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Editorial - SI Lateral habenula

The lateral habenula belongs to the habenular complex, a small pair of nuclei situated in mammals dorsally to the midline thalamus. Early anatomists named the habenula in reference to its oblong shape in the rostro-caudal plane. It is interesting to consider that habenula comes from the latin *habena*, or « *rein* », so that anatomists metaphorically conferred to this structure a position of guide within the central nervous system. Initial seminal data obtained in awake monkeys revealed that the lateral habenula provides to the dopamine system a negative reward signal, entry point to the notion that the lateral habenula, if not a guide in the brain, is at least of great importance for the modulation of fundamental and complex functions and behaviors; those range from sleep and stress coping to high cognitive functions. In addition, preclinical and clinical data demonstrated that not only a dysfunction of the lateral habenula is causal in the occurrence of mood symptoms in major depressive disorder, but that negative signs of withdrawal from drugs of abuse such as cocaine or alcohol appear consecutive to disturbances in lateral habenula function.

Although the present Special Issue remains non exhaustive, it includes a series of review articles providing current state of research and thinking regarding the role of the lateral habenula, with anatomical, physiological and behavioral considerations.

The special issue starts with a series of articles describing the lateral habenula at the anatomical level. *Daniel Zahm and David Root* accurately summarize the lateral habenula connectivity, also describing its cellular organization especially in light of its projections to the dopamine and serotonin systems. The serotonin system is the focus of the review provided by *Martin Metzger, Debora Bueno and Leandro Lima*. The authors describe the importance of the reciprocal connections between the lateral habenula and the midbrain raphe nuclei and their role in the response to stress and the pathophysiology of depression. *Ewoud Schmidt and Jeroen Pasterkamp* describe molecular mechanisms leading to peculiar morphogenesis aspects of the habenula in vertebrate species such as the zebrafish. *Franziska Wagner, Torsten Weiss and Rüdiger Veh* describe at the cellular level the different types of neurons based on their intrinsic electrophysiological properties. Overall, these articles give a very accurate description of the complexity of the lateral habenula at the anatomical level.

The special issue then includes several articles addressing the role of the lateral habenula in various aspects of brain functions. *Beatriz Bano-Otalora and Hugh Piggins* first address the crosstalk between the lateral habenula, the retina and the circadian clock in the suprachiasmatic nucleus, describing circadian activity within the lateral habenula; they further propose that such activity is at the origin of the tonic control exerted by the lateral habenula over midbrain dopamine and serotonin neurons. The possibility that the circadian activity of the lateral habenula serves to modulate the activity of the monoamine systems is further developed by *Jorge Mendoza* who proposes that such rhythmicity plays a key role in motivated behaviors (mostly those with circadian profiles) and links its dysfunction to mood and eating disorders. The cognitive implications of the lateral habenula are developed by *Phillip Baker and Sheri Mizumori*, who propose that the lateral habenula integrates changes in contextual parameters in order to favor behavioral flexibility facing the changing constraints of the environment. Such cognitive aspects are further discussed by *Victor Mathis and Lucas Lecourtier* who describe the role of the lateral habenula in spatial reference as well as working memory, and propose that the lateral habenula also integrates both cognitive and emotional aspects of a given situation in order to generate relevant behavioral strategies. *Meghan Flanigan, Hossein Aleyasin, Aki Takahashi, Sam Golden and Scott Russo* propose that the lateral habenula, likely by interacting with the dopamine and serotonin systems, plays a key role in the attribution of emotional and motivational valence in the context of aggressive behaviors.

The last part of the Special Issue is devoted to the analysis of lateral habenula hyperactivity in the genesis of symptoms occurring during withdrawal from drugs of abuse. *Frank Meye, Massimo Trusel, Mariano Soiza-Reilly and Manuel Mameli* describe intra-lateral habenula alterations of glutamatergic plasticity mechanisms, induced by cocaine intake, causally linking it to the emergence of negative affective state upon drug withdrawal; *Avi Shah, Wanhong Zuo, Seungwoo Kang, Jing Li, Alex Bekker, Rao Fu and Jiang Ye* describe intra-lateral habenula molecular mechanisms leading to withdrawal symptoms following alcohol intake.

In summary, in this Special Issue the readers will find important sets of recent data regarding the physiological and pathological aspects of lateral habenula functions. These reviews are orientated to an audience interested in the fundamental properties of the lateral habenula, but also to those interested in the possible clinical implications of the disturbances of lateral habenula functions.

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