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Review article

The role of the habenula in the transition from reward to misery in substance use and mood disorders

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ABSTRACT

The habenula (Hb) is an evolutionary well-conserved structure located in the epithalamus. The Hb receives inputs from the septum, basal ganglia, hypothalamus, anterior cingulate and medial prefrontal cortex, and projects to several midbrain centers, most importantly the inhibitory rostromedial tegmental nucleus (RMTg) and the excitatory interpeduncular nucleus (IPN), which regulate the activity of midbrain monoaminergic nuclei. The Hb is postulated to play a key role in reward and aversion processing across species, including humans, and to be implicated in the different stages of transition from recreational drug intake to addiction and co-morbid mood disorders. The Hb is divided into two anatomically and functionally distinct nuclei, the lateral (LHb) and the medial (MHb), which are primarily involved in reward-seeking (LHb) and misery-fleeing (MHb) behavior by controlling the RMTg and IPN, respectively. This review provides a neuroanatomical description of the Hb, discusses preclinical and human findings regarding its role in the development of addiction and co-morbid mood disorders, and addresses future directions in this area.

1. Introduction

The habenula (Hb) (from the Latin, little rein) is a phylogenetically old structure highly conserved among vertebrates located in the dorsomedial portion of the thalamus (Benarroch, 2015; Loonen and Ivanova, 2015). The habenular nuclei are paired structures and belong to the epithalamus, which also harbors the pineal gland and the stria medullaris. The Hb is considered to be an important relay between cortical and subcortical structures implicated in emotion and reward processing (Hetu et al., 2016). The Hb receives inputs from the septum, basal ganglia, lateral hypothalamus, anterior cingulate and medial prefrontal cortex, and projects to several midbrain centers, most importantly the tail of the ventral tegmental area (also known as the rostromedial tegmental nucleus [RMTg]) and to the interpeduncular nucleus, which regulate the activity of midbrain monoaminergic nuclei (Bianco and Wilson, 2009; Herkenham and Nauta, 1977). As emotional and reward-related impairments are relevant across psychiatric disorders, particularly within addiction and mood disorders (Goya-Maldonado et al., 2015; Jentsch and Pennington, 2014), the function of the Hb in humans is of great clinical importance.

Functionally, the Hb is divided into lateral (LHb) and medial (MHb) parts (Benarroch, 2015; Klemm, 2004). The MHb is connected to the amygdalo-hippocampal system through fornix and medial septal area and to the LHb via the striatopallidal (i.e. extended) amygdala and lateral hypothalamus (Loonen and Ivanova, 2016b). The LHb plays an important role in brain reward responses, and has been linked to drug

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addiction, as well as reward-related processes in major depression (Matsumoto and Hikosaka, 2007; Sartorius et al., 2010). The MHb – which has not yet been studied as extensively as the LHb – has been mainly associated with the regulation of nicotine intake (Fowler et al., 2011; Salas et al., 2009) and may also be implicated in the regulation of depressive mood (Viswanath et al., 2013). It has been postulated that the LHb might be more implicated in the initial stages of recreational drug intake (associated with positive reinforcement), while the gradual shift towards compulsive drug use in addiction, strongly associated with negative affect (negative reinforcement), might be mediated by an enhanced activity of the LHb and a gradually greater involvement of the MHb (Loonen et al., 2017; Loonen et al., 2016).

The structure and function of the Hb have been mainly explored in preclinical studies using rodent and monkey models. The study of the Hb in humans has been hampered by its small size and difficulties resolving its boundaries (Ely et al., 2016; Kim et al., 2016; Lawson et al., 2013). Despite this limitation, several groups have attempted to study the Hb at conventional fMRI resolutions (Erpelding et al., 2014; Garrison et al., 2013; Ide and Li, 2011; Li et al., 2008; Noonan et al., 2011; Schiffer et al., 2012; Ullsperger and von Cramon, 2003) and more recently at high resolutions (Ely et al., 2016; Hennigan et al., 2015; Hetu et al., 2016; Lawson et al., 2016; Lawson et al., 2014; Salas et al., 2010), providing fairly consistent findings of Hb activation when studying punishment and reward processing.

The present review focuses on the neuroanatomical description of the Hb, and discussion of preclinical and human findings regarding the role of the Hb in the transition from recreational drug intake to addiction and co-morbid mood disorders. We first describe the neuroanatomical properties of the LHb and MHb together with their afferent and efferent projections. Second, we review animal studies showing how the Hb is involved in reward processes and aversive states, and how this may mediate the transition from recreational to compulsive drug use and development of co-morbid mood disorders. Third, we review neuroimaging studies investigating the structure and function of the Hb in humans, as well as its role in reward, aversive states, addiction and depression. Finally, we propose a model of transition from recreational drug use to substance use and mood disorders, we discuss the limitations of the existing findings and we offer suggestions for future work in this area.

2. Habenula neuroanatomy

2.1. Connections of the habenula with other brain structures

2.1.1. Inputs

The Hb receives signals from the septum, hippocampus, ventral pallidum, lateral hypothalamus, global pallidus, and other areas of the basal ganglia (Fig. 1). The main input to the MHb comes from the septum, particularly the medial septum and the adjacent nucleus of the diagonal band of Broca (Benarroch, 2015; Klemm, 2004). The input to the MHb from these septal areas is primarily cholinergic and gamma-aminobutyric acid (GABA)ergic, although some inputs are glutamatergic (Benarroch, 2015). Moreover, the MHb receives dopaminergic input from the ventral tegmental area (VTA), adrenergic (norepinephrine) input from the locus coeruleus and serotonergic (5-hydroxytryptamine, 5-HT) input from the raphe nuclei (Benarroch, 2015; Bianco and Wilson, 2009; Xie et al., 2016). The LHb primarily receives glutamatergic afferents from the preoptic area, lateral hypothalamus, the entopeduncular nucleus (EPN; analog of globus pallidus in primates), the anterior cingulate and medial prefrontal cortex (Benarroch, 2015). The LHb also receives strong GABAergic innervations (Poller et al., 2013) from various other brain regions, including e.g. the EPN, nucleus accumbens and VTA. However, most of the inputs of the Hb functional inputs are still unknown (Shabel et al., 2012). Hence, there is a large heterogeneity in GABAergic inputs onto LHb neurons. Although the input from the basal ganglia is thought to be primarily inhibitory, Shabel et al. (2012) have shown that transmission from the basal ganglia to the LHb can also be excitatory glutamatergic, and suppressed by serotonin. These neurons may correspond to part of the habenula-projecting globus pallidus (GPh) of human's earliest vertebrates ancestors, a structure primarily involved in decision making in reward-driven behavior (Loonen and Ivanova, 2015). Additionally, the LHb receives dopaminergic innervation from the VTA, serotonergic innervation from the medial raphe nucleus, and adrenergic input from the locus coeruleus (Benarroch, 2015; Stamatakis et al., 2013). The LHb neurons express tyrosine hydroxylase (TH) and DA type 2 and 4 receptors (Aizawa et al., 2012; Geisler et al., 2003; Good et al., 2013; Gruber et al., 2007). A single-pulse stimulation of the VTA inhibits the firing of ~90% of the LHb neurons, whereas tetanic stimulation increases the activity of LHb units (Shen et al., 2012). Although the MHb sends projections to the LHb, there is no connection from LHb to the MHb (Kim and Chang, 2005).

2.1.2. Outputs

Information encoded by the LHb and the MHb is transmitted through the fasciculus retroflexus (FR) axon bundle to several midbrain monoaminergic nuclei (Hikosaka, 2010). However, the majority of the output is given to two specific midbrain areas: the rostromedial tegmental nucleus (RMTg) and the interpeduncular nucleus (IPN) (Fig. 1).

The FR is divided into two regions, the *outer* and the *inner* areas. The *outer* region originates in the LHb and projects mainly to the RMTg, next to numerous monoaminergic nuclei in the mid- and hindbrain (Bianco and Wilson, 2009). These efferents are predominantly glutamatergic, but some are GABAergic and cholinergic (Bianco and Wilson, 2009). The RMTg is a small nucleus that contains mainly inhibitory GABAergic cells and thereby regulates activity of VTA/substantia nigra compacta (SNc) and the dorsal raphe nucleus (Benarroch, 2015). More specifically, LHb neurons predominantly inhibit dopaminergic (DA) neurons of the midbrain (Ji and Shepard, 2007; Matsumoto and Hikosaka, 2007). Electrical stimulation of LHb abolished the firing of ~ 90% of DA neurons of VTA and SNc (Christoph et al., 1986; Matsumoto and Hikosaka, 2007). Vice versa, lesion of LHb increased DA turnover in terminal projection areas of these midbrain nuclei (Lecourtier et al., 2008). Similarly, through its RMTg projection, stimulation of the LHb caused transient inhibition of the firing activity of serotonergic neurons in the raphe nucleus (Wang and Aghajanian, 1977). LHb neurons also directly target the DA VTA (Lammel et al., 2012) and substantia nigra pars compacta, the serotonergic medial and dorsal raphe nuclei, cholinergic laterodorsal tegmentum and noradrenergic locus coeruleus (Herkenham and Nauta, 1979).

The *inner* area of the FR originates in the MHb and projects to the IPN (Benarroch, 2015; Bianco and Wilson, 2009; Klemm, 2004; Sutherland, 1982). The MHb contains both cholinergic neurons (in its ventral two-thirds) and dorsally located substance P-containing neurons, which innervate the ventral and dorsal versus the lateral IPN, respectively (Artymyshyn and Murray, 1985; Contestabile et al., 1987). This neuronal pathway is highly conserved across various species (Broms et al., 2015). The results of Qin and Luo (2009) suggest that, at least in mice, also glutamate is used as a neurotransmitter next to acetylcholine and substance P (Qin and Luo, 2009). The MHb is the main source of input for the IPN (Bianco and Wilson, 2009; Klemm, 2004; Morley, 1986), although cholinergic fibers may also originate in the posterior septum (Contestabile and Fonnum, 1983; Fonnum and Contestabile, 1984). The IPN is a singular, unpaired structure located at the ventral midline of the midbrain (Klemm, 2004; Morley, 1986). The major efferent pathways originating in the IPN project to the dorsal tegmental nucleus (Morley, 1986), the VTA (Klemm, 2004) and the raphe nuclei (Bianco and Wilson, 2009; Klemm, 2004). However, the IPN is well known for its widespread ascending and descending projections (Klemm, 2004; Morley, 1986). Apart from a low number of serotonergic neurons (continuous with the B8 cell group of the medial raphe nucleus) numerous peptidergic neurons (substance P, met-