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Primer

The habenula

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The habenula is a tiny brain region the size of a pea in humans. This region is highly conserved across vertebrates and has been traditionally overlooked by neuroscientists. The name habenula is derived from the Latin word *habena*, meaning "little rein", because of its elongated shape. Originally its function was thought to be related to the regulation of the nearby pineal gland (which Rene Descartes described as the "principal seat of the soul"). More recent evidence, however, demonstrates that the habenula acts as a critical neuroanatomical hub that connects and regulates brain regions important for divergent motivational states and cognition. In this Primer, we will discuss the recent and converging evidence that points to the habenula as a key brain region for motivation and decision-making.

The habenula as an anatomical hub

The habenula is part of the epithalamus, along with the pineal gland. It is surrounded by the thalamus and is located very close to the midline (Figure 1), bordering on the third ventricle. It is split into two main subregions in mammals: the medial and lateral habenula. These two subregions display distinct gene expression profiles and anatomical connectivity and, hence, are thought to subserve different functions. In lower vertebrates, the habenula is often split into dorsal habenula and ventral habenula, homologous respectively to mammalian medial and lateral habenula. In all vertebrates, the habenula is highly elongated along the rostrocaudal axis, the feature for which it is named. Its main input pathway is the stria medullaris, whereas its main output pathway is the fasciculus retroflexus.

The gene expression profiles in medial and lateral habenula are distinct. The lateral habenula neurons are almost entirely glutamatergic, as ascertained by the widespread expression of *VGLUT2*, which encodes a vesicular glutamate transporter. In contrast, while medial habenula also consists mainly of glutamatergic neurons, ventral medial habenula neurons tend to co-release acetylcholine and dorsal medial habenula neurons co-release the neuropeptide substance P. A fuller list of genes expressed in these subregions can be found in Figure 2.

The two subregions are also quite different in their neuroanatomical connectivity with the rest of the brain. Medial habenula primarily receives inputs from the medial and lateral septal nuclei. Its output is almost entirely to the interpeduncular nucleus of the midbrain. On the other hand, the lateral habenula is uniquely positioned as a hub connecting various structures, including septum, hypothalamus, basal forebrain, globus pallidus and prefrontal cortex, with the dopaminergic, serotonergic and noradrenergic systems (Figure 2).

In the rest of the primer, we will give an overview of the various behavioral functions attributed to the habenula. Because of the numerous differences between medial and lateral habenula, we will discuss their individual roles in controlling behavior separately.

Reward processing in the lateral habenula

As mentioned above, the lateral habenula regulates brain monoaminergic systems to modulate motivated behavior, affective states, cognition, and social behavior. Early studies of its function focused on the effects of lesions. More recently, it has been studied carefully using *in vivo* electrophysiology during behavior in rhesus monkeys (Figure 3A). The wealth of evidence from monkeys has been bolstered over the last few years by optogenetic studies in rodents and genetic studies in fish (Figure 3B,C).

Lateral habenula signals negative reward prediction errors

Animals strive to generate appropriate actions to sensory cues in order to maximize reward and minimize punishment. One of the major targets of the lateral habenula — the midbrain dopaminergic neurons in ventral tegmental area and substantia nigra pars compacta — are key regulators of such action selection and evaluation. In order to evaluate possible actions to a sensory cue, animals must create representations of the predicted value of performing those actions. Ventral tegmental area dopaminergic neurons play a major role in action evaluation by signaling

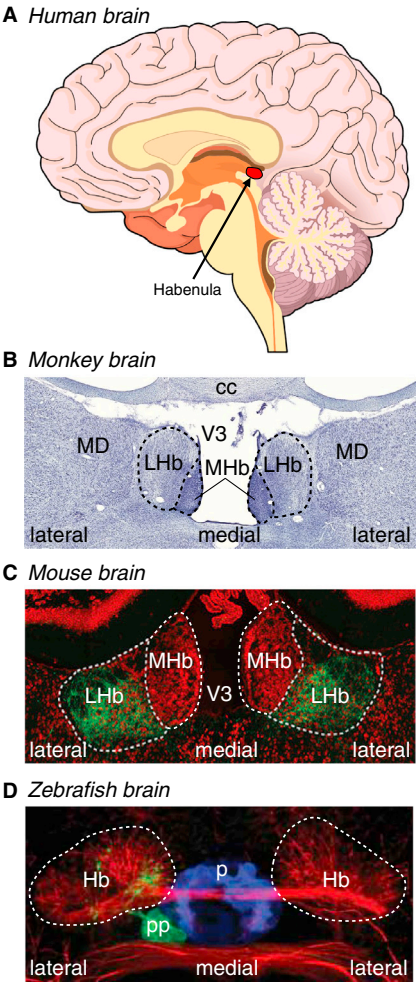

Figure 1. Location of the habenula.
(A) Human brain, sagittal view, indicating the location of the habenula. (B) Rhesus macaque brain, coronal view: Nissl stained sections show the division between lateral habenula (LHb) and medial habenula (MHb) below the corpus callosum (cc) and next to the medi-odorsal thalamus (MD). V3, third ventricle. (The NIH Blueprint Non-Human Primate Atlas, NIH Contract HHSN-271-2008-00047-C to the Allen Institute for Brain Science, Seattle, WA.) (C) C57 mouse brain, coronal view: section showing ventral tegmental area terminals (green) in the lateral habenula, not medial habenula (red). (Adapted from Stamatakis *et al*., 2013.) (D) Zebrafish brain, coronal view: section showing the habenula (Hb, red), pineal (p, blue), and the asymmetric projection from the parapineal (pp, green). (Adapted from Bianco *et al*., 2008.)

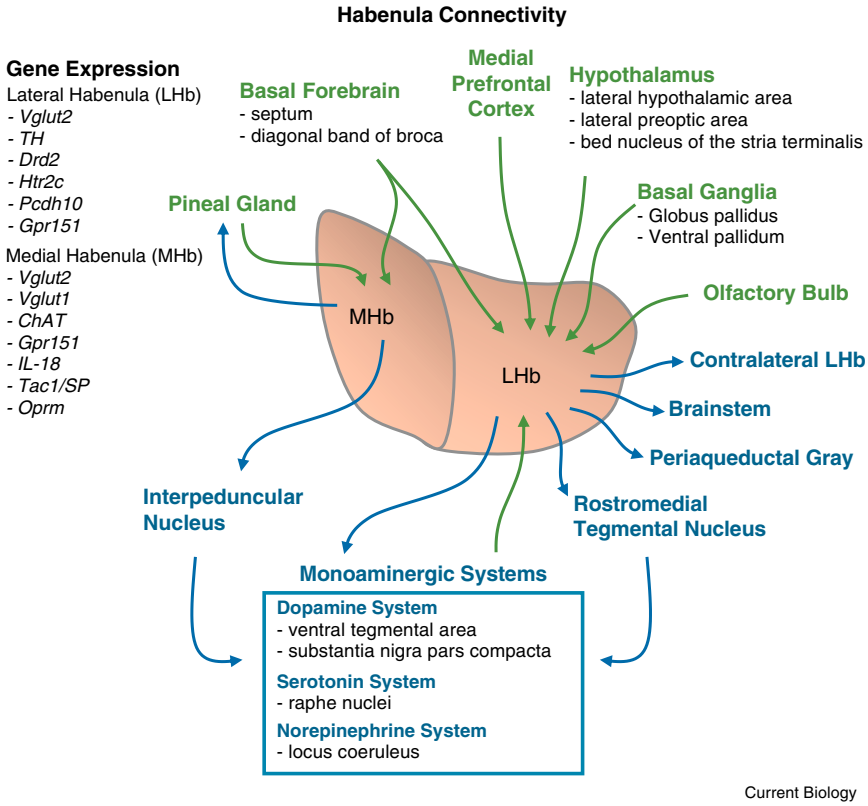

Figure 2. Anatomical organization of the habenula.
Inputs (green) and outputs (blue) to and from the lateral habenula (LHb) and medial habenula (MHb) subnuclei. Left inset: gene expression in medial and lateral habenula (as shown in Aizawa *et al*., 2012).

the discrepancy between the received outcome and the predicted outcome. This variable is known as the reward prediction error; the more positive the reward prediction error, the higher the actual outcome is compared to the predicted outcome, thereby increasing the 'value' representation of the action. In contrast, a negative reward prediction error indicates a lower outcome compared to expectation, thereby reducing the 'value' of performing that action in the future.

In vivo electrophysiological recordings of lateral habenula neurons in monkeys exhibit negative reward prediction error signals (Figure 3A). In other words, the more positive the reward prediction error, the lower the activity in lateral habenula, and the more negative the reward prediction error, the higher the activity in lateral habenula. In contrast, the pattern of activity of dopaminergic neurons within the ventral tegmental area/substantia nigra pars compacta is in the opposite direction, where high activity occurs with a positive reward prediction error and low activity occurs with a negative reward prediction error. Furthermore, electrical activation of lateral habenula neurons inhibits dopaminergic neurons.

Thus, the lateral habenula provides an important input source for reward prediction error encoding by midbrain dopaminergic neurons. These findings, made almost a decade ago, provided a conceptual framework for studying the role of lateral habenula and, hence, reinvigorated the research of lateral habenula circuitry and behavior.

Lateral habenula conveys reward prediction error and value signals to the monoaminergic systems

The lateral habenula inhibits dopaminergic activity in the midbrain via its projections to rostromedial tegmental nucleus and GABAergic cells of the ventral tegmental area. In addition, the lateral habenula also sends direct glutamatergic projections to some midbrain dopaminergic neurons. Thus, neural activity in lateral habenula could potentially have complex effects on the activity of dopaminergic neurons. One possible reason for such architecture can be hypothesized based on the response of lateral habenula neurons following punishment. Lateral habenula neurons are excited by the receipt of a punishment, so the activity in lateral habenula may act to inhibit the probability of performing an action, via inhibition of dopaminergic neural activity.

However, it is not always sufficient to suppress actions while expecting punishments; sometimes, it is important to actively perform actions to avoid punishments. Thus, it might be necessary to drive specific dopaminergic neurons that are involved in promoting behavioral avoidance, while also suppressing other dopaminergic neurons to minimize the performance of actions that lead to punishments. Indeed, neurons in the dorsal ventral tegmental area and medial substantia nigra pars compacta tend to be inhibited by punishments, whereas neurons in the ventral ventral tegmental area and lateral substantia nigra pars compacta tend to be excited by punishments. Thus, it is possible that this diversity in neuronal responses in ventral tegmental area/substantia nigra pars compacta to punishment might result from a shift in the balance between the direct and indirect projections from lateral habenula to dopaminergic neurons.

The roles of these direct and indirect projections were recently tested by optogenetic studies. These studies found that the activation of lateral habenula inputs to rostromedial tegmental nucleus promotes behavioral avoidance in a real time place preference assay — that is, activation of lateral habenula projections to the rostral medial tegmental nucleus in a particular spatial location produced avoidance of that location (Figure 3B). This is consistent with indirect inhibition of dopaminergic neurons by lateral habenula. In contrast, activation of the direct projection from lateral habenula to ventral tegmental area excites dopaminergic neurons but, nevertheless, promotes behavioral avoidance. Thus, activating either the

direct or indirect projections to ventral tegmental area dopaminergic neurons results in behavioral avoidance. Future studies are needed to address whether these effects are mediated by activation of different dopaminergic neurons receiving differentially biased direct and indirect inputs.

In addition to their effect on midbrain dopaminergic neurons, lateral habenula neurons also project to the raphe nuclei containing serotonergic neurons. While the neurons projecting to dopaminergic neurons tend to be found in the lateral part of lateral habenula, those projecting to raphe nuclei tend to be found in the medial part of lateral habenula. Though their activity dynamics during behavior is unclear, it is thought that these neurons provide a longer term value signal compared to the ones projecting to the dopaminergic neurons. Consistent with this hypothesis, serotonergic neurons show a long-term change in their activity when reward value is updated. Thus, lateral habenula projections to dorsal raphe nucleus supports long-term value coding and might directly influence mood, whereas the projections to ventral tegmental area/substantia nigra pars compacta might influence the learning or execution of motivated behaviors.

Lateral habenula integrates multiple inputs related to reward prediction error

While the outputs from lateral habenula are relatively well studied, less is known about what inputs mediate negative reward prediction error in lateral habenula. Interestingly, ventral tegmental area neurons project back to lateral habenula. In fact, a unique population of ventral tegmental area neurons expressing dopaminergic markers sends GABAergic projections to lateral habenula. Activating this projection reduces the activity of rostromedial tegmental nucleus neurons, thereby activating dopaminergic neurons and promoting a rewarding state. There are also glutamatergic neurons in ventral tegmental area that project to lateral habenula. In contrast to the GABAergic projections, the glutamatergic projections produce real time place avoidance. These results establish that there are reciprocal projections between lateral habenula and ventral tegmental area. However, whether or not these projections have specific roles in conveying reward prediction error signals to lateral habenula is not known.

The most promising input to lateral habenula for mediating negative reward prediction error is that from the globus pallidus interna. This is one of the output nuclei of the basal ganglia. In addition to providing motor output from the basal ganglia, a small subset of neurons in globus pallidus interna send glutamatergic projections to lateral habenula. These habenula projecting globus pallidus interna neurons are inhibited by the presence of cues predicting reward and are activated by negative reward prediction error due to omission. Modulating neural activity in these neurons bidirectionally affects activity in lateral habenula. Thus, globus pallidus interna is likely the major source of input conveying reward prediction error to lateral habenula.

Another major source of input to the lateral habenula comes from the lateral hypothalamic area. Projections from lateral hypothalamic area to lateral habenula can directly stimulate or suppress feeding. Glutamatergic projections from lateral hypothalamic area to lateral habenula negatively regulate feeding behavior. In other words, inhibiting this projection was is sufficient to cause animals to consume caloric rewards. In addition to this direct effect on reward consumption, inhibiting this projection causes a rewarding state in a real-time place preference assay. In contrast, activation of this projection caused behavioral avoidance.

An interesting feature of the afferent connectivity to lateral habenula is that almost all input sources to lateral habenula co-release glutamate and GABA. In fact, it has been shown that single axons and even single vesicles release both glutamate and GABA onto lateral habenula neurons. Lateral habenula is the only known structure in the brain where almost all inputs co-release glutamate and GABA. The function of such co-release is as yet unclear, though it has been shown that the balance of glutamatergic and GABAergic signaling can determine the role of lateral habenula in driving maladaptive states including depression and substance abuse.

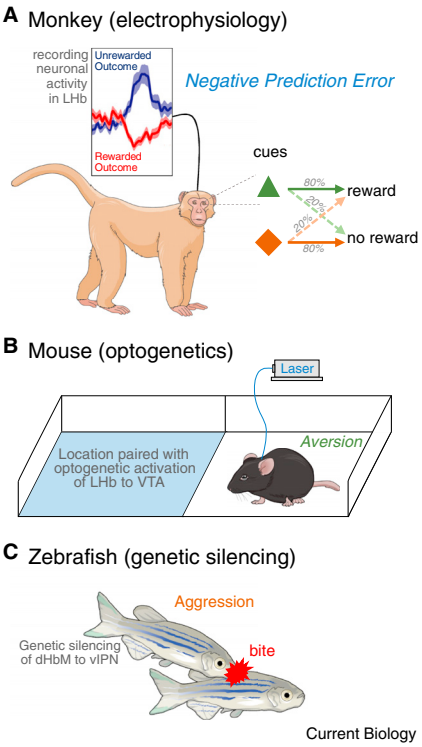

Figure 3. Behaviors studied across different species.
(A) In rhesus monkeys, the primary focus is in elucidating the role of the habenula in decision-making using electrophysiology to record the activity of lateral habenula (LHb) neurons (adapted from Bromberg-Martin *et al.*, 2010). (B) In mice, the role of the habenula in motivated behaviors has been studied using optogenetics to activate specific inputs such as the projections from lateral habenula to ventral tegmental area (LHb-VTA). (As shown in Stamatakis and Stuber, 2012.) (C) In zebrafish, one of the aims is to study the role of the habenula in socially mediated behaviors, such as aggression, using fish that have certain genes silenced, such as genes in cells that project from medial dorsal habenula (dHbM) to ventral interpeduncular nucleus (vIPN). (As shown in Chou *et al.*, 2016.)

Lateral habenula is involved in abstract inference

The neuroanatomical connectivity of lateral habenula also makes it ideally suited to influence various cognitive processes, including the gathering of information, flexible reasoning and spatial memory. In a task wherein monkeys have the option to gather information about upcoming rewards

without being able to change those rewards, the lateral habenula conveys a prediction error signal for information, much as it conveys one for reward. Thus, lateral habenula neurons could underlie our ability to seek information about the future.

Similarly, these neurons also convey abstract inference of future value. In a task in which monkeys infer value of cues either by experiencing those cue-reward pairings multiple times or by inference of the cue-reward pairing based on the reward statistics of the task, lateral habenula neurons convey reward prediction error signals that take into account inferred values as well as experienced values. Furthermore, lateral habenula neurons are also important in flexible choice behavior, as inactivating the lateral habenula is sufficient to disrupt such behavior.

Lateral habenula functions beyond reward processing

While not as well established, there are a number of studies that show various roles for lateral habenula beyond reward processing. In the following sections, we will briefly describe these roles.

Role of lateral habenula in spatial memory

There is increasing evidence that the lateral habenula plays a role in spatial memory. Inactivation of lateral habenula disrupts spatial memory in multiple tasks. While spatial memory requires the hippocampus, the lateral habenula does not directly receive inputs from or project to the hippocampus. Thus, it is surprising that disrupting its activity can affect spatial memory. In fact, activity in the lateral habenula can directly modulate and be modulated by the hippocampal theta rhythm, showing that some indirect functional connectivity exists between lateral habenula and hippocampus. The commonly accepted explanation is that this results from the modulation of serotonin and/or norepinephrine release by lateral habenula.

A role for lateral habenula in mediating stress responses

There is a recent surge in evidence that demonstrates a role for lateral habenula in mediating stress responses. Various stressors, including noxious thermal or pain stimuli, physical restraint, open field/elevated plus maze and social defeat, have been found to activate the lateral habenula (and the medial habenula). Modulating the activity in lateral habenula disrupts appropriate defensive responses to stress. This involvement of the lateral habenula in defensive behaviors is widely considered to be mediated by its projections to the raphe nuclei and periaqueductal gray.

Social signals in lateral habenula

The lateral habenula is also implicated in a host of other functions. Recently, it has been shown to have a role in social behaviors, including aggression and maternal behavior (Figure 3C). Activity in a GABAergic projection from basal forebrain to lateral habenula drives conditioned place preference of an aggressor mouse to a location paired with a submissive intruder. Furthermore, earlier studies that lesioned lateral habenula found that female rats have disrupted maternal behavior: this is likely mediated by the inputs from the preoptic area to lateral habenula.

Circadian rhythms in the lateral habenula

One of the major roles of lateral habenula is in sleep and circadian rhythms. Activity in lateral habenula is modulated by circadian rhythms and retinal illumination and is elevated during sleep and hibernation. Further, lesions of the fasciculus retroflexus (the output pathway of the habenula) in rodents reduce random eye movement sleep.

Involvement of the lateral habenula in depression and addiction

Aberrant activity in lateral habenula is strongly implicated in several maladaptive states, including mood regulation and substance abuse. Functional magnetic resonance imaging (fMRI) studies have suggested that depressed patients show elevated activity in the habenula. But because of the limited spatial resolution of functional magnetic resonance imaging, these studies cannot dissociate the activity of the lateral and medial habenula.

Consistent with a role for habenula in depression, rodent models of depression show elevated activity in lateral habenula. Furthermore, lesions or inactivation of the lateral habenula in rodents ameliorate depressive-like behaviors. Enhancement in excitatory synaptic inputs onto lateral habenula neurons and their output to rostromedial tegmental nucleus is present in rodent models of depression. Two major putative molecular mechanisms that underlie the increased synaptic drive onto lateral habenula neurons in depression are increased activity of the protein kinase CaMKIIβ and reduced co-release of GABA onto lateral habenula neurons from basal ganglia inputs. Hence, lateral habenula is a novel potential therapeutic site for ameliorating depression.

Lateral habenula activity is also strongly implicated in substance abuse, especially of cocaine and alcohol. During cocaine withdrawal, activity in lateral habenula increases due to a reduction in the corelease of GABA from the mouse entopeduncular nucleus (homologous to primate globus pallidus interna) and a general increase in glutamatergic drive. These mechanisms mediate the negative symptoms of withdrawal. Furthermore, activating lateral habenula also reduces voluntary ethanol consumption in rats. Therefore, lateral habenula is also a novel potential therapeutic site for addictive disorders.

Negative motivational states in the medial habenula

In comparison to the lateral habenula, relatively little is known about the functions of the medial habenula. This is primarily due to technical difficulties associated with studying medial habenula, because of its extremely small and elongated shape and proximity to ventricles. These issues make it extremely challenging to perform *in vivo* neuronal recordings during behavior in the medial habenula. Hence, most of what is known about the medial habenula is from histological, lesion or genetic ablation studies.

Involvement of medial habenula in nicotine addiction

While cocaine acts primarily in lateral habenula, nicotine abuse is highly correlated with decreased nicotinic acetylcholine receptors in the medial habenula. The balance of α5 and β4 subunits of the nicotinic receptors in medial habenula determines the amount of aversion induced by high dosages of nicotine. Also, knocking out the gene encoding the α5 subunit in medial habenula blocks the inhibition of reward pathways by high nicotine doses.

An emerging role for medial habenula in mood regulation and fear

Medial habenula is implicated in the regulation of mood, as targeted genetic lesions of medial habenula result in depressive-like behaviors in rodents. In addition, studies in zebrafish looking at the role of dorsal habenula (homolog of the medial habenula) have established roles in mediating social hierarchy by aggression and for experience-dependent modification of fear responses (Figure 3C). A recent study in mice, looking at the cholinergic neurons in medial habenula, found that activation of these neurons reduces the expression of fear memory. Surprisingly, these neurons mediate extinction of fear memory by $GABA_B$ receptor-mediated excitation of their axon terminals in the interpeduncular nucleus, thereby providing an extra-amygdalar pathway for fear regulation. Thus, while relatively little is known about the functional role of medial habenula in normal behavior, it appears to perform important functions for the maintenance of appropriate affective states.

Conclusion

In this Primer, we have provided a brief introduction to the recent accumulation of knowledge about the habenula. While there is renewed interest in its function, concerted effort is needed to understand the various circuits formed by the variety of different cell types in the habenula. To this end, future work should expand the study of the various inputs and outputs of the habenula in the context of its well-established functions. Habenula circuits must also be investigated in the context of lesser studied behaviors, such as feeding and social behaviors. Lastly, it is important to establish the identities of different cell types that are present in the habenula. While there are multiple cell types based on projection targets, input sources, and gene expression, the functions of these cell types remain unknown. Despite these unaddressed questions, it is clear that the habenula is a critical functional hub regulating complex behaviors such as motivation, decision-making and affective states.

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