Lateral habenula: Significance in pain and depression

Dear Editor,

The habenula is a tiny structure situated bilaterally in the posteromedial aspect of the dorsal thalamus, situated on the floor of the third ventricle above the pineal complex [Figure 1]. Habenula processes many functions like olfaction, ingestion, mating, endocrine, reward function, and addiction. Recent research has demonstrated that habenula also mediates pain, analgesia, and depressive symptoms caused due to them.[1]

Habenula receives direct and indirect afferent signals for processing via lateral hypothalamus which is sent via spinal cord afferents (lamina I of the spinal dorsal horn and trigeminal nucleus). Habenular area has been found to be dense with μ-opioid receptors with relatively lesser density of delta and kappa opioid receptors. Direct habenular morphine injections in animals provided relief to pain induced in them.[2]

When pain persists for more than three or six months, it is referred to as chronic pain. In acute pain, habenula processes all signals received from spinal cord via voltage gated calcium channels. When the pain persists i.e., becomes chronic either due to inadequate management or non-addressal of the cause mediating pain, the circuitry of spinal cord, and habenula gets disrupted thereby affecting the homeostasis. Due to this the release of dopamine and serotonin is affected which thus manifests as depression in patients suffering from chronic pain.[3] The increased activity of habenula due to continuous firing and disrupted homeostasis eventually leads to hyperalgesia which is often seen in patients seen with chronic pain. The continuous noxious stimulus leading eventually to chronic pain also leads to changes in function and interpretation of structures of brain like cerebral cortex, hippocampus, amygdala, thalamus, ventral tegmental area, and dorsal raphe nucleus which also manifests in the form of emotional changes and depression. This possibly is the explanation why a drug which facilitates serotonin, dopamine and noradrenaline reuptake inhibition helps in managing chronic pain.

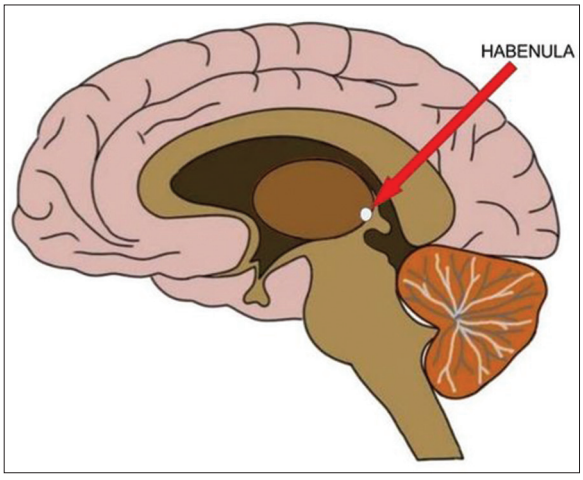

Figure 1: Image showing location of habenula at the floor of third ventricle. (Image reproduced with permission from: "https://www.neuroscientificallychallenged.com/")

Li Y *et al*. used chronic constriction injury model of sciatic nerve in experiments involving rats and created a neuropathic pain model.[4] At 28 days they observed increased activity of lateral habenula nucleus and decreased activity of dorsal raphe nucleus leading to reduced serotonin levels. Authors concluded that pain when chronic leads to depressive episodes owing to disturbances becomes in hormonal milieu mediated by lateral habenula through dorsal raphe nucleus.

In another study by Li J *et al*., rats were injected in hind paw with formalin to induce chronic pain and depression (based on a model) and were compared with control.[5] The experimental group of rats showed higher discharge from lateral habenula in the form of increased percentage of c-Fos–positive cells compared to control and the discharge was inhibited by intraperitoneal injection of clomipramine.

To conclude although role of lateral habenula and its connections to dorsal raphe nucleus and other areas in manifestation of pain and associated depression is understood in experimental animal studies, further research needs to be done so as to extrapolate this important association in preventing chronic pain and depression in susceptible patients by starting medications and therapies up front.

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Conflicts of interest

There are no conflicts of interest.

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References

1. Shelton L, Becerra L, Borsook D. Unmasking the mysteries of the habenula in pain and analgesia. Prog Neurobiol 2012;96:208-19.

2. Shelton L, Pendse G, Maleki N, Moulton EA, Lebel A, Becerra L, *et al*. Mapping pain activation and connectivity of the human habenula. J Neurophysiol 2012;107:2633-48.
3. Guang-Fen Z, Guo J, Jian-Jun Y. The lateral habenula: Role in chronic pain and depression. Transl Perioper Pain Med 2020;7:271-8.
4. Li Y, Wang Y, Xuan C, Li Y, Piao L, Li J, Zhao H. Role of the lateral habenula in pain-associated depression. Front Behav Neurosci 2017;11:31.
5. Li J, Li Y, Zhang B, Shen X, Zhao H. Why depression andpain often coexist and mutually reinforce: Role of the lateralhabenula. Exp Neurol 2016;284(Pt A):106-13.

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