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## Unmasking the mysteries of the habenula in pain and analgesia

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## ABSTRACT

The habenula is a small bilateral structure in the posterior-medial aspect of the dorsal thalamus that has been implicated in a remarkably wide range of behaviors including olfaction, ingestion, mating, endocrine and reward function, pain and analgesia. Afferent connections from forebrain structures send inputs to the lateral and medial habenula where efferents are mainly projected to brainstem regions that include well-known pain modulatory regions such as the periaqueductal gray and raphe nuclei. A convergence of preclinical data implicates the region in multiple behaviors that may be considered part of the pain experience including a putative role in pain modulation, affective, and motivational processes. The habenula seems to play a role as an evaluator, acting as a major point of convergence where external stimuli is received, evaluated, and redirected for motivation of appropriate behavioral response. Here, we review the role of the habenula in pain and analgesia, consider its potential role in chronic pain, and review more recent clinical and functional imaging data of the habenula from animals and humans. Even through the habenula is a small brain structure, advances in structural and functional imaging in humans should allow for further advancement of our understanding of its role in pain and analgesia.

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Abbreviations: MHb, medial habenula; LHb, lateral habenula; NAc, nucleus accumbens; VTA, ventral tegmental area; PAG, periaqueductal gray; fMRI, functional magnetic resonance.

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## 1. Introduction

The habenula is a small bilateral structure in the posteriormedial aspect of the dorsal thalamus, located on the floor of the third ventricle above the pineal complex (together known as the epithalamus). It has been implicated in a remarkably wide range of behaviors including olfaction, ingestion, mating, endocrine, reward function, addiction and pain (Hikosaka, 2010). Given the broad involvement across numerous functions and behaviors, the region seems to have a basic but vital role as an evaluator, and acts as a major point of convergence where external stimuli is received, evaluated, and redirected for motivation of appropriate behavioral response.

In this review, we address the role of the habenula in five main sections: (1) Anatomy of Habenula and Known Connectivity with Afferent and Modulatory Pain Systems – here, we report on the known anatomy of the structure; (2) The Habenula in Pain and Analgesia – we provide a summary of preclinical data suggesting a major role for the structure in pain and analgesia; (3) Potential Role of the Habenula in Chronic Pain – given the pivotal role in a number of putative processes that are part of the chronic pain experience (e.g., depression) we integrate data on habenula functions that are salient to chronic pain; (4) Therapeutic Targets and the Habenula – is a section that focuses on pharmacological modulation of the structure; and (5) in the section, Functional Imaging – Potential to Further Understanding the Habenula's Role in Pain and Analgesia, we look to the future in utilizing such approaches in the clinical domain in chronic pain.

## 2. The habenula and afferent and efferent connections

The connectivity of the habenula is complex (Herkenham and Nauta, 1979; Sutherland, 1982; Bianco and Wilson, 2009). The habenula is present across species, being larger relative to the whole brain in subhuman mammals. As shown in Fig. 1, it a small bilateral structure in the dorsal-posterior thalamus, and sits astride the inferior lateral ventricles and above the pineal complex. It is divided into medial and lateral components that have different afferent and efferent connections that underlie differences in their function. Afferent and efferent pathways to and from the medial and lateral habenula show a segregation of functional connectivity. Fig. 2 shows connectivity of the medial (MHb) and lateral (LHb) habenula from other central brain and spinal cord regions. The habenula seems to be organized into multiple channels conveying parallel streams of information to the contralateral habenula, midbrain, and brainstem (Kim, 2009). In addition, inter and intrahabenular connections have been defined. The connections between the habenula nuclei are asymmetrical; only the medial habenula sends projection to the lateral habenula (Kim and Chang, 2005) while the commissural projection arises primarily in the lateral nucleus (Kim, 2009).

Pain inputs to the habenula include direct and indirect (via structures such as the lateral hypothalamus) afferents from the spinal cord. The lateral hypothalamus is involved in pain modulation (Dafny et al., 1996). Of the known afferent inputs that may be involved in pain transmission, the lateral hypothalamus projects to the habenula complex (Herkenham and Nauta, 1977; Parent et al., 1981). Stimulation of the habenula significantly

modulates lateral hypothalamus noxious-evoked activity. The lateral hypothalamus receives afferents from deep and superficial lamina in the spinal cord (Burstein et al., 1990). Others have also reported direct spinal-habenula connections in the cat (Craig, 2003), where spinal lamina I injections of the anterograde tracer



**Fig. 1.** Habenula neuroanatomy. (A) Rat habenula. A Nissl stain coronal segment of the rat brain, clearly demonstrates the relatively large (when compared with whole brain) rat habenula. This image is from an online atlas (http://brainmaps.org/, accessed May 2011). (B) Monkey habenula. A Nissl stain habenula in the monkey (Hikosaka, 2010 with permission). (C) Human habenula. (C1) An anatomical MRI image of the coronal, sagittal and horizontal view of the human habenula (from fsl). Numbers indicate the slice coordinates. (C2) Localization of the habenula in a coronal magnetic resonance imaging section (Savitz et al., 2011 with permission); (C3) Nissl and fiber staining of a coronal axial slice of the human brain. This image is from Zoomable Human Brain Atlas (http://zoomablebrain.bio.uci.edu/, accessed May 2011).



**Fig. 2.** Habenula afferent and efferent connections. *Key*: FrCtx = frontal cortex, NAc = nucleus accumbens, Lateral Hypo = lateral hypothalamus, EP = entopenduncular nucelus, CPu = caudate/putamen, Hippo = hippocampus, M = medial habenula, L = lateral habenula, P = pineal, IPN = interpeduncular nucleus, PAG = periaqueductal gray, Raphe = raphe nuclei, VTA = ventral tegmental area, and SNc = substantia nigra pars compacta. Adapted from Bianco and Wilson (2009) with permission.

Phaseolus vulgaris leucoagglutinin (PHA-L) terminate in the lateral habenula. Within the structure, the lateral habenula (LHb) may be more sensitive to the inhibitory effects of  $\mu$  opioid receptor agonist, morphine, on nociceptive stimuli (Wu et al., 2005), supporting a more prominent role of the lateral habenula in pain processing. Dense  $\mu$  opioid receptor levels are described in the habenula (Mansour et al., 1987) while delta and kappa receptors are less dense in the region.

Other indirect effects of pain may take place through multiple inputs to the habenula from CNS structures such as the frontal cortex and nucleus accumbens (NAc) (see Fig. 2). Of these, the inputs from limbic forebrain structures, well known to be involved in pain processing (Casey, 1999), include the NAc (Becerra and Borsook, 2008), and the basal ganglia (Chudler and Dong, 1995; Borsook et al., 2010).

As shown in Fig. 2, the medial habenula (MHb) projects predominantly to the interpeduncular nucleus in the midbrain (Herkenham and Nauta, 1979) while the lateral habenula has projections to the ventral tegmental area (VTA) and the substantia nigra pars compacta (SNc). The two latter structures contain dopaminergic neurons (Bromberg-Martin et al., 2010). The lateral habenula also has projections to the dorsal and median raphe nuclei that contain serotonergic neurons (Ferraro et al., 1996; Alenina et al., 2006). Prior studies initially suggested that periaqueductal gray (PAG), nucleus accumbens, and habenula might constitute a unidirectional loop to play their roles in pain modulation (Ma and Han, 1991). More recent works indicate that intrahabenular naloxone injections inhibit analgesia produced by

morphine injected into the PAG. In addition, intra-accumbens injections of naloxone diminish the analgesic effects of intrahabenular morphine injections (Ma et al., 1992), suggesting that the habenula acts as a relay in descending pain modulation from the nucleus accumbens to the PAG (Yu and Han, 1990). Acetylcholinergic projections from the MHb to the IPN are, also, well described (Fasolo et al., 1992).

The projections to the midbrain regions such as the PAG and raphe are important in habenula-mediated analgesia. As noted, electrical stimulation or morphine injection into the habenula produces analgesia. The PAG has a well described role in descending modulation of pain (Behbehani, 1995; Ren and Dubner, 2002) and the dorsal raphe, which sends afferents directly to the spinal cord via the raphe magnus in the medulla, also contribute through serotonergic mediated pain modulatory processing (Wang and Nakai, 1994). Both serotonergic and dopaminergic systems have important roles in pain processing - including pain modulation (serotonin) (Fields, 2004; Benarroch, 2008) and reward (dopamine) (Wood, 2008). Finally, the interpenducular nucleus receives a major output from the medial habenula and modulates cells in the raphe magnus (Hentall and Budhrani, 1990) in a manner that may enhance a pain response (Meszaros et al., 1985).

The habenula maintains an array of cross-talk between networks through different neurotransmitter systems. For example, main outputs of the LHb are to the midbrain *serotonergic system* where it targets the dorsal raphe and median raphe, the *dopaminergic system* where it targets the ventral tegmental area (VTA), and the *cholinergic system*, that targets the lateral dorsal tegmental nucleus (Sutherland, 1982; Klemm, 2004).

## 3. The habenula in pain and analgesia

Convergent preclinical data have implicated the habenula in numerous behaviors including pain and analgesia. Direct afferent inputs to the structure have been reported to originate in lamina I of the dorsal horn and trigeminal nucleus (Craig, 2003). Other inputs, notably from the hypothalamus (a structure also involved in pain processing as described earlier), have afferent inputs to the habenula (Goto et al., 2005). Thus, the structure is directly connected to pain processing through these pathways. Other pathways (see section above) have also been reported that may also convey information related to pain and analgesia. For example, anatomical and electrical studies show connections to the midbrain central gray and serotoninergic raphe nuclei (Ferraro et al., 1996), both involved in pain modulation.

Further evidence can be found from activation observed in electrophysiology or electrostimulation studies. Neurons in the lateral habenula respond to noxious stimuli (but not non-noxious stimuli) that may be excitatory or inhibitory depending on the intensity of the stimulus (Gao et al., 1996). Electrical stimulation of the habenula produces analgesia in a formalin test (Cohen and Melzack, 1986) and is reversible when naloxone is directly injected into the habenula (Mahieux and Benabid, 1987). Other markers of activity include neuronal markers and functional imaging. Using cfos immunohistochemistry as a marker of neuronal activity shows increases in neuronal stains in the lateral habenula in experimental pain (Smith et al., 1997; Lehner et al., 2004). In a chronic model of pain (compression of the dorsal root ganglion) fos expression has been reported to be transiently increased in the habenula (Sun et al., 2002). In a measure of functional activity utilizing 2deoxyglucose, diabetes-induced pain with streptozotocin (STZ) in rats, habenula activation was decreased in response to evoked pain inducing stimuli compared with control rats (Paulson et al., 2007), suggesting that habenula activation may represent part of a modulatory pain system. Further details on imaging the habenula are noted in Section 5.

Preclinical data have also evaluated the effects of analgesics on habenula function. For example, morphine injections into the habenula, a region containing high levels of opioid receptors (Neal et al., 1999), result in analgesia (Cohen and Melzack, 1985). In addition, heroin decreases habenula glucose utilization supporting a role of opioid mediated responses of neurons (Martin et al., 1997). Opioids, including morphine, may have a dual modulation of glutamatergic inputs in the structure to produce these changes.

Taken together, the data support a role of the habenula in pain processing. As noted in the section on anatomy of the structure, it is situated to receive information from forebrain structures and the dorsal diencephalic conduction (DDC) system – one of two major pathways that interconnect the limbic forebrain and sites in the mid- and hindbrain (Bianco and Wilson, 2009). As such, the emotional components of pain may interact with pain modulatory systems through this structure. This is perhaps highly salient given emotional changes in chronic pain (including cognitive and reward) are clearly part of what makes chronic pain difficult for patients.

#### 4. Habenula and behaviors associated with chronic pain

Chronic pain is associated with a number of behaviors and complex interactions including sensory, emotional, and cognitive alterations. Given the involvement of the habenula in pain (see Section 2), research related to behaviors that are considered part of overall pain behavior including analgesia suggests a potential integrative role for this structure. As noted above, the structure may be an important interactive pathway linking the limbic forebrain and brainstem nuclei to the midbrain. Chronic pain is associated with a number of alterations including a deficient reward state due to changes in reward-aversion processing; stress; in co-morbid conditions such as anxiety, depression or addiction; and in more complex processes such as defensive behaviors and prediction errors. It is perhaps highly salient that stimulation of the habenula may reverse some of these behaviors including depression (Sartorius et al., 2010) or potentially addiction (Luigjes et al., 2011).

## 4.1. Reward and aversion

The habenula has been implicated in reward (Hong and Hikosaka, 2008; Hikosaka, 2010). Inhibitory input from the lateral habenula (LHb) shows major influence in determining the reward-related activity of dopamine neurons (Matsumoto and Hikosaka, 2007). A projection from the globus pallidus to the lateral habenula is one pathway where reward prediction processing is activated in the habenula by pallidal inputs (Hong and Hikosaka, 2008). Given the connections of the habenula to dopaminergic regions in the VTA and SNc, the structure likely plays a role in reward-related signals. Analgesia may be a process driving these reward related activities (Schweinhardt et al., 2009). Consistent with a putative role of the habenula in negative reinforcement or responses to aversive stimuli (such as pain), stimulation of the lateral habenula results in a reward decrease as measured by sucrose self administration (Friedman et al., 2011).

Pain and addiction are considered to be at the opposite ends of the reward-aversion spectrum (Elman et al., 2011). A putative role of the structure in addiction has been supported by data relating to increased activity during drug-seeking behaviors (Zhang et al., 2005), and controlling nicotine intake (Fowler et al., 2011). Furthermore, attenuation of dopamine sensitization in the accumbens is observed following treatment with 18-Methoxycoronaridine (18-MC), an iboga alkaloid congener (Taraschenko et al., 2007). Behaviorally 18-MC inhibits morphine self-administration in rats (Glick et al., 2006) through actions on the medial habenula. The issue of addiction and pain are complex, and it is a major focus of research as to whether pain enhances addiction potential given that chronic pain may be considered a 'reward deficit state' (Elman et al., 2011) while opioid addicts have altered pain processing (Ren et al., 2009) and purported to have opioid induced hyperalgesia (Fishbain et al., 2011).

## 4.2. Stress and defensive behaviors

Pain is a stressor, and the habenula, as understood from its relationship with aversive events, acts as a behavioral mediator to stressors. Implications of pain as a stressor are particularly prominent if chronic or repeated (e.g., in migraine). Studies of the medial habenula (MHb) have shown involvement in neuroendocrine and immunological responses to various kinds of stress (Blake et al., 1990). Measures of c-fos expression in primates suggests that the habenula maintains prolonged activation under traumatic stress and appeared to play a role in the process of longterm stress (Kazi et al., 2004). Such data support a function in longterm behavioral alterations after uncontrollable stress (Amat et al., 2001). Habenular influence over other behavioral functions, also appear to be enhanced with higher induced stress levels. For example, habenular lesions in rat shock avoidance experiments showed little differences to sham operated controls, until stress levels were heightened by more demanding tasks, or higher shock levels (Thornton and Bradbury, 1989). Thus, the habenula seems to maintain a role in promoting decision-making and survival driven reactions (Hikosaka, 2010) to aversive stressors that would include pain.

An extension of fear, stress, and anxiety are the resultant defensive behaviors associated with them. Serotoninergic systems have been implicated in defensive behaviors through the lateral habenula (LHb that may differ depended on the 5-HT receptor subtype involved (Pobbe and Zangrossi, 2010)). Habenula lesions eliminate 5-HT increases in the dorsal raphe to inescapable shocks (Amat et al., 2001). Rats subject to swim tests after habenular lesions did not utilize escape behaviors which was not enhanced by an antidepressant nomifensine (despite promoting the escape behavior in control animals) (Thornton et al., 1985). It seems habenula-signaled adaptive behaviors to fear, anxiety, or stress further promote follow-up performance such as escape, removal, or avoidance suggesting that the habenula regulates defensive response to fear and anxiety-related inputs (Pobbe and Zangrossi, 2008). The structure seems to play a significant role in defensive behaviors including present and future avoidance. In the context of chronic pain, fear avoidance is a major problem (Rainville et al., 2011).

#### 4.3. Fear and anxiety

Fear and anxiety also have a significant role in both acute and chronic pain (Ploghaus et al., 1999; den Hollander et al., 2010). The expectation of the pain modulates (usually increases) the pain sensation as well as playing a role in anxiety and phobia (Ploghaus et al., 2003). These interactions are a part of the important adaptive behaviors that lend to the avoidance of pain-causing agents, where fear and anxiety are the emotional mitigators to those behaviors. The habenula link to anxiety has been shown in lesioning studies where habenula efferent pathway damage resulted in enhanced levels of anxiety behaviors in rats (Murphy et al., 1996). The authors postulate that the effects on anxiety related to either a disruption of lateral habenular (LHb) projections to dopaminergic neurons in the ventral tegmentum or to regions high in benzodizepine receptors. Further support is found in maternity studies; sensory inputs from infants or pups modulate anxiety during the postpartum period (Smith and Lonstein, 2008). Zebrafish studies have reported anxiety regulation by the habenula (Jesuthasan, 2011) and habenula efferents in controlling experience-dependent fear response (Agetsuma et al., 2010). Specifically, the dorsal habenula-interpeduncular nucleus-griseum central pathway is critical for the modification of response in an experience-dependent manner. Some have considered the habenula as a "switching board for selection of behavioral strategy to cope with fear and anxiety" (Okamoto et al., 2011). As such it may potentially control a variety of emotional behaviors in chronic pain.

## 4.4. Depression

Pain and depression are frequently co-morbid (Borsook et al., 2007). Functional, chemical and anatomical changes from chronic pain can, in time, alter the sensory system, emotional and motivational systems and result in comorbidity such as depression. These changes, in turn, will affect the reward/aversion process and are plausible contributors to psychiatric disorders that have been seen to develop in chronic pain sufferers (Borsook et al., 2007). Consistently, many therapies for chronic pain and depression overlap (Borsook et al., 2007). Major depressive disorder (MDD), in general, is associated with dysfunction of the central serotonergic system. The principal source of serotonin is in the raphe nuclei in the midbrain. The influence of serotonin (5-HT) manipulation on emotional state and depression patients has been studied through tryptophan manipulation (Morris et al., 1999;

Roiser et al., 2009; Evers et al., 2010). Following tryptophan depletion, habenula blood flow increases significantly in remitted major depressive disorder patients when subject to emotional stimuli (Roiser et al., 2009). The result suggests that in addition to a consistent habenular response to negative feedback, it further shows a specific sensitivity with depressive patients and might play a role in the pathogenesis of MDD. Magnetic imaging studies of the habenula volume in MDD and bipolar disorder suggest that a volume reduction might contribute to the risk of developing or the result of such affective disorders (Savitz et al., 2011). In treatment resistant depression, trials of deep brain stimulation (DBS) have been used in different regions including the major afferent bundle of the lateral habenula, which was reportedly successful in a therapy resistant patient (Sartorius et al., 2010).

## 4.5. Higher level functioning – cognition and prediction errors

A habenular role in cognition can be synthesized from behaviors following dysfunction. Symptoms of altered memory and attention in rats follow from habenula lesions (Lecourtier et al., 2004). These deficits have improved and in some cases declined over repeated testing, a plausible scenario for the habenula having multiple roles in cognition. In human populations, schizophrenia patients report deficits in utilizing feedback to promote appropriate problem-solving skills and learning. This is consistent with the habenular activity and dopamine damper to negative feedback as a way to guide follow-up responses. In human studies alteration of habenula activity is reported in schizophrenia patients that have altered processing to negative outcomes (Shepard et al., 2006). Lacking this activity through a limited functioning habenula seems to promote feedback-processing deficits in schizophrenia patients (Shepard et al., 2006).

Prediction error is a theoretical signal promoting learning by encoding midbrain dopamine neurons to inform the rest of the brain of expectancy and outcome mismatch (Schultz, 2010). The relationship between habenula and error evaluation has been studied in both animals (Shepard et al., 2006; Ji and Shepard, 2007; Matsumoto and Hikosaka, 2007) and humans (Ullsperger and von Cramon, 2003). It is thought that mesencephalic dopaminergic neurons are inhibited by the habenula through glutamatergic afferent input onto GABAergic neurons in the VTA (Omelchenko et al., 2009; Brinschwitz et al., 2010) and SN (Christoph et al., 1986). When expected rewards are not received or negative feedback is solicited (Christoph et al., 1986), the habenula fires through the emotional system to reinforce behavior avoidance. Supporting data are found from electro-stimulation of habenula where there is a substantial 80-95% dopamine decrease (Ji and Shepard, 2007), and in lesion studies where dopamine levels show an increase (Nishikawa et al., 1986). Detection likely occurs from dopamine levels in the rostral cingulate motor area (rCMA) and reward values are associated with the neural pathway controlling the dopamine system, the pallidus-habenula-dopamine pathway, relying on a combination of stimulus reward pairing and abstract inference as the mechanism for determination (Bromberg-Martin et al., 2010). It seems plausible that neuronal pathways excited during pain stimulation would similarly be filtered through a negative reward analysis system. Regions involved in prediction errors for aversive events have been reported, but the habenula was not (Ploghaus et al., 2000). However, the relationship of pain and reward circuitry, noted in a report from our group (Becerra et al., 2001) remains an area of intense interest and involves structures including the nucleus accumbens. More recent human studies (see below - imaging the habenula) have evaluated negative prediction errors (Salas et al., 2010). The issue of error detection and chronic pain may be considered in light of interoceptive behaviors (Ray and Slobounov, 2002) that may be altered in chronic pain as a result of alteration in anterior insula and cingulate dysfunction (Baliki et al., 2006; Coen et al., 2009).

## 4.6. A model for habenula's interactions in chronic pain

Conceptually, it is useful to consider functional features of the habenula in the context of interactions between its afferent and efferent connections which, based on preclinical data, suggest some form of functional loop. Fig. 3 is a model of alterations in habenula functional loops in chronic pain. As noted in Fig. 2, afferent inputs to the lateral and medial habenula send efferents to brainstem regions. These in turn feed back onto many of the afferent pathways. These can be divided into analgesia/hyperalgesia, sensory-motor, stress, and reward/aversion habenula loops. Each loop or circuit relates to basic functions of the habenula that are altered in acute and chronic pain (see Fig. 3). As noted in the figure, in the chronic pain condition there are increases or decreases in these functional circuits (e.g., reward loop diminishes and stress circuits increase). The model, derived from preclinical data showing increased activation (electrophysiology, fos) in acute pain, and increased metabolism in chronic pain (see Fig. 3) is expressed in terms of expected functional activity in the habenula. Clearly, while the structure is not the epicenter of altered function in chronic pain (since pain is a distributed function), it would seem that it could play a significant role in sensory, emotional and modulatory processing of pain.

#### 5. Analgesics and the habenula

Early preclinical studies indicate that the habenula is involved in analgesia through direct electrical stimulation (Cohen and Melzack, 1993). While many brain structures are involved in analgesia (e.g., PAG and cingulated), there is growing evidence that the habenula, too, plays a role in analgesia through direct effects on neurotransmitter systems present in the structure or secondary effects, say for example, by enhancing frontal (cortical and subcortical) inputs into a structure where treatments may alter these inputs and drugs may enhance brainstem processes well known to play a role in chronic pain. Overall, the structure is modulated or directly modulates systems or pathways involved in pain processing including operidergic, seronintergic, dopaminergic, and noradrenergic.

## 5.1. Opioidergic systems

Opioids are present in the habenula. Indeed, some of the highest levels of  $\mu$  receptor RNA in the brain have been reported in the medial habenula (Zastawny et al., 1994; Bunzow et al., 1995). Morphine acts directly on habenula neurons to produce analgesia (Zhou et al., 1981; Cohen and Melzack, 1985). Such information clearly implicates an analgesic effect that is observed when morphine is directly injected into other brain structures including the cingulate cortex (LaGraize et al., 2006) and the periaqueductal



## B: Functional Loops and Acute Pain

C: Functional Loops and Chronic Pain



**Fig. 3.** Conceptual model of habenula circuits in chronic pain. (A) Normal condition. The figure shows habenula circuit-loops that confer potential functions of the structure. The formulation of the loops is based on known afferent outputs to structures that may have connections to other brain regions that send efferents to the habeula. Thus, four basic loops are shown: (1) *analgesia/hyperalgeic loop* – reflects the integration of outputs from the lateral habenula to regions of the brain that have known pain inhibitory or pain facilitatory action; (2) *reward-aversion loop* – outputs from the lateral habenula to the VTA through dopaminergic process and connections to the frontal cortex; (3) *stress loop* – medial habenula projections to the IPN send afferents to the hippocampus a region involved in a number of processes including stress response (but also memory); and the (4) *sensory-motor loop* – from the lateral habenula connections from the SNc project to basal ganglia regions; the complexity of function may include sensory, emotional and cognitive features and not simply sensory-motor integration. (B) Acute pain. Under acute pain conditions he activity of the habenula is shown to increase all circuits. This is a homeostatic response to a reversible physiological stimulus. (C) Chronic pain. Under chronic pain conditions loop homeostasis is disrupted. For example, the chronic pain state is an aversive state that is a hedonic deficit state where reward systems become dysfunctional; outputs from the pain modulator regions (normally inhibit pain) may now facilitate pain and thus signals form the periphery are enhanced. Stress loop may show enhanced drive with consequent alterations in the hippocampus that may include evoked pain under acute pain conditions, and displays maximal drive in chronic pain conditions.

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gray (Carstens et al., 1988; Bernal et al., 2007). While it can inhibit and facilitate excitatory synaptic transmission (Hashimoto et al., 2009), how it affects analgesia through direct action on the habenula is unclear, but assumed to be through activation of brainstem modulatory systems. In regard to the latter, such a drive could potentially act on facilitatory or inhibitory systems through serotonergic systems as has been shown in animal models of chronic pain (Dogrul et al., 2009). In addition, a complex interaction between opioids and dopaminergic systems may disrupt pathways such as efferent systems that include the habenulo-interpeduncular pathway that may modulate a dopaminergic mesolimbic pathway. Levels of other opioids including nociception in the habenula (Schulz et al., 1996; Florin et al., 2000) suggest alternate functions of opioid induced neural processing. Furthermore, at least what may be deduced from other drugs of abuse is that chronic use results in degeneration in axons from the lateral habenula to midbrain (including the SN, VTA and raphe) (Ellison, 2002). Thus opioids may modulate habenula function and if given chronically may alter habenula-brainstem connectivity.

## 5.2. Dopaminergic systems

Dopamine is involved in reward processing (Wise and Rompre, 1989; Schultz, 2007) and also in pain and analgesia (Wood, 2008; Lapirot et al., 2011; Sarkis et al., 2011). Given the projections of the lateral habenula to dopaminergic nuclei (Goncalves et al., 2011), some of these inputs are inhibitory on midbrain dopaminergic cells (Balcita-Pedicino et al., 2011); specifically glutmatergic habenula neurons act on inhibitory GABAergic cells (Brinschwitz et al., 2010). Consistent findings show electrical stimulation of the LHb results in inhibition of neural activity of dopamine neurons (Matsumoto and Hikosaka, 2007). The effects of dopaminergic drugs on the habenula have also been evaluated. The dopaminergic agonist apomorphine produces excitation of individual LHb neurons (specifically in the lateral division of the LHb) (Kowski et al., 2009). There is also a complex regulation of habenula involvement in dopamine and reward: neurons in the LHb are known to encode reward-related signals that are opposite dopamine neurons; thus, LHb neurons are inhibited by reward and sensory stimuli predicting reward and excited by reward omission (Matsumoto, 2009). In addition, the habenula affects prefrontal and NAc dopamine release (Lecourtier et al., 2008). Thus, the habenula is intricately involved in reward processing thorough control of dopaminergic neurons in the forebrain and brainstem (Matsumoto and Hikosaka, 2007; Matsumoto, 2009; Bromberg-Martin and Hikosaka, 2011).

## 5.3. Noradrenergic systems

Peripheral (superior cervical ganglionectomy) and central (striatal) lesions result in increases in norepinephrine in the habenula (Gottesfeld, 1983). The former produced increases in the LHB and the latter in both the LHb and MHb (Gottesfeld, 1983). Brain NA systems are activated by stress (Morilak et al., 2005). High levels of serotonin receptors subtypes (5-HT5) are reported to be present in the medial habenula of wild type (Waeber et al., 1998). Taken together, the effects of SNRIs in the treatment of chronic pain (Wright et al., 2011) may reflect these drug effects on the habenula.

#### 5.4. Serotoninergic systems

Both human and animal (Meng et al., 2011) models of habenula stimulation seem to reverse depression, implicating the serotonergic systems. Supporting data have shown excitatory amino acids in the lateral habenula–dorsal raphe pathway (see Fig. 2) are involved in the regulation of striatal 5-HT release (Kalen et al., 1989). In addition, fluoxetine, a selective serotonin reuptake inhibitor (SSRI) reduced metabolism in the habenula (Shumake et al., 2010). The potential mechanism of this may be through local serotonergic receptors, notably (5HT-B) (Kinsey et al., 2001), 5-HT2C (Pompeiano et al., 1994) and 5-HT5 which is similar to the 5HT1D family (Plassat et al., 1992). Thus pharmacological agents that are effective in chronic pain may also contribute to their analgesic action via habenula serotonergic systems.

# 5.5. Other habenula neurochemical systems that may be related to pain processing

A number of other neurochemical systems are implicated in habenula function. These include the NMDA receptor antagonists which decrease activity in the habenula (Weissman et al., 1989; Eintrei et al., 1999); calcitonin gene related peptide CGRP (Skofitsch and Jacobowitz, 1985) as is substance P (Neckers et al., 1979) which is present in high levels in rat habenula. However, the involvement and distribution of these peptides is complex; for example, NK-1 and NK-3 receptor agonists excite habenula neurons and electrophysiological recording suggest that these receptors are found on different populations of neurons in medial habenula (Norris et al., 1993; Waeber et al., 1998). A cholinergic pathway from the medial habenula to the IPN has been defined (Fasolo et al., 1992). A putative role in pain is unclear but may relate to addictive propensity for nicotine (Fowler et al., 2011) and it is well documented that chronic pain and smoking are frequently comorbid.

#### 5.6. Habenula and anesthesia

In addition to analgesics, the structure may also contribute to the underlying effects of anesthetics. Anesthesia results in loss of sensation with or without loss of consciousness and may also affect pain systems. Interestingly, a number of reports show the involvement of the habenula in anesthesia. For example, the anesthetic althesin a steroid anesthetic produced increased metabolic activity in the habenula that is inhibited by lesioning inputs from the stria terminals (McQueen et al., 1984). Thiopental also increased habenula activation in rats exposed to a noxious stimulus and the authors postulated that it may have a role in pain processing (Archer et al., 1995). So while a specific role is not understood, the habenula's interaction with anesthesia seems to relate to its role in analgesia.

# 5.7. Habenula deep pain stimulation – potential therapy for chronic pain

Both animal and human reports of lateral habenula stimulation provide a potential future therapeutic avenue for this approach in chronic pain patients refractive to other treatments. In studies on depression, deep brain stimulation (DBS) has been used in animal models of depression (Meng et al., 2011). In a report of a depressed patent refractory to other treatments DBS (see Fig. 4) reportedly produced remission (Sartorius et al., 2010). In addiction, DBS of the lateral habenula also resulted in decreased drug or reward seeking behavior (thought to be through increases of glutamatergic drive to the VTA) (Friedman et al., 2010, 2011). Given the overlap of neural circuits in depression, addiction and pain (Borsook et al., 2007; Elman et al., 2011), the issue of whether DBS of the habenula produces pain relief in chronic pain models needs to be studied, not only to better understand the role of the structure in pain processing but also as a potential therapy.

Few studies have evaluated analgesic responses of the habenula in chronic pain models. It is likely that drugs that target the



**Fig. 4.** Human habenula stimulation. The transversal and coronal view from fluorodeoxyglucose positron emission tomography (FDG-PET) imaging of the metabolic effects from LHb deep brain stimulation of a treatment resistant depression patient is used with permission (Sartorius et al., 2010). Note the regional correspondence to the anatomical image in Fig. 1.

habenula may provide a useful model for chronic pain because of its integrative role in pain and analgesia. Perhaps, rather than a role in pain sensitivity or intensity, it is more likely to play a role in chronic pain conditions including migraine. Thus, it may be an ideal "light-house" or indicator of the potential effects of analgesics on chronic pain. This is particularly salient given new insights such as activation of inhibition of the rosto-ventro-medial medulla in inhibiting neuropathic pain (De Felice et al., 2011) and the habenula's modulation of these regions as well as issues related to tonic pain (King et al., 2009).

## 6. Functional imaging of the habenula

As noted in the Introduction, functional markers of habenula to pain activity include measures of neuronal markers (e.g., c-fos), electrophysiology (Andersen and Dafney, 1983; Hua et al., 1998), and metabolic markers (Paulson et al., 2005, 2007). More recently the use of imaging techniques such as functional magnetic resonance imaging (fMRI) has been applied in humans in nonpain paradigms.

#### 6.1. Functional imaging of the habenula in animals

Unlike most neuroimaging of pain, the animal data have preceded the human data. Pain and analgesic functional imaging studies have been performed in animals (Borsook and Becerra, 2011) but few have reported habenula activation. Studies employing imaging measures in pain models suggest prominent activation in the habenula (Fig. 5A). Using a marker of neuronal activity (99m)Tc-HMPAO, two studies report activation in the habenula. In a model of diabetes-induced neuropathic pain, decreased activation (compared with control animals) was seen in animals shown to have hypersensitivity to pain (Paulson et al., 2007). The conclusion of this study was that the habenula contributed to modulation (inhibition of pain) since the midbrain displayed a similar decrease in activity (Fig. 5B, top row) in contrast to activation in other regions particularly those encoding pain intensity (somatosensory cortex, ventrobasal thalamic nuclei). In an earlier study from the same group, spinal cord damage produced similar changes in the habenula (Paulson et al., 2005) (Fig. 5B, bottom row).

## 6.2. Functional imaging of the habenula in humans

While functional imaging techniques have advanced in humans with higher field systems (3 T and 7 T for fMRI), there are challenges imaging the habenula because it is a small structure, approximately  $3 \text{ mm} \times 3 \text{ mm} \times 3 \text{ mm}$  in humans. Current fMRI



**Fig. 5.** Activation in habenula to pain. (A) Fos activation. Fos increase with pain representative digitized image of the LHb, is used with permission (Smith et al., 1997). *Key*: 3V = third ventricle, PVp = paraventricular thalamus, and fr = fasciculus retroflexus. (B) 2-DG measures of chronic pain activation. Spinal cord injury-induced activation in the rat habenula, is used with permission (Paulson et al., 2005); in the upper right corner contrast with a control rat to the left, and in diabetic neuropathic pain, is used with permission (Paulson et al., 2007); pictured on the bottom right versus a control rat habenula pictured to the immediate left. (C) fMRI activation to pain in humans.

Coghill et al. (2003) with permission.

imaging protocols acquire images with a resolution of 3–5 mm. This is barely large enough to cover the habenula with one voxel. Accordingly, it is necessary to optimize current protocols to focus in the area. However, defining its location in imaging studies is made somewhat easier by its alignment to the third ventricle as well as its proximity to the pineal gland in the horizontal plane. A few functional imaging studies have reported activation in the habenula using either fMRI (Ullsperger and von Cramon, 2003; Roiser et al., 2009), or positron emission tomography (PET) (Morris et al., 1999; Sartorius et al., 2010). In a study by Morris et al., the effect of altering tryptophan (a precursor of serotonin) levels in patients with affective disorders was evaluated. Since the habenula projects to the raphe nucleus, the study took advantage of its ability to influence the activity of serotonergic neurons in the raphe nuclei and modulate release of cerebral serotonin. Subjects performed simple tasks (verbal fluency and word repetition) under these conditions during PET scans. Results show that the extent of mood change following tryptophan depletion is related to the covariation of activity between two serotonergic sub-cortical nuclei, the habenula and dorsal raphe (an increase drive to these areas with less tryptophan). Highly correlated activity between these structures was present only in subjects with high post-depletion depression ratings (Morris et al., 1999).

In an fMRI study monitoring habenular function for error and reward prediction, data were acquired during informative and non-informative feedback stimuli amid a task involving subject decisions (Ullsperger and von Cramon, 2003). The aim of the study was to determine specific regions of brain activity relating to negative and positive feedback. The expectation was a larger hemodynamic activity of habenular region on errors with negative feedback and a lower hemodynamic activity on correct responses with positive feedback. Positive feedback raised hemodynamic activity in the ventral striatum (nucleus accumbens) and the putamen, negative feedback activated the rCMA, the inferior anterior insula, and the epithalamus (habenular complex). Functional connectivity analysis has shown the direction of interaction between amygdala and VTA/SN, determining the habenula as the mediator during error detection (Ide and Li, 2011). A review of the literature suggests habenula activation may be present some human fMRI reports on brain activation by pain although not specifically reported (Fig. 5C). Based on the animal literature of increased activation in acute and chronic pain, we provide a summary of extpected activation levels within the structure for fMRI activation for acute and chronic pain (Fig. 5) and to be reversed following analgesic administration (not shown).

In a habenula targeted deep brain stimulation (DBS) in a patient who had suffered from treatment resistant depression, localization of neurological changes over time were made by co-registering PET T1 and T2 and subtracting for a difference image. This image and a post-operation CT image were both co-registered to a high resolution T1 MRT scan with the same transformation parameters (Sartorius et al., 2010). Metabolic effects can be seen in the fluorodeoxyglucose positron emission tomography images in Fig. 4. Although a small structure, these and other fMRI studies (D'Ardenne et al., 2008; Li et al., 2008) thus define that habenula can be imaged in humans and that the approaches may have important implications for pain and analgesia (viz., error and reward, depression, etc.) because of the putative role of the structure.

Under separate fMRI studies where pain itself was the research topic, activation that is likely to overlap the habenula can be seen in many of the resulting images. While determination of activation for such a small region cannot visually be determined with 100% accuracy, the data are nonetheless convincing and warrants further exploration with more robust imaging methods. A habenular response to pain could help devise a much-sought quantitative measure for the pain experience of an individual, removing subjectivity that can interfere with diagnostic and pain treatment. It has the potential to lead to a determinant that distinguishes an injury or disease that will lead to chronic pain. It would seem further understanding of the function in humans through neuroimaging would provide exciting new information on brain systems involved in pain and analgesia.

#### 7. Conclusions

The habenula is involved in numerous behavioral functions that are implicated in pain processing (viz., cognition, addition, aversion, learned helplessness, and reward, Hikosaka, 2007; Matsumoto and Hikosaka, 2007; Frahm et al., 2011; Friedman et al., 2011; Paul et al., 2011; Li et al., 2011; Paul et al., 2011). Through various loops, habenula outputs modulate the inputs from forebrain structures and thus the structure may modulate the interactions between frontal brain regions involved in cognitive, reward, and various brainstem functions including pain modulation. With respect to the latter, these outputs to brainstem regions modulate sensory gating (Ellison, 1994), protective behaviors (Pobbe and Zangrossi, 2010) and endogenous tone in response to pain and may be thus construed as involved in stress evasion (Hikosaka, 2010). However, the role of the habenula in chronic pain in the human condition is yet to be determined. Given the insights of this structure on conditions that are seen with chronic pain including addiction (Fowler et al., 2011) and depression (Sartorius et al., 2007), abnormal functioning in the habenula may have a significant role in the chronic pain state. In this chronic pain, abnormal function of habenula may contribute to pain behavior through dysfunction of "intrinsic central process that coordinates various selective functions (including perceptual, visceral, and reinforcement processes) into a global dysfunctional state" (Ikemoto, 2010). The use of neuroimaging should provide new insights of the habenula in the human chronic pain condition.

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