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Consider Role of Glutamatergic Habenula-projecting Globus Pallidus in OCD

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Key words

habenula, amygdala, CSTC circuitry, OCD, habenula-projecting Globus pallidus

ABSTRACT

Recently, in a review article in this journal, Vlček and colleagues described the putative role played by the glutamatergic system in obsessive-compulsive disorder (OCD) and how this might explain the effects of certain treatments. They describe a neuroanatomical model, which includes a specific role of the amygdala-hippocampus complex (AHC) and would complete the classic cortico-striatal-thalamo-cortical (CSTC) mechanism of OCD. The role of the AHC can perhaps be better understood when considering its ancient relationship to the rest of the forebrain of mammals. This leads to distinguishing between primary (lamprey-like), secondary (amphibian-like) and tertiary (mammal-like) parts of the forebrain including amygdaloid, ventral extrapyramidal and dorsal extrapyramidal systems, respectively. A specific role in OCD may be played by the habenula-projecting part of the pallidum, which evaluated the result of behaviour in human's earliest vertebrate ancestors. The addition of these primary relationship to the authors' description could be fruitful when planning the future research, as suggested by them.

Consider Role of Glutamatergic Habenula-projecting Globus Pallidus in OCD

Recently, in a review article in this journal, Vlček and colleagues described the putative role played by the glutamatergic system in obsessive-compulsive disorder (OCD) and how this might explain the effects of certain treatments [1]. They describe a neuroanatomical model, which includes a specific role of the amygdala-hippocampus complex (AHC) and would complete the classic cortico-striatal-thalamo-cortical (CSTC) mechanism of OCD. The role of the AHC can perhaps be better understood when considering its ancient relationship to the rest of the forebrain of mammals. This leads to distinguishing between primary (lamprey-like), secondary (amphibian-like) and tertiary (mammal-like) parts of the forebrain including amygdaloid, ventral extrapyramidal and dorsal extrapyramidal systems, respectively. A specific role in OCD may be played by the habenula-projecting part of the pallidum, which evaluated the result of behaviour in human's earliest vertebrate ancestors. The addition of these primary relationship to the authors' description could be fruitful when planning the future research, as suggested by them [1].

We have recently studied the evolution of the brain structures regulating distress-avoiding and reward-seeking behaviours [2, 3]. Since these behaviours are essential to maintain life, they should have been regulated by the brains of all our human vertebrate ancestors [4]. We discovered that the earliest vertebrates with a brain comparable with modern lamprey were the first species with a separate end-brain consisting of a dorsal pallidum (cf. human cerebral cortex) and ventral subpallidum (cf. human basal ganglia). The subpallidum of these animals contained a relatively modern extrapyramidal system which regulated (motor) behaviour by controlling hy-

pothalamic and brainstem motor centres. Similar to the situation in humans, the activity of this ancient extrapyramidal system was regulated by ascending monoaminergic neurons originating within the upper brainstem. In a more recent amphibian-like ancestor, the ancient subpallidum of the lamprey-like ancestors is represented by the central and medial amygdala and the bed nucleus of the stria terminalis. This extended amygdala in humans corresponds to the striatopallidal part of the amygdaloid complex. The cortex-like medial and lateral pallidum of the oldest ancestors is represented by the human hippocampal and corticoid amygdaloid complexes.

Anterior to this ancient 'amygdaloid' extrapyramidal system, the origin of the mammalian ventral extrapyramidal system has evolved in amphibian-like ancestors [3, 4]. The newly developed part of the pallidum of these ancestors is, in humans, represented by limbic cortical areas such as the orbitofrontal (OFC), subgenual cingulate (sCg) and anterior cingulate (ACC) cortices. This ventral CSTC system contains two types of re-entry circuits regulating the intensity of distress-avoiding and reward-seeking behaviours [3, 5]. The AHC modulates the activity of these re-entry circuits based on its input to the ventral striatum within the context of the ventral CSTC circuitry [6], but also via the habenula [3].

A very interesting component of the lamprey's pallidum is the glutamatergic habenula-projecting Globus pallidus (GPh) [2–4]. This structure is involved in evaluating reward-seeking behaviours, and inhibits this conduct when it is not successful [7]. The GPh stimulates the lateral division of the habenular complex which results in decreased activity of ascending dopaminergic neurons from the upper brainstem. In mice, these neurons have been identified within the homologue of the human globus pallidus [8]. The habenula is a small nuclear complex which regulates the activity of ascending dopaminergic, serotonergic and

adrenergic neurons, and which, as a consequence, plays an important role in regulating the intensity of misery-fleeing and reward-seeking behaviour. This habenular function was well-conserved in all vertebrate species during evolution [2, 9].

We should emphasize how highly we value Vlček et al.'s overview of the role of the glutamatergic system in OCD. We want to add that we could distinguish between primary (lamprey-like), secondary (amphibian-like) and tertiary (mammal-like) parts of the forebrain including amygdaloid, ventral extrapyramidal and dorsal extrapyramidal systems, respectively [4]. The secondary forebrain regulates motivation to distress-avoiding and reward-seeking behaviours. The efficacy of these behaviours is evaluated by glutamatergic GPh neurons which inhibit ascending dopaminergic neurons by stimulating the lateral habenula. When this structure is involved in evaluating the effectiveness of cognitive and motor programs similar to its role in lampreys, little imagination is necessary to predict involvement in the typical repetition of obsessions and compulsions. The GPh receives input from the subthalamic cells located in the 'limbic' region of the subthalamic nucleus (STN) [8]. Recently, Cano et al. described decreased functional connectivity between the right STN and the lenticular nuclei of patients with OCD in comparison with controls [10]. This context of the AHC and GPh could be added to the neuro-anatomical model described by Vlček et al. in their paper.

Conflict of Interest

No conflict of interest has been declared by the author(s).

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