhibitory effects of glutamatergic projections from the LHb on ventral tegmental area (VTA) dopaminergic neurons [18]. These interneurons may not, however, be in the VTA itself. There is evidence that another target of projections from the LHb, the rostromedial tegmental nucleus (RMTg) may mediate its effects on the VTA. Several lines of evidence demonstrate that the LHb acts by activating GABAergic neurons in the RMTg, which project to and inhibit VTA dopaminergic neurons [29], suggesting that it could play a similar role in mediating LHb effects on the DRN.

Injection of the retrograde tracer choleratoxin B subunit (CTb) into the RMTg labeled somata in the LHb, and similar injections into the DRN also labeled RMTg neurons, indicating a potential indirect route for the LHb to influence DRN neurons. Injecting the anterograde tracer Phaseolus vulgaris lectin (PHA-L) into the RMTg also labeled projections reaching the DRN, further confirming this projection. Double-labeling with GAD67, a marker of GABAergic neurons, confirmed that the projections from the RMTg to the DRN are GABAergic [30]. Other findings also support the hypothesis that there is a robust disynaptic projection linking the LHb to the DRN via the RMTg [31,32], which may play an important role in mediating inhibitory effects of the LHb on the DRN.

Substance P (SP) is found in some Hb neurons projecting to the DRN, as demonstrated by the fact that lesion damage to the Hb reduces SP levels in the DRN [33]. There is, however, conflicting evidence as to the origin of this projection. Studies using different methods have concluded either that the SP projection to the raphe originates in the MHb [19,34], or that it originates in the LHb [35]. It is clear that the LHb shows SP immunoreactivity, but some studies attribute this finding to the presence of SP terminals from a projection originating in the MHb [34]. These conflicting conclusions might be attributable to limitations of the different methods used, particularly lesion-based approaches. It is beyond the scope of this review to discuss these methodological issues in detail.

Regardless of whether one or both Hb nuclei contribute to SP projections to the DRN, these have a major impact on DRN function. SP receptors are found on GABAergic and glutamatergic neurons in the DRN [36–38]. Treatment with SP antagonists increases the firing rates of serotonergic neurons in the DRN [39,40], and stimulation of the Hb inhibits DRN neuronal firing [16]. Since SP is thought to be generally excitatory, the inhibitory effect of the SP projection from the Hb is likely mediated by inhibitory interneurons in the DRN. This mechanism is similar to that proposed to account for the inhibitory effect of activating glutamatergic projections from LHb to the DRN and for the net inhibitory effects of SP release on other target regions [33].

DRN 5-HT neurons project widely to many regions of the brain. Injection of the anterograde tracer PHA-L into the DRN generated labeling in the periaqueductal gray (PAG), the VTA, the substantia