Seminars in Cell & Developmental Biology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Seminars in Cell & Developmental Biology

journal homepage: www.elsevier.com/locate/semcdb

Review

The blueprint of the vertebrate forebrain – With special reference to the habenulae

Sten Grillner, Arndt von Twickel, Brita Robertson

Department of Neuroscience, Karolinska Institutet, SE-17177 Stockholm, Sweden

ARTICLE INFO

Article history:
Received 15 August 2017
Received in revised form 16 October 2017
Accepted 23 October 2017
Available online xxx

Keywords:
Lamprey
Evolution
Dopamine
Lateral habenula
Medial habenula

ABSTRACT

The medial and lateral habenulae are conserved throughout vertebrate evolution, and form an integrated part in the forebrain control of behavior together with the basal ganglia, the dopamine and serotonin systems and cortex. The lateral habenula plays a role in the control of dopamine activity in the context of aversive behavior and the converse, a reward situation. These circuits are important for a value-based evaluation of the success of prior actions. The medial habenula is involved in mediating escape and freezing behavior. These structures are reviewed with a focus on the lamprey, belonging to the oldest group of now living vertebrate, showing that most aspects of the habenular structure and function have been conserved throughout vertebrate phylogeny.

Contents

1. Introduction

The forebrain of the lamprey is in many aspects conserved over more than 500 million years and can be regarded as a blueprint for the mammalian forebrain. For instance, pallium, the area corresponding to the mammalian cortex, provides projection neurons to virtually the same targets in lamprey as in mammals (striatum, midbrain, brainstem and rostral spinal cord [1]). Similarly, the basal ganglia have the same intrinsic organization regarding connectivity, transmitters and ion channels expressed. Thus, the striatal subtypes of projection neurons expressing either D1 or D2 dopamine receptors form the origin of the "direct" and "indirect" pathways, which contribute importantly to the mechanisms underlying selection and evaluation of behavior [2–4]. Furthermore, the dopamine neurons project in an almost identical way to that of rodents and also receive the same type of input from different parts of the brain including the lateral habenula [5].

The medial and lateral habenulae are present in all vertebrates extending from lamprey to man [6,7,9]. The habenulae represent an integrated part of the forebrain involved in evaluation of action and control of behavior [7–9]. Both structures can be lateralized (asymmetric) in that the left and the right side contain different functional compartments. This has been well established in lamprey and zebrafish [7,10], but recent evidence suggest that this may also be true in other vertebrates including humans [11,12]. The aim here is to provide a short overview of the lateral and medial habenulae and their role in an evolutionary perspective, with a focus on the lamprey.

E-mail address: sten.grillner@ki.se (S. Grillner).

https://doi.org/10.1016/j.semcdb.2017.10.023
1084-9521/

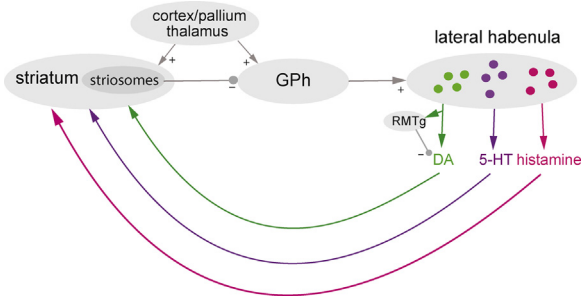

Fig. 1. Circuitry for evaluation. The striosomal compartment in striatum projects to the glutamatergic GPh [3], which targets the lateral habenula. The lateral habenula contains three different compartments in the lamprey, and likely also in mammals, each of which is concerned with the control of the level of activity in either dopamine (DA), 5-HT or histamine neurons. The dopamine neurons receive a direct projection from the lateral habenula and also a disynaptic inhibitory control via the rostromedial tegmental nucleus (RMTg). All three modulatory systems send direct projections back to striatum.

2. The lateral habenula – control of modulator systems

The lateral habenula provides a central hub for the control of the level of activity in three different modulator systems, those of dopamine, 5-HT and histamine [7], all of which provide input to striatum, the input stage of the basal ganglia (Fig. 1). The control from the lateral habenula is individualized in that separate subpopulations of neurons within the lateral habenula target the:

1) dopamine neurons in the lamprey substantia nigra *pars compacta* directly or via GABA interneurons in the RMTg (the rostromedial tegmental nucleus)
2) 5-HT neurons in the ventral mammillary area
3) Histamine neurons in the dorsal and ventral hypothalamic nuclei

In the lamprey, as in mammals, the lateral habenula axons make both direct excitatory connections to dopamine neurons and indirect inhibitory connections via the GABAergic cells in RMTg [7,13,14]. In mammals, the net effect of activity in the lateral habenula on dopamine neurons tends to be inhibitory.

2.1. Lateral habenula – modulation via GPh, basal ganglia and cortex

A subset of neurons of the globus pallidus that projects to the lateral habenula (GPh) are excitatory and tonically active at rest in lamprey as well as mammals, including primates [3,7,8,9,14]. GPh (Fig. 2) in turn receives excitatory input from pallium (lamprey cortex) and thalamus and inhibitory input from striosomes, a subset of GABAergic neurons in the striatum [3,7,8]. For details of connectivity see also Fig. 4.

2.2. Evaluation of action – relation to the lateral habenula

Modulation of the lateral habenula via GPh has been linked to aversive behavior and a decline of dopamine activity in both primates and rodents [8,9,14]. In behavioral experiments in rodents it has been shown that an optogenetically induced increase in activity in GPh is linked to a negative effect on behavior similar to an aversive response, but a decreased GPh activity instead as positive incentive as in reward [8].

It is clear that a value-based evaluation about the success of a given action is critical for the control of behavior in all animals. This may be at a simple level evaluating actions in the context of foraging as in the lamprey, but also at a more advanced cognitive

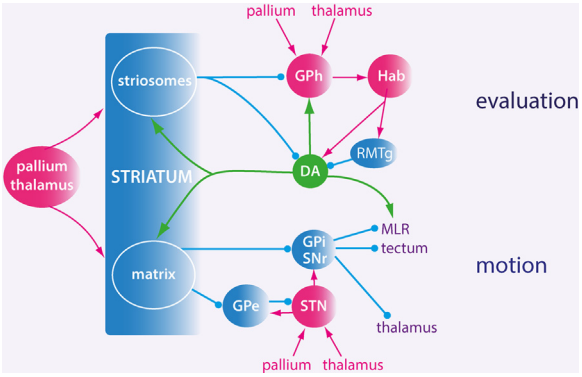

Fig. 2. Overview of the basal ganglia/habenular circuits underlying the control of motion and evaluation. The lower part of the diagram shows that the matrix component of striatum projects to both globus pallidus interna and substantia nigra pars reticulata (GPi/SNr), and further to the brainstem motor programs. In addition, it shows the indirect pathway with GPe (globus pallidus externa) and the subthalamic nucleus (STN). The color code is blue for GABAergic, red for glutamatergic and green for dopaminergic neurons (DA). The evaluation circuit in the upper part of the diagram contains the lateral habenula (Hab) with its projection to dopamine neurons directly and indirectly via the GABAergic RMTg. The lateral habenula has input from the glutamatergic habenula-projecting globus pallidus (GPh), which in turn is excited from pallium and thalamus, whereas it receives inhibition from the striosomal compartment of striatum. Dopamine neurons also send projections to the mesencephalic locomotor region (MLR) and tectum. (Modified from Fig. 4 in Ref. [6]).

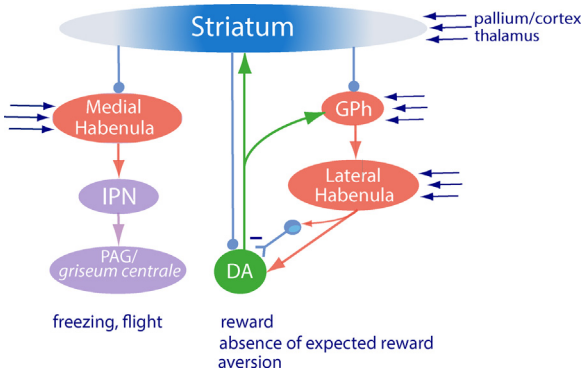

Fig. 3. The connectivity of the medial and lateral habenula is shown in relation to striatum, and their respective roles in behavior. The following abbreviations are used: interpeduncular nucleus (IPN), the excitatory globus pallidus projecting to the lateral habenula (GPh), dopamine (DA), periaqueductal gray (PAG). The arrows indicate different types of input as specified further in Fig. 4.

level as in primates [3,4,7,8,14]. Available evidence suggest that the circuit depicted in Fig. 2 is critical in this context with the striosomal compartment of the basal ganglia together with its output nucleus GPh, the lateral habenula, RMTg, and the dopamine neurons that project back to the entire striatum, and also actually to GPh on which they act via D2 receptors, and provide a net depression of GPh activity [3,7].

An enhanced activity in the striosomes (see Fig. 2) will thus inhibit the glutamatergic GPh (tonically active at rest), and thereby decrease lateral habenula activity, and reduce the inhibition via RMTg resulting in an increase of activity in dopamine neurons, which have a resting background activity [8,15]. This could in turn lead to a reinforcement of the behavior just performed [16–19]. The dopamine action would target also the matrix compartment of the striatum that is concerned with the control of action (see Fig. 2) and also actually affect downstream motor centres in both lamprey and mammals [5,7,20–22]. Conversely, an activation of GPh from cortex/pallium or thalamus will enhance activity in the lateral habenula with a final effect of decreasing the dopamine activity.

Please cite this article in press as: S. Grillner, et al., The blueprint of the vertebrate forebrain – With special reference to the habenulae, Semin Cell Dev Biol (2017), https://doi.org/10.1016/j.semcdb.2017.10.023