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Abstract of the doctoral dissertation entitled: **"Molecular characterization of the habenula in rats with a treatment-resistant depression phenotype and the effect of psilocybin on neurobiological changes in the lateral nucleus".**

The treatment of mental disorders remains one of the most significant challenges in contemporary medicine, mainly due to the limited understanding of their molecular bases and underlying pathophysiological mechanisms. A particularly critical clinical issue is treatment-resistant depression, which affects approximately one-third of patients diagnosed with depression and is characterized by a lack of response to standard antidepressant therapies. Growing evidence implicates habenular dysfunction as a key contributor to the pathogenesis of mood disorders.

The present doctoral dissertation aimed to molecularly characterize differences within the habenular nuclei between healthy rats and animals with a treatment-resistant depression phenotype – the Wistar Kyoto strain. In the search for novel therapeutic strategies, the effects of psilocybin – a compound with documented antidepressant potential – on the function of the lateral habenula were also investigated.

Using a combination of biochemical and molecular approaches, significant alterations in miRNA, mRNA, and proteins expression were identified. Special attention was given to the GIRK4 potassium channel, encoded by the *Kcnj5* gene, which emerged as a potential molecular target of psilocybin. Electrophysiological analyses demonstrated that psilocybin administration modulated inwardly currents in the lateral habenula, suggesting a mechanism of action involving the restoration of excitation-inhibition balance within this structure.

These findings provide novel insights into the molecular and functional disturbances of the habenula in animals with a treatment-resistant depression phenotype and highlight psilocybin as a potential modulator of lateral habenula neuronal activity through regulation of the GIRK4 channel. Collectively, the results provide a basis for future research aimed at elucidating the mechanisms underlying treatment resistance and developing innovative antidepressant therapies.

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