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The dorsal diencephalic conduction system in reward processing: Spotlight on the anatomy and functions of the habenular complex

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ABSTRACT

The dorsal diencephalic conduction system (DDC) is a highly conserved pathway in vertebrates that provides a route for the neural information to flow from forebrain to midbrain structures. It contains the bilaterally paired habenular nuclei along with two fiber tracts, the stria medullaris and the fasciculus retroflexus. The habenula is the principal player in mediating the dialogue between forebrain and midbrain regions, and functional abnormalities in this structure have often been attributed to pathologies like mood disorders and substance use disorder. Following Matsumoto and Hikosaka seminal work on the lateral habenula as a source of negative reward signals, the last decade has witnessed a great surge of interest in the role of the DDC in reward-related processes. However, despite significant progress in research, much work remains to unfold the behavioral functions of this intriguing, yet complex, pathway. This review describes the current state of knowledge on the DDC with respect to its anatomy, connectivity, and functions in reward and aversion processes.

1. Introduction

The discovery by Olds and Milner that electrical stimulation of certain brain structures in rats is rewarding provided empirical evidence for the existence of a neural substrate of reward and goal-directed behaviors [1]. Early studies using electrical brain stimulation showed that rats and other vertebrates will work vigorously to stimulate specific brain areas [2–4], and that the rewarding effect encompassed by this stimulation could substitute for naturally occurring stimuli such as food and water [5,6]. The reinforcing effect of brain stimulation is largely mediated by cell bodies within the medial forebrain bundle (MFB), though there exist several other regions whose activation can have gratifying effects. Because of the conspicuous behavioral changes that follow its destruction or damage, the MFB has been the focus of a wide array of neuroanatomical and behavioral studies [7,8]. Findings from studies using pulse-pair stimulation suggest that the MFB includes fine myelinated fibers with short refractory period and fast conduction velocities, and trajectories that extend from anterior regions of the lateral hypothalamus (LH) to the ventral tegmental area (VTA) and terminate in brainstem nuclei [9–12]. Although the MFB has been the focus of the preponderance of neuroanatomical and behavioral studies, another pathway is emerging as an important player in connecting limbic forebrain to midbrain regions and in modulating the reward signal induced by brain stimulation. Such pathway is the dorsal diencephalic conduction system (DDC).

The DDC is a neural pathway composed of the stria medullaris (SM), the habenula, and the fasciculus retroflexus (FR). It constitutes a rostrocaudal conduction system that merges with the MFB at its rostral and caudal poles. The information received by the DDC travels from the anterior portion of the LH to the habenula through the SM, and gets transmitted to midbrain regions via the FR [7,13]. Sites within the DDC, including the SM and the habenula, have all been shown to support operant responding for brain stimulation, indicating that this pathway plays crucial roles in the modulation of reward and goal-directed behaviors [14–16]. However, until recently, the role of the DDC in reward processing has largely been overlooked in favor of the MFB. Following Matsumoto and Hikosaka's seminal work on the LHb as a source of negative reward signals in monkeys [17], the DDC has undergone a resurgence of scientific interest, paving the ways for many subsequent studies [18,19]. Numerous functions have been ascribed to the DDC, including the regulation of sleep homeostasis [20,21], stress response [22,23], anxiety [24], pain [25] and analgesia [26]. However, the overarching goal of this paper is to provide an overview of the neuroanatomical and behavioral findings aimed at deciphering the functions of the DDC in reward processing, with a special focus on the habenular complex. This paper first starts by describing the cellular and synaptic profile of habenular neurons and their interconnectivity with monoaminergic systems, to finally draw on findings delineating the reward-related functions of the DDC.

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2. The habenula: morphological, cellular and electrophysiological profile

Centrally located along the DDC, the habenula acts as an interface between forebrain and mesencephalic regions. It is an evolutionary conserved epithalamic structure that shows striking asymmetry in most groups of vertebrates [27,28]. In the lamprey, the right habenula is substantially larger than the left, while in most species of cartilaginous fishes, the habenular nucleus is enlarged on the left side [27]. Size differences between the right and left habenula have also been observed in rodents. In the albino rat, the left habenula is slightly larger compared to the right [29], whereas in the albino mouse, the right habenula is markedly enlarged and displays a more complex arrangement of neurons compared to the left habenula [30]. Anatomically, the habenula is divided into two functionally distinct subclei; the medial (MHb) and the lateral (LHb) habenula. The MHb is comprised of a superior (MHbS), inferior (MHbI), central (MHbC), and lateral (MHbL) part, and is characterized by a remarkably high density of cells that show striking differences in somatodendritic and axonal morphology [31,32]. On the other hand, the LHb is comprised of a medial (LHbM) and lateral (LHbL) part, each one further subdivided into distinct sets of nuclei on morphologic and cytochemical grounds [32–34]. Morphological analysis also reveal the presence of four major types of cells within the LHb, namely the spherical, fusiform, polymorphic, and vertical cells [35], and unlike the MHb, cells in this nucleus are more loosely dispersed [31]. Although morphologically different from each other, LHb neurons share similar electrophysiological profile and intrinsic membrane properties; they have a high input resistance and produce long-lasting discharges in response to transient synaptic hyperpolarization [35,36]. Such similarity most likely suggests that the formation of functional entities within the LHb is achieved by specific synaptic inputs to particular neurons rather by individual differences in intrinsic membrane properties [35].

LHb neurons are mainly glutamatergic, with enriched expression of the vesicular glutamate transporter VGluT2 [32,37]. These neurons exhibit different patterns of spontaneous action potential firing, including tonic regular, tonic irregular and burst firing [38]. Electrophysiological evidence suggests that glutamatergic transmission in the LHb is primarily driven by calcium-permeable α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, and to a lesser extent, calcium-impermeable AMPA receptors [39–41]. Excitatory glutamatergic transmission in LHb neurons also relies on the activation of N-methyl-D-aspartate (NMDA) receptors [41] and metabotropic glutamate receptors (mGluR1) [42], though synaptic currents mediated by these receptors are relatively small compared to those mediated by AMPA receptors. The LHb also receives strong gamma-Aminobutyric acid (GABA)ergic inputs, which are mainly driven by the activation of GABA type-A ($GABA_A$) and type-B ($GABA_B$) receptor subunits [39,43]. These GABAergic projections most likely originate from extrinsic sources since local interneurons are relatively scarce [44]. Besides glutamate and GABAergic receptors, the LHb contains DA type-2 (D_2) and type-4 (D_4) receptors postsynaptically [32,45], as well as serotonin receptor 2 C (5-HT_{2C}) [46], suggesting that it may be subject to dopaminergic and serotonergic modulation.

The cellular and electrophysiological profile of the MHb is very different compared to that of the LHb [31,32]. A known feature of the MHb is that it has one of the highest concentrations of $GABA_B$ receptors in the brain, indicating the existence of strong inhibitory inputs [43,47–49]. MHb neurons are mostly homogeneous in their electrophysiological profile, exhibiting tonic firing of action potentials [31]. They receive glutamate- and ATP-mediated synaptic inputs [50] and contain functional AMPA receptors of low calcium permeability [51]. Recent observations also indicate that the MHb contains glutamate-expressing neurons with enriched expression of VGluT1 and VGluT2 [52,53] and with the ability to co-release acetylcholine at synaptic terminals [54]. Unlike the LHb, which expresses several subunits of $GABA_A$ receptors at both the mRNA and protein level, the MHb only expresses the α2-subunit of $GABA_A$ receptors [55]. The MHb is also distinctive from the LHb in that it expresses at very high level the α3, α4, α5, α6, β2, β3 and β4 subunits of the nicotinic acetylcholine receptors (nAChRs) [56,57], and shows strong immunoreactivity for mu-opioid receptors (MORs) [58], suggesting that it most likely play a crucial role in modulating the behavioral effects of nicotine and morphine.

Last but not least, evidence indicates some degree of functional specialization within MHb neurons. For instance, gene expression analysis of medial habenular subnuclei in the rat reveal that the superior MHb is glutamatergic, the dorsal-central part of the MHb is both substance P-ergic and glutamatergic, and that the ventral-center and lateral part of the MHb are both cholinergic and glutamatergic [32]. More recently, Chou and colleagues identified two subregions in the evolutionarily homologous dorsal habenula (dHB) of the zebrafish, namely the lateral subregion of the dHb (dHbL) and the medial subregion of the dHb (dHbM), which antagonistically regulate the outcome of conflict. Silencing the dHbL or dHbM in zebrafish caused a stronger predisposition to lose or win a fight, respectively, indicating that these subregions differentially regulate the resolution of social conflict [59].

3. Afferent and efferent pathways of the habenula

As shown in Fig. 1, the habenula is an epithalamic structure divided into a lateral and medial component that lie in close proximity to the pineal gland. The connection between the two habenular subnuclei is asymmetrical inasmuch as only the MHb sends axonal projections to the LHb [31]. Despite sharing some sources of afferent inputs and efferent targets, the LHb and MHb are characterized by different connectivity that underlie differences in their functions. In delineating the afferent and efferent circuitry of the habenula, the primary focus will be on the rat, which has been well studied. Some subtle differences in connectivity may exist across species, however, a description of the comparative neuroanatomy of the habenula is outside the scope of this paper.

Much of the knowledge on the connectivity of the habenula have been acquired through studies employing retrograde and anterograde tracing. Findings from these studies suggest that the LHb receives strong GABAergic inputs from structures of the limbic system including the medial septum, diagonal band of Broca, lateral preoptic area and the substantia innominate [60–62], as well as bilateral and topographically organized inputs from the anterior insular, cingulate, prelimbic and infralimbic cortices [63,64]. By far, the strongest inputs to the LHb originate from the lateral hypothalamus and the entopeduncular nucleus (EP), the latter being the internal segment of the globus pallidus in non-primate mammals [60]. Projections from these regions to the LHb are primarily excitatory and glutamatergic, though evidence of a GABAergic input originating from these regions has also been demonstrated [40,65]. Dopaminergic projections from the BNST, dorsomedial hypothalamic nucleus, periaqueductal gray, substantia nigra pars compacta (SNc), and VTA [66] as well as inputs from 5HT-containing neurons of the median (MR) and dorsal (DR) raphe nuclei [67,68] also densely innervate the LHb. On the other hand, the LHb innervates a wide range of structures by projecting caudally through the FR or rostrally through the SM. One of the major targets of the LHb efferent pathway is the rostromedial tegmental nucleus (RMTg); a GABAergic region located posterior to the VTA, which is also referred to as the tail of the VTA (tVTA) [69,70]. The dense projections from the LHb to the RMTg are glutamatergic [71], mainly ipsilateral, and organized in a topographical manner, with medial and lateral portions of the LHb targeting medial and lateral portions of the RMtg, respectively [69,70]. Direct excitatory projections from the LHb to DA and GABA neurons of the VTA have also been reported, though these constitute only a small proportion (~16%) of LHb projecting axons [72,73]. Other caudal targets of LHb efferents include the DR and MR [74], the