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Invited review

The habenulo-interpeduncular pathway in nicotine aversion and withdrawal

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ABSTRACT

Progress has been made over the last decade in our understanding of the brain areas and circuits involved in nicotine reward and withdrawal, leading to models of addiction that assign different addictive behaviors to distinct, yet overlapping, neural circuits (Koob and Volkow, 2010; Lobo and Nestler, 2011; Tuesta et al., 2011; Volkow et al., 2011). Recently the habenulo-interpeduncular (Hb-IPN) midbrain pathway has re-emerged as a new critical crossroad that influences the brain response to nicotine. This brain area is particularly enriched in nicotinic acetylcholine receptor (nAChR) subunits α5, α3 and β4 encoded by the *CHRNA5-A3-B4* gene cluster, which has been associated with vulnerability to tobacco dependence in human genetics studies. This finding, together with studies in mice involving deletion and replacement of nAChR subunits, and investigations of the circuitry, cell types and electrophysiological properties, have begun to identify the molecular mechanisms that take place in the MHb–IPN which underlie critical aspects of nicotine dependence. In the current review we describe the anatomical and functional connections of the MHb–IPN system, as well as the contribution of specific nAChRs subtypes in nicotine-mediated behaviors. Finally, we discuss the specific electrophysiological properties of MHb–IPN neuronal populations and how nicotine exposure alters their cellular physiology, highlighting the unique role of the MHb–IPN in the context of nicotine aversion and withdrawal.

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1. Introduction

The habenula is a small bilateral structure located in the epithalamic region of the diencephalon. Together with its associated afferent and efferent tracts, it forms part of the dorsal diencephalic conduction system, which connects the limbic forebrain with nuclei in the midbrain and hindbrain (Sutherland, 1982). The habenula is phylogenetically highly conserved across vertebrates, and serves to connect more recently evolved structures involved in executive function with ancient brain areas that process pain and reward. In fish, amphibian, and reptiles, the right and left sides of the habenula exhibit a remarkable asymmetry in size, molecular properties, connectivity and associated behaviors (Aizawa et al., 2005; Concha and Wilson, 2001; Dadda et al., 2010). In mammals, the habenula is symmetric and is located on the posterior medial end of the dorsal thalamus, adjacent to the third ventricle. Highlighting its ancient origin, a recent study of human fetuses demonstrated that the habenulo-interpeduncular (Hb-IPN) tract is one of the first major fiber tracts to form in the developing brain, present as early as eight weeks gestation (Cho et al., 2014).

Abbreviations: 3V, third ventricle; 4V, fourth ventricle; ACh, acetylcholine; AP, action potential; BAC, bed nucleus of the anterior commissure; ChAT, choline acetyltransferase; CPA, conditioned place aversion; DR, dorsal raphe; DTg, dorsal tegmental nuclei; EC, entorhinal cortex; EPSP, excitatory postsynaptic potential; FR, fasciculus retroflexus; Hb-IPN, habenulo-interpeduncular; HC, hippocampus; HCN, hyperpolarization-activated cyclic nucleotide-gated; Hyp, hypothalamus; IL-18, interleukin 18; IPA, interpeduncular nucleus apical; IPC, interpeduncular nucleus central; IPDL, interpeduncular nucleus dorsolateral; IPDM, interpeduncular nucleus dorsomedial; IPI, interpeduncular nucleus intermediate; IPL, interpeduncular nucleus lateral; IPN, interpeduncular nucleus; IPR, interpeduncular nucleus rostral; KCC2, K^+/Cl^- co-transporter 2; LC, locus coeruleus; LDTg, laterodorsal tegmental nuclei; LHb, lateral habenula; LV, lateral ventricle; MHb, medial habenula; MHbD, medial habenula dorsal; MHbS, medial habenula superior; MHbV, medial habenula ventral; MHbVc, medial habenula ventro-central; MHbVl, medial habenula ventro-lateral; MHbVm, medial habenula ventro-medial; MnR, median raphe; MS, medial septum; nAChR, nicotinic acetylcholine receptor; NDB, nucelus of diagonal band; NI, nucleus incertus; Oprm, μ-opioid receptor; PAG, periaqueductal gray; sEPSC, spontaenous excitatory postsynaptic current; Sfi, septofimbrial nucleus; SNP, single nucleotide polymorphism; SP, substance P; Thal, thalamus; TRAP, translational ribosomal affinity purification; TS, triangular septum; VGlut, vesicular glutamate transporter; VTA, ventral tegmental area.

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The habenula is subdivided into the medial habenula (MHb) and the lateral habenula (LHb) (Andres et al., 1999), each having different anatomical connections and serving different functions (Herkenham and Nauta, 1977, 1979; Klemm, 2004; Lecourtier and Kelly, 2007). Recent studies suggest that the MHb-IPN pathway should be included as part of several of the more well-known circuits that regulate reward, withdrawal and addiction (Koob and Volkow, 2010; Lobo and Nestler, 2011; Tuesta et al., 2011; Volkow et al., 2011). In this review, we will discuss the current understanding of the MHb and its role in nicotine dependence. The MHb receives input mainly from the septum through the stria medularis and projects to the interpeduncular nucleus (IPN) through the fasciculus retroflexus (FR) (Herkenham and Nauta, 1979; Qin and Luo, 2009; Swanson and Cowan, 1979) (Fig. 1). Besides the peculiar anatomical traits of the MHb–IPN pathway, such as the remarkable high density of cell bodies in the MHb, the long axons that bundle together to form the FR and terminate in an ipsilateral manner in the IPN, the MHb–IPN tract also highly expresses a unique subset of nicotinic acetylcholine receptor (nAChR) subunits, the α5, α3 and β4 subunits encoded by the *CHRNA5-A3-B4* gene cluster (Fig. 2A,D). This gene cluster has been associated with higher levels of nicotine consumption and dependence in human genetics studies (Berrettini et al., 2008; Bierut et al., 2008; Lips et al., 2010; Liu et al., 2010; Ware et al., 2011). In agreement with these association studies in smokers, cumulative evidence from animal models points to the MHb–IPN pathway as a key modulator of nicotine aversion and nicotine withdrawal (Fowler et al., 2011; Frahm et al., 2011; Salas et al., 2009).

2. Anatomy and connectivity: the medial habenula and its output to the interpeduncular nucleus

MHb afferents derive mostly from the posterior septum, specifically from the septofimbrial nucleus (SFi), the triangular septum (TS) and the bed nucleus of the anterior commissure (BAC) (Herkenham and Nauta, 1977). Topographic connections have been revealed from the TS and the BAC to the ventral and dorsal subnuclei of the medial habenula (MHbV and MHbD) respectively (Yamaguchi et al., 2013). The MHb also receives input from the medial septum (MS) and nucleus of diagonal band (NDB) in the basal forebrain; from the interfascicular nucleus of the ventral tegmental area (VTA) (Phillipson and Pycock, 1982), from the mesencephalic raphe in the midbrain (Herkenham and Nauta, 1977; Staines et al., 1988) and from the locus coeruleus (LC) and superior cervical ganglion (Gottesfeld, 1983) (Fig. 1).

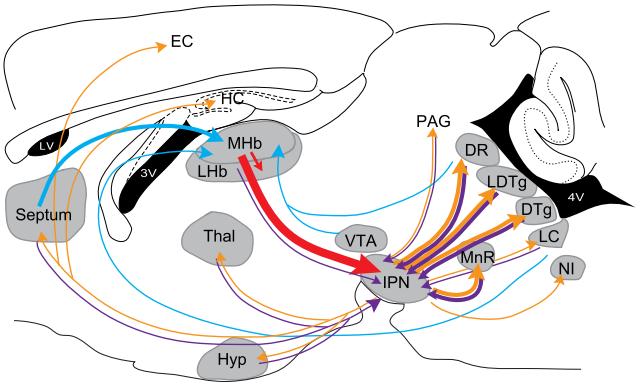

Fig. 1. MHb–IPN connectivity. Schematic sagittal view of a mouse brain showing known MHb afferents (blue), MHb efferents (red), IPN afferents (purple) and IPN efferents (orange). The thickness of the arrows reflects the strength of the connection. 3V, third ventricle; 4V, fourth ventricle; DR, dorsal raphe; DTg, dorsal tegmental nucleus; EC, entorhinal cortex; HC, hippocampus; Hyp, hypothalamus; IPN, interpeduncular nucleus; LC, locus coeruleus; LDTg, laterodorsal tegmental nucleus; LHb, lateral habenula; LV, lateral ventricle; MHb, medial habenula; MnR, median raphe; NI, nucleus incertus; PAG, periaqueductal gray; Thal, thalamus; VTA, ventral tegmental area.

The MHb has been subdivided into five subnuclei (Aizawa et al., 2012; Wagner et al., 2014) according to the expression of output neurotransmitters (Aizawa et al., 2012) (Fig. 2A). However, as many as 15 subnuclei have been described based on different ultrastructural, morphological and cytochemical properties (Andres et al., 1999; Geisler et al., 2003; Aizawa et al., 2012; Wagner et al., 2014). Neurons in the MHbD express the neuropeptide substance P (SP), also known as Tachykinin 1 (Fig. 2A–C). Neurons in the superior part of the MHb (MHbS) show strong glutamatergic character and lack of SP expression (Fig. 2A). The lower two-thirds of the MHb comprise the ventro-medial (MHbVm), the ventro-central (MHbVc) and the ventro-lateral (MHbVl) subnuclei. These three subnuclei display strong expression of the acetylcholine synthesizing enzyme choline acetyltransferase (ChAT) and the vesicular glutamate transporters 1 and 2 (VGlut1 and VGlut2) (Aizawa et al., 2012) (Fig. 2A,C). Intermingled with ChAT positive neurons, there are also ChAT negative neurons expressing nAChRs (Shih et al., 2014). In addition to the differential expression of neurotransmitters, expression of other markers has been shown to be subnuclei specific. For instance, the μ-opioid receptor (Oprm) is only expressed in the MHbVl part, and interleukin 18 (IL-18) is only expressed in the MHbS and MHbD parts (Aizawa et al., 2012) (Fig. 2A).

The MHb efferents target the single midline IPN via the FR. The IPN can be subdivided into 3 unpaired and 4 paired subnuclei based primarily on cytoarchitecture and to a lesser extent on marker localization: the median, unpaired subnuclei are the apical (IPA), rostral (IPR) and central (IPC) nuclei, while the paired subnuclei comprise the dorsolateral (IPDL), dorsomedial (IPDM), lateral (IPL) and intermediate (IPI) subnuclei (Hemmendinger and Moore, 1984; Lenn and Hamill, 1984) (Fig. 2D). Projections from MHb to the IPN are topographically organized, such that a 90-degree lateral turn of the MHb corresponds to the target areas within the IPN (Herkenham and Nauta, 1979). SP neurons in the MHbD project to the IPR and IPL subnuclei of the IPN, while ChAT neurons in the MHbV part project to the IPC and IPI subnuclei of the IPN (Contestabile et al., 1987), and ChAT negative neurons of the MHbVl project to the IPR (Shih et al., 2014) (Fig. 2E). The axons from MHb criss-cross through the entire extent of the IPN, forming *en passant* synapses, before terminating ipsilaterally in the IPL (Herkenham and Nauta, 1977). Within the IPI, cholinergic MHb axons terminate to form a special type of synapse, termed the crest synapse, where a single disc-shaped IPN dendrite, or "crest", receives paired innervation from both the left and right MHb (Lenn et al., 1983). These synapses form and undergo extensive remodeling during the post-natal period in rodents (Lenn, 1978b), and it is possible that in birds and mammals, this is the predominant form of asymmetry within the habenulo-interpeduncular pathway. Ultrastructurally, however, the vast majority (~90%) of crest synapses receives input from both the left and right MHb (Hamill and Lenn, 1983; Lenn, 1976, 1978a; Lenn et al., 1983; Murray et al., 1979).

While the IPN receives considerable input from the MHb, this is not the only source. The IPN also receives projections from forebrain nuclei such as the septum (Contestabile and Flumerfelt, 1981; Gottesfeld and Jacobowitz, 1978; Hamill and Fass, 1984; Swanson and Cowan, 1979), the medial preoptic area (Vertes and Fass, 1988) the ventral thalamus (Moore et al., 2000), the central and ventral hypothalamus (Jennes, 1987; Villalobos and Ferssiwi, 1987), and midbrain nuclei such as the dorsal and dorsolateral tegmental nuclei (DTg and LDTg), both dorsal and median raphe nuclei, the central gray and the locus coeruleus (Cornwall et al., 1990;