Habenula – the role in depression

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SUMMARY: Major depressive disorder is common mental disorder nowadays. It affects both men and women, especially when 25-44 years old. Person with MDD cannot function normally and experience typical symptoms of major depression such as psychomotor and emotional retardation. Recently, habenula has emergead as an important brain structure in many peripheral and cognitive functions like prediction of reward information, stress, pain processing and depression. On the one hand various studies showed that medial habenula has crucial role in motor function, primary reinforcement and hedonic state, while on the other hand the importance of lateral habenula lies in memory, reward prediction and depression. Although, most of the experiments with habenula were performed on mice, they built an important foundation for further research.

KEYWORDS: habenula, depression, immunohistochemistry, neuroanatomy

The word "habenula" originates from the Latin habena, meaning rein.[1] In general, the habenula is a relatively small nucleus situated in the diencephalon. Little is known of the physiological functions of habenular nuclei but it has been suggested that the nuclei participate in sleep mechanisms, learning and memory, outcome prediction, maternal behavior, stress[3]. There are several studies that have shown increased habenular activity in patients suffering from depression.

Neuroanatomy

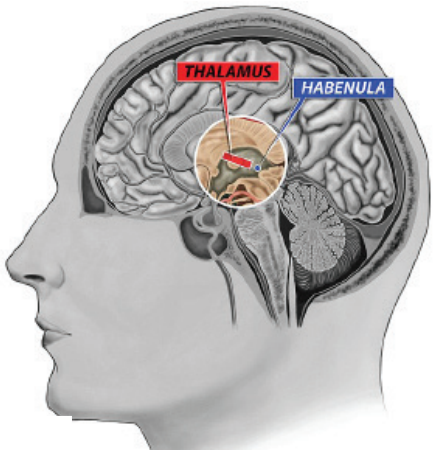
The habenula is a phylogenetically old brain structure and has evolutionarily been very well preserved ever since the amphibian era. It is a part of the epithalamus and it is divided into the lateral (limbic) and medial (motor) part. The medial habenular nucleus sends efferent fibres to the interpeduncular nucleus (IPn) of the midbrain and to the pineal gland. It receives afferent fibres from the septofimbrial nucleus interfascicular nucleus of the ventral tegmental area (VTA) as well as from the locus ceruleus.1 Most of the pathways end in the lateral nucleus. The lateral habenular nucleus sends fibres to the raphe nuclei and the adjacent reticular formation of the midbrain, to the pars compacta of the substantia nigra (SNc) and the ventral tegmental area (VTA) and to the hypothalamus and basal forebrain.[11] Furthermore, the lateral habenula is a powerful monoaminergic modulator and functions as a relay station for various inputs.[7] According to a research study at Harvard University, connection tracts to the habenula come from caudate, putamen, hypothalamus, frontal cortex and NAc – these are afferent fibres. As opposed to that, efferent connections are found with IPn, periaqueductal gray (PAG), Raphe, VTA, SNc.

Physiology

Although little is known about the physiological functions of the habenular nucleus, scientists are certain that it is a centre of integration of diverse visceral and somatic afferent paths, such as pain processing, voluntary activity, motor function, sleep mechanism, stress responses and learning. [11] For example, researches demonstrated bilateral habenula activation during noxious heat stimulation which proved its function in pain processing.[2] Hyperactivation of the habenula causes anhedonia (inability to experience pleasure from activities usually found enjoyable), extensive change in motivation and social interaction. For instance, social isolation induced c-fos expression in rat habenula and temporary inactivation of the habenula reduced social play behaviour in rats. It may be concluded that neuronal activation in the habenular nucleus is reduced after social interaction. Moreover, there is a correlation between the lateral habenula (LHB) and reward processing. Also, coherence in theta waves between the LHB and the dorsal hippocampus suggests a role in spatial memory.[9]

Learned negative motivational value of stimuli and prediction of reward information

Humans and animals have the ability to predict future events. In humans, the habenula has shown to code negative emotional value attributed to a cue; the response profile of the right habenula to increasingly aversive cues was linear suggesting a role of the habenula in conditioned behavior. This appears to be lateralised in the right habenula. However, researchers aren't sure whether that's due to the shocks (negative cues) having been administered to the left forearm.[10] At the Laboratory of Sensimotor Research, researchers performed an experiment on monkeys. Two monkeys were taught to choose between different types of cues that carry information about a reward. Then they received either a big or a small reward based on the information carried by the cue they had chosen. During that test they were recording the neuronal activity in the lateral habenula. They found a subpopulation of neurons in the lateral habenula that signalled both types of prediction errors: excitation for negative prediction errors and inhibition for positive ones. Moreover, the



activity of neurons depends on the value of the cue. However, it seems that the effect of habenular activation isn't the decision-making itself but a reaction to an already made decision.[5]

Pain processing

While habenular function in pain processing has been shown in the animal literature, there are several studies that report habenular activation in response to noxious stimulation in humans. According to a research study at Harvard University, the habenula is included in processing pain information. Seven out of eleven subjects reported pain during the noxious heat stimuli. Individual subject maps showed the habenula activation in 10 of the 11 subjects. Also, they noted an afferent connection from the putamen, a basal nuclei involved in pain processing. Furthermore, the habenula has an efferent projection to PAG, through which it could affect pain modulation.[2]

Stress

Learned helplessness is based on the concept that some individuals, who perceive their environment as out of their control and unmanageable, lose the ability to cope with future stressors. That loss can result in anxiety and depressive symptoms. The researchers from New York hypothesized that the metabolic dysfunction in habenula could be related to helpless behaviour. Because the study was conducted on rats, it is not a very favourable model to be applied on humans. They examined metabolic signatures associated with the depressive-like behaviour induced by uncontrollable stress. They identified the habenula and the lateral septal nuclei as central brain structures whose activation during uncontrollable stress leads to helpless behaviour. Over-activation of the habenular and septal neurons has been shown to lead to depression. Furthermore, the lateral septum contains highly interconnected GABAergic projection neurons. Therefore the metabolic increases may result from enhanced excitatory input and glutamate recycling with recurrent inhibitory collaterals leading to escape deficits causing depressive episodes. The researchers also concluded that habenular hyperactivity reduction through DBS could be utilised as a treatment for depression and proved so in a case.[4]

Social play behaviour

Many studies indicated an important role of the habenula in the processing of positive and negative social information. Imbalance in its activity may lead to several psychiatric disorders. It has been proved that habenula was activated after 24 hours of social isolation in rats and that subsequent social play interaction reduced neuronal activity in the medial parts of the lateral habenula, moreover after 3.5h of isolation 50% of the peak activity was observed. In addition, it has been proved that stressful stimuli enhance neuronal activity in the lateral habenula which leads to decreased activity of dopaminergic and serotoninergic neurons. Thus, the conclusion is that habenula was activated as a consequence of the negative emotional effects of social isolation which may lead to depression. However, pharmacological inactivation of the habenula led to reduced social play behaviour, probably through the depression of serotonin and dopaminergic pathways ceasing positive social behaviour prolongation and solicitation, thus the habenula can encode both positive and negative valence of social behaviour.[7]

Major depressive disorder

Major depressive disorder (MDD), also known as major depression or clinical depression is one of the most prevalent mental disorders. It affects both genders. People with MDD experience psychomotor retardation, loss of emotional expression, depressed mood, sleep disturbance, insomnia or hypersomnia, fatigue or loss of energy, feelings of worthlessness, psychomotor agitation or restlessness. Furthermore, it has a significant potential of morbidity and mortality, contributing to suicide.[13] Recently, the lateral habenula, a nucleus that relays information from the limbic forebrain to multiple monoamine centres, has emerged as a key brain region in the pathophysiology of depression.[8]

The role in depression

The lateral habenula receives projections from the limbic forebrain, making this structure critically positioned to receive information from a number of reward and anxiety relevant structures. Neuroimaging studies have identified increased habenular activity in the depressed state. There are several studies that tried to find correlation between the increased activity in the lateral habenula and depression. A study at Shanghai Institute compared habenular protein (βCaMKII) expression of wild-type control and congenitally learned helpless rats, a model of depression. It was noticed that βCaMKII was significantly upregulated in the habenula of congenitally learned helpless rats. Habenular protein samples increased to 1.86-fold of the control level. Furthermore, immunohistochemically, it was proven that the βCaMKII protein level increase occurred in the lateral part of the habenula. Also, chronic antidepressant treatment with

imipramine caused significant down-regulation of βCaMKII protein in the habenula of congenitally learned helpless rats.8 They also investigated to what extent the change of βCaMKII levels in lateral habenula is necessary to cause depressive behaviour. βCaMKII overexpression also caused anhedonia, evident from a reduction in the preference for the sucrose solution and wheel turning time. GluR1 is a downstream molecular target of βCaMKIIand the inactivated form GluR1Ct delivered into the habenula through viral vectors caused rats with overexpressed βCaMKII to perform normally in stressful conditions.[8] At the Medical University of South Carolina scientists performed an experiment on rats which were stressed by the elevated plus maze and the shock probe burying test. Also, researchers noted inactivation of the lateral habenula supressed stress related behaviour only under conditions of heightened anxiety produced by yohimbine. In addition, the lateral habenula does not appear to directly impact cocaine seeking unless it occurs in the context of heightened anxiety. Using optogenetic stimulation the medial habenula (MHB) has shown to facilitate a hedonic state, whereas the silencing of the MHB caused acute place aversion. Its main efferent target is the interpeduncular nucleus. Thus the MHB is a part of the pathway which regulates hedonic states and motivation and could be a vital part of the circuitry responsible for primary reinforcement.[3]

Conclusion

Considering its numerous connections to the limbic systems and monoaminergic projections it isn't surprising that the habenula has an immense influence on emotions, learning etc. The MHB regulates mood states and primary reinforcement whereas the LHB has been proved responsible for depression, anxiousness, memory, and reward prediction. Results of various experiments show that the habenula is a promising target for the treatment of severe depression, furthermore one treatment-resistant case has already shown progress, however when the DBS was discontinued there was a recurrence of depressive symptoms. However promising the results of the experiments maybe, one must take in consideration that most of them were done on mice and so far no treatment aside from DBS has been proposed.

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Habenula- uloga u depresiji

SAŽETAK: U današnje doba, depresivni poremećaji se javljaju često. Zahvaćeni su i muškarci i žene, osobito u dobi između 22 i 24 godine. Osoba koja pati od depresije pokazuje tipične simptome kao što su psihomotorna i emocionalna zakočenost. Habenula se ovdje pokazala kao važna komponenta te se osim s kognitivnim funkcioniranjem povezuje i s procesima kao što su: predviđanje nagrade, stresnom reakcijom, moduliranje boli. Medijalni dio habenule ima važnu funkciju u motoričkim zadacima i procesiranju ugode, dok lateralni dio pokazuje veću važnost za pamćenje, sustav nagrađivanja i nastanak depresije. Iako je većina istraživanja temeljena na mišjem modelu, ta saznanja predstavljaju temelj za buduće proučavanje.

KLJUČNE RIJEČI: habenula, depresija, imunohistokemija, neuroanatomija