The thalamo-habenula projection revisited

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Abstract

The thalamus is one of the most highly connected hubs of the vertebrate brain, with roles in perception, arousal, navigation, memory and consciousness. One connection that is missing from contemporary maps is a link to the habenula. This link was reported in the early part of the last century, but appears to have slipped into obscurity. Here, I review the evidence for the existence of this innervation and consider the potential roles it could play. In particular, the possibility that this pathway is involved in non-visual responses to ambient illumination, including emotional responses, is examined.

Introduction

An essential step in understanding how any biological system functions is to build a connectivity map of all the elements within the system [1]. This knowledge provides a framework for identifying what types of information is fed into the network and how it is processed. In the case of the brain, a knowledge of connectivity leads to an understanding of how sensory inputs and internal states are processed to affect behavior. To understand the role of the habenula, one would thus ideally like to know all the afferent pathways, internal connectivity as well as output pathways. Considerable progress has been made in recent years in mapping inputs and outputs. An example can be seen in work in the area of reward: information about negative reward is conveyed to the habenula from the globus pallidus [2]; the habenula then stimulates the rostromedial tegmental nucleus [3], which in turn inhibits dopaminergic neurons.

In his article "The structure and fiber connections of the human habenula", published in 1944, Otto Marburg lists a number of brain structures that provide input to the habenula [4]. Some of these, such as the globus pallidus and hypothalamus, are familiar to contemporary neuroscientists who are interested in the function of the habenula in regulating mood or learning. Marburg also noted that the habenula is innervated by fibers from the anterior nucleus of the dorsal thalamus, as well as from the pulvinar. However, these inputs are not mentioned in any recent review. The most widely cited classical references for mammalian habenula connectivity, such as Sutherland [5] and Herkenham and Nauta [6] do not describe an input from the thalamus, nor is such a pathway mentioned in a study of the habenula of rat, cat and squirrel monkey [7]. Given

that the thalamus is one of the most highly connected hubs of the vertebrate brain, this omission is striking. Could it be that there is a whole aspect of habenula function in the human that is currently unseen? Or was Marburg simply mistaken?

Marburg's conclusions were based on the study of three human brains and several sets of sections. The brains contained lesions caused by disease, and the statement about innervation from the dorsal thalamus is based on loss of fibers in a lesioned brain. The statement about innervation from the pulvinar is based on observations of the sections from normal brains, prepared with Nissl and Weigert-Pal staining; these label cells and myelin respectively. Given the lack of direct tracing, it is possible that the conclusions are not valid. One approach to address the question of whether the thalamus innervates the habenula would be to examine other vertebrates, ideally where direct tracing has been performed. Many other sources of input, such as the basal ganglia, are present in lamprey [8], fish [9] and in other vertebrates, reflecting evolutionarily conserved mechanisms in brain development in the embryo. A thalamic input in other vertebrates would suggest that such an input in humans is plausible, although it cannot be ruled out that such a connection has been lost. Another approach would be to assess information from current connectome projects [10], for example those based on reconstruction of serial section electron micrographs. Additionally, functional connectivity can be assessed from brain imaging studies.

The evidence for a thalamus projection to the habenula in various vertebrates

The existence of a thalamo-habenula projection has been proposed in several different species, based on a number of different techniques. In 1961, Cragg published a paper reporting a set of lesion studies in rabbits, with the goal of identifying inputs to the habenula. Within these, 4 lesions were targeted to the thalamus, in particular the anteroventral and reticular nuclei [11]. These caused a pattern of degeneration in the habenula that was distinct from lesions to pre-optic regions, which also sends fibers to the habenula. A limitation of this approach, however, is that damage is not restricted only to the area of interest, but can extend to neighboring structures.

Tracing can provide another approach, as the extent of label can be assessed more directly. Working with the lizard *Gallotia galloti*, Diaz and Puelles injected horseradish peroxidase into the habenula to identify inputs [12]. Within the thalamus, retrogradely labeled cells were found in the nucleus dorsolateralis and in the ventral lateral geniculate nucleus. In the frog *Rana esculanta*, Kemali and colleagues also found that injection of horseradish peroxidas into the habenula led to retrograde label of neurons in the nucleus dorsomedialis anterior thalami [13]. In a shark, injection of the lipophilic tracer DiI into the habenula led to labeling of cells in the dorsal thalamus [14]. In zebrafish, a similar approach was used, and labeling in the nucleus rostrolateralis of the thalamus was seen [9]. A similar projection has been independently confirmed by Zhang et al [15] and Cheng et al [16], although in the former case the thalamic nucleus was suggested to be the eminentia thalami, a structure that gives rise to the bed nucleus of the

stria medullaris [17]. Using a number of criteria to define the thalamus, including position relative to the zona limitans intrathalamica as well as presence of GABAergic neurons, we propose that the innervating nucleus is a part of the thalamus [16], as suggested by Turner et al [9].

The situation in mammals is less clear-cut, although a number of tracing experiments have been carried out. Moore and colleagues examined efferent projections of the lateral geniculate complex in rat using a lectin [18]. Among the large number of projections, some labeled axons can be seen in the medial region of the lateral habenula (see figure 5C of Moore et al). However, it is unclear whether the label originates from the ventral lateral geniculate nucleus, which was the site of injection, or from adjacent neurons. In their experiment to trace efferent connections from the habenula, Herkenham and Nauta injected tritiated proline and leucine into the habenula [19]. Among other targets, label was seen in the ventro-medial thalamus. Although this was taken as evidence that the habenula innervates the thalamus, radioactive amino acids can act as retrograde tracers [20]. Confirmation of the direction of connectivity will require better labeling and imaging, for example with transgenic lines where expression is well-defined. Clearing for three-dimension visualization of the projection in an intact brain would allow also help in determining the precise origin of fibers.

A recent advance in establishing network architecture in the mammalian brain is the mesoscale connectome project in mouse [21]. Here, injections of a virus enabling anterograde tracing with eGFP were made into different regions of the brain. A number of injections were targeted to the thalamus. Of these, eight have

axons labeled in the habenula. A caveat of this approach again is that the injections may have inadvertently labeled cells outside the thalamus proper, so the label may not originate from thalamic neurons, but from surrounding structures such as the hypothalamus or septum. Thus, more precise labeling, preferably with transgenic methods, would be required before the existence of a thalamo-habenula projection in the mouse can be confirmed unambiguously.

In addition to considering anatomical networks, another approach would be to examine functional connectivity. In the 1990s, Biswal et al noted that activity in different region of the human brain can be synchronized in the absence of any activity or overt stimulus [22]. This activity implies connectivity between the regions. Resting state activity is widely characterized using functional magnetic resonance imaging (fMRI) [23], and this method has been used to determine connectivity of the human habenula [24-26]. Earlier studies, which used a 3 Tesla magnet, found functional connectivity with the thalamus. A more recent study with an ultra-high field 7T magnet, which has significantly better signal to noise ratio, has confirmed this connection [26]. This study in fact found that the thalamus has the highest degree of functional connectivity with the habenula. However, functional connectivity does not guarantee direct anatomical connectivity [27,28]. Moreover, the direction of information flow cannot be easily determined given the low temporal resolution of the BOLD signal. There is thus a need to complement fMRI with additional methods of investigation. Diffusion tensor imaging can provide some information about major axon tracts, but has limited resolution.

To summarize, there is strong evidence that the thalamus projects to the habenula in lower vertebrates, but no firm conclusions can yet be made about mammals. We now turn our attention to the function of this projection, for which there is some data in lower vertebrates. First, however, we will briefly review the thalamus, so that potential functions can be viewed in the broad context of what the thalamus is known to do.

Potential functions of the thalamo-habenula projection

There is a long history to the study of the thalamus, especially in mammals, which provides a detailed description of its cytoarchitecture and function in many different species [29]. A striking feature of the thalamus is its importance – lesion of the thalamus can lead to coma or death; in contrast, animals remain alive and can function to some extent despite loss of the cortex [30] (or of the habenula [31,32]). A series of experiments, beginning with degeneration-based tracing and progressing onto the use of labels such as horseradish peroxidase and now with diffusion tensor imaging [33], has shown that the mammalian thalamus forms reciprocal connections with multiple brain regions. There is extensive connectivity with the cortex, as well as connections with subcortical areas such as the amygdala and cerebellum. The position of the thalamus as a major hub is consistent with the broad effect seen with lesions.

The human thalamus contains approximately fifty nuclei. At least five of these, the first-order relay nuclei, receive sensory input. These are the lateral geniculate, medial geniculate, ventrolateral, posterior ventromedial and ventrocaudal, which mediate visual, auditory, tactile, pain and taste processing

respectively. The most highly studied nucleus of the thalamus is the lateral geniculate nucleus [34]. Information from retinal ganglion cells (the driver input) is fed to this structure, where it is subject to modulation by several regions including layer 6 of the cortex [35], superior colliculus, thalamic reticular nucleus, dorsal raphe and periaqueductal gray [30]. The mammalian thalamus can be viewed as a gatekeeper, allowing only certain sensory information to be relayed to the cortex depending on modulatory inputs. Nuclei such as the pulvinar, which receive cortical input and are termed higher-order relays, may function in attention and arousal.

What might the function of a thalamo-habenula projection be? In the zebrafish, a habenula response to light was first reported by Dreosti et al [36], who showed that there is a strong depolarization in the dorsal left habenula to a pulse of light. Subsequent tracing and functional recording by Zhang et al [15] and Cheng et al [16] showed that the dorsal left habenula is innervated by axons from the thalamus, specifically from neurons that extend dendrites into an anterior thalamic neuropil called AF4 [37,38]. This neuropil receives retinal input [37,38]. Burrill and Easter, who first described this neuropil, could not attribute a precise identity to it, and suggested several possibilities including the nucleus accesorius opticus dorsalis. This may be equivalent to the nucleus rostrolateralis that has been extensively described in other fish [39,40].

By two-photon calcium imaging across the whole brain of larval zebrafish exposed to pulses of light of different wavelengths, Qian and Jesuthasan [41] found that AF4 and the dorsal left habenula display a strong sustained excitation

to blue light. Other wavelengths only triggered transient activity in AF4. Zhang et al [15] found that retinal ganglion cells that express *opn4xa* [42], an opsin related to the blue sensitive melanopsin [43,44], innervate AF4. Thus, a defining feature of this nucleus may be its response to blue light. Given this, the thalamo-habenula pathway in zebrafish could mediate non-visual responses to blue light. It may contribute to the preference of larval fish for light over darkness [15] and vertical migration [45] that is evoked by blue light [41], possibly by reducing fear [46].

In mammals, blue light has effects that are independent of visual perception and the circadian clock [47]. In mice, abnormal exposure to light can cause depression-like behavior, as characterized by anhedonia and increased immobility in the forced swim test [48]. In addition, mice exposed to abnormal periods of light have defects in learning. These effects are mediated by melanopsin-expressing retinal ganglion cells (mRGCs) [49], and can be reversed by fluoxetine [48], suggesting an involvement of the neuromodulator serotonin. In humans, blue light has strong effects on mood, arousal and cognitive performance [50], which is again dependent on melanopsin [51]. It also has acute effects on processing of emotional stimuli [52]. Functional imaging shows that blue light causes a response in the thalamus [53], in an area that is proposed to be the pulvinar [54]. Whether there is a response in the habenula remains to be established. Although its small size (~15 – 30 mm^3) [55,56] makes functional imaging a challenge, fMRI has been used to demonstrate a role for the human habenula in reward processing [57] and in depression [58]. It should be possible

to use this approach to determine whether blue light has an effect on the human habenula.

In the mouse, mRGCs project to multiple regions in the brain, including the thalamus, where there are terminals in the intrageniculate leaflet as well as within a field adjacent to the lateral habenula [59]. The mRGC termination field near the lateral habenula has not been investigated in detail. It is not known if this contributes to the habenula response to light, which has been demonstrated in both medial and lateral subdivisions by electrophysiology [60,61]. Intriguingly, the position of this terminal field is similar to that of *opn4xa*-expressing RGCs in zebrafish that appear to drive the habenula response to blue light, i.e. adjacent to the lateral margin of the habenula. This termination zone, which has been referred to as the parahabenular region, includes the anterodorsal thalamic nucleus (AD) [62]. Genes that are expressed in this nucleus of the mouse thalamus include *tcf7l2*, *gbx2*, *prox1, netrin1* and *id4* [63]. Zebrafish has thalamic expression of *tcfl27* [64], *gbx2* [65], *prox1* [66,67], *netrin-1a* [68] and *id4* [69], with the latter two appearing to be expressed in the anterior thalamus, as is the case in mouse [63]. Further work will be required to determine whether zebrafish thalamic neurons projecting to the habenula express markers of the mouse AD, and if efferent connectivity in the mouse AD is similar to that of zebrafish. If so, this would suggest that the thalamo-habenula projection is evolutionarily conserved.

To conclude, experiments in a simple vertebrate – the zebrafish – show that an anterior thalamic nucleus mediates habenula response to ambient illumination.

Given the ability of the habenula to influence mood through its regulation of neuromodulators such as serotonin, it is tempting to speculate that a thalamo-habenula projection provides one route for light to influence mood in mammals. Testing this should be fairly straightforward, and may expand our understanding of the thalamus in mammals and yield insights into how behavior and mood is shaped by simple stimuli from the world around us.

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