Translating the Habenula – From Rodents to Humans

Supplemental Information

ANALGESIA

Rodents

Very early animal studies have shown that electrical stimulation of Hb in rats produces analgesia in the formalin test, involving notably opioid mechanisms (1, 2), and a recent gene knock-down experiment identified RSK2, a Ser/Thr kinase responsible for the Coffin-Lowry syndrome, as a mu opioid receptor signaling effector contributing to morphine analgesia in MHb (3). Preclinical evidence is growing to show Hb activation under acute and chronic pain conditions, with reversal upon administration of analgesic drugs (extensively reviewed in (4)). Altogether, behavioral pain research in rodents led to the view that Hb acts as an integrative hub for pain control, regulating nociceptive processes, as well as emotional and cognitive aspects of persistent pain that involve defensive behaviors, deficient reward and altered mood (4).

Humans

Shelton *et al.* conducted the first fMRI measures of human Hb activation under acute experimental pain (5). Subjects were administered noxious heat stimuli on the left foot while scanned in a 3T MRI. Brain activation mapping showed cortical, subcortical and cerebellar signals, among which well-localized and bilateral habenula activation was detected in both early- and late- stimulation phases. Partial correlation analysis further showed significant connectivity between periaqueductal gray (PAG) and Hb, as well as putamen and Hb blood oxygen level dependent (BOLD) signals, thus incorporating Hb activity into pain processing functional networks. Finally, probabilistic tractography revealed afferent (putamen) and efferent

(PAG) structural connectivity fully matching our current knowledge of Hb anatomical circuits in rodents (5).

A further study by the same group investigated resting-state functional connectivity (rsFC) in pediatric patients with complex regional pain syndrome, using MHb and LHb as seed regions (6). In healthy controls, Hb functional networks largely overlapped their previous structural connectivity. Interesting to note is that Hb rsFC also matched Hb circuitry description in animal research to a large extent, demonstrating for example MHb functional connectivity with IPN, NAc, CPu and several frontal areas, or LHb onto frontal cortex, subcortical and brain stem structures. In addition, Hb-centered rsFC analysis of normal subjects revealed previously undescribed connections for both MHb (thalamus, insula, amygdala, anterior cingulate cortex and rostro ventromedial medulla (RVM)) and LHb (PAG and RVM) relevant to pain processing. Analysis of normal subjects, therefore, lends support to the translational validity of rodent studies, and also highlights the higher complexity of Hb networks in humans. In this study, Hb rsFC was drastically modified in chronic pain patients (6), with reduced overall connections to the rest of the brain, and connectivity patterns limited to a few brain structures, including the thalamus, locus coeruleus and dorsal raphe nuclei (DRN). The overall reduction of Hb rsFC with forebrain areas integrating motor, affective and cognitive aspects of pain was proposed to support part of the symptomatology (6), and likely contributes to the broader picture of pain as a major deficient reward/enhanced anti-reward syndrome (7).

Supplemental References

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