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Review

A *little rein* on addiction

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ABSTRACT

Rewarding and aversive experiences influence emotions, motivate specific behaviors, and modify future action in animals. Multiple conserved vertebrate neural circuits have been discovered that act in a species-specific manner to reinforce behaviors that are rewarding, while attenuating those with an adverse outcome. A growing body of research now suggests that malfunction of the same circuits is an underlying cause for many human disorders and mental ailments. The habenula (Latin for "little rein") complex, an epithalamic structure that regulates midbrain monoaminergic activity has emerged in recent years as one such region in the vertebrate brain that modulates behavior. Its dysfunction, on the other hand, is implicated in a spectrum of psychiatric disorders in humans such as schizophrenia, depression and addiction. Here, I review the progress in identification of potential mechanisms involving the habenula in addiction.

Contents

1. Introduction

The habenula complex has once again emerged as a brain region whose functions are being probed with great enthusiasm. Investigations into the role of this structure have spiked periodically in the past [1–5]. Current interest in its function gained momentum since reports suggesting its likely role in encoding "disappointment" in monkeys were published a decade ago [6,7]. Its name, "the little rein", indicating its small size and shape (habenula is diminutive of *habena* or a rein in Latin) predates the works of Ramon y Cajal. At the turn of 20th century, Cajal used silver chromate staining to describe its anatomy. He was struck by the habenular efferents traversing the interpeduncular nucleus (IPN) multiple times and made note of it in his studies [8]. Cajal's original observations were subsequently reconfirmed using modern microscopy techniques [2]. As has often been the case for so many brain regions, his interpretation of the anatomy of the habenula and the IPN has turned out to be highly accurate and insightful [9].

The habenula complex is a bilateral brain structure located close to the midline, above the thalamus and has at least four subnuclei. It is broadly divided into two anatomically, biochemically, and genetically distinguishable units – the medial and the lateral

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habenula [10]. Its axons traverse the IPN multiple times, which is one of the many unusual aspects of the habenula complex. Its bilateral asymmetry in many vertebrates [9,11–14] and its local microcircuitry [15–17] are two examples that have been the focus of extensive research. The convergence of afferents from the basal and the limbic system and the control of numerous neuromodulators through its efferents have also attracted a lot of attention in recent years resulting in the habenula being compared to a conductor of "an orchestra" modulating behavior, or to "a switchboard" selecting different action modules [18–20]. Though the habenula complex has been implicated in basic functions like sleep and motivation in the past [10,21], more recent formulation is that its normal function is required in the expression of aversive behaviors and in the evaluation of negative outcomes. The dysfunction of different portions of the complex have been associated with different psychiatric disorders including schizophrenia, depression and addiction in humans [22–24]. Comorbidity of one or more of these disorders hints at a possible mechanistic link at the circuit level. Among the two sub-divisions of the complex, the lateral habenula has received most attention as a center that computes reward prediction error and regulates monoaminergic release [19,25–28]. The role of medial habenula, particularly in the development of addiction to nicotine and other substances of abuse has also been studied intensely [24,29–33].

2. An ancient set of circuits and their role in modern human conditions

Habenulae have been found in all vertebrates examined, irrespective of cognitive and behavioral sophistication attributed to the animal [12]. Detailed investigation of the organization of these nuclei in the lamprey, a phylogenetially old lineage of vertebrates, has been instrumental in the postulate that these are anatomically conserved vertebrate circuits [27]. This study identified that different populations of neurons from the lateral habenula homolog control both dopamine and serotonin release in lamprey, either directly or via an interneuron. Further, even though inputs from the limbic structures to the medial habenula homolog are not evident, the output neurons project to the IPN. The target of the output hence matches the description of habenula projection neuron target in mammals. Another series of studies using transgenic zebrafish and genetic markers have also addressed the evolution and phylogenetic conservation of the habenular pathways [34,35]. These studies reveal a mediolateral positional change of the habenula complex in such a manner that the ventral and dorsal subdivisions of the habenula complex of fish are homologous to the lateral and the medial habenula respectively in mammals. The authors combined their results with observations in other animals to propose a progression of anatomical changes that explain the current differences in the neuroanatomy of the habenula complex in species across the vertebrate divisions [11,20]. Experiments in both fish and rodents focusing on anxiety and learned fear lends credence to their interpretation of anatomical and functional conservation of the habenula complex in vertebrates [36–41].

Studies researching depression have shown a functional convergence between clinical and animal studies. A proposal to use Deep Brain Stimulation (or DBS) to counter an overactivation of the lateral habenula in treatment resistant depression was initially based on the findings of a clinical imaging study examining the habenulae after tryptophan depletion [42,43]. Subsequently, DBS was applied to the stria medularis or the afferents into the lateral habenula in a clinical trial involving two patients with severe therapy-refractory depression. Both patients showed remission from depressive symptoms during stimulation [44]. Other studies have shown both structural [45] and functional [23] abnormalities in the habenula complex among patients clinically diagnosed as suffering from major depressive disorder compared to matched controls. Studies in rodents in parallel evaluating anti-depressants or the physiology of neurons in a depression model also identify hyperactivity of the lateral habenula as a reason for depressive symptoms [16,46]. Both human and rodent studies thus suggest that activity of lateral habenula is a critical node that regulates mood.

Human and animal studies of response to psychostimulants have also converged independently to support another function of the habenula complex. In humans, this translates to a vulnerability to substance dependence or to drug addiction [47]. Large-scale studies (with a combined total of over 80,000 subjects) of human genome wide associations (GWAS) with nicotine or other substances of abuse have identified polymorphisms at a locus with genes for the nicotinic acetylcholine receptor (nAChR) subunits [48–53]. While studies in rodents implicate the same subunits and the medial habenula-IPN circuit in the development of addiction and/or in the expression of withdrawal symptoms [29,31,54–58].

Among these similarities the phylogenetic differences in bilateral symmetry and relative sizes of habenular nuclei among vertebrates stands out [12,59]. The asymmetry in the neural architecture conspicuous in fish, amphibians, and reptiles, is less clear in mammals and birds. The developmental mechanisms leading to the asymmetric subnuclei and its functional consequences are fascinating and continue to be an active area of investigation [60–64].

Overall, however the examples above among others [65] point towards molecular, genetic and anatomical continuity of the habenula complex as a common vertebrate circuitry that plays a critical role in reward processing and in modulating behavior. As the tools to interrogate the human habenula activity improve further, functional similarities and differences will become clearer [23,66]. Based on current studies though it is reasonable to interpret that the habenula complex functions as a regulator of reinforcing behaviors in humans as well. As a consequence several researchers have placed habenular dysfunction at the epicenter in the pathophysiology of several human disorders [22].

Studies have emphasized examining either one or the other subdivision's function, making the two habenular subdivisions appear as parallel circuits controlling neuromodulators in differing contexts. Newer studies, however, suggest that the two subdivisions share roles and their functions may not be as segregated as it has been assumed in the past. One role, for example, that both lateral and medial habenula seem to modulate is behavior in response to addictive substances such as nicotine, cocaine, opioids, and alcohol. Differences still exist with respect to the type of substance and its direct target among the two subdivisions. In the following sections I focus on reviewing recent studies that implicate the habenula complex in substance use disorder or addiction.

3. The habenula complex and addiction

In the Diagnostic and Statistical Manual of mental disorders (DSM-V), the Substance Related Disorders Work Group recommended use of the term "substance use disorder" and categorized severity of the disorder on a scale, instead of categories like substance abuse, substance dependence and addiction [67]. However, the term addiction is currently used by most studies, often interchangeably with substance dependence (for example [32,68–70]), based on recommendations of previous iterations of the manual (DSM-III and IV). It has also been argued that the term addiction is often more appropriate as a general descriptor [71]. To avoid confusion, in this review I use the term "addiction" instead of "substance use disorder", or use the same terms as used by the authors of a study being referenced.

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