

Understanding the molecular mechanisms of aggression in BALB/c and TPH2-deficient mice

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Valorization

Relevance for society

The World Health Organization categorizes aggression among the top 20 causes of disability. Negative social impact associated with the prevalence of violence and aggression is increasing, and with this rise is the need to understand the molecular changes that underpin aggressive behavior, and thus pharmacological methods of treatment.

In our work we identified new and validated molecular correlates of aggression that can be possible targets for pharmacological treatment of excessive aggression in the clinic. The expression of AMPA receptor GluA2 subunit was upregulated, while the expression of 5-HT6 receptor was downregulated in two different models of stress-induced aggression: an ultrasound model of emotional stress, and mice with partial deficit of the gene encoding tryptophan hydroxylase-2 (TPH2), the key enzyme of the neuronal serotonin synthesis, which were subjected to rat exposure stress. We also demonstrated increased neuroinflammation, decreased hippocampal plasticity and oxidative stress to be associated with aggression in mice. Because of this, we studied antioxidant compounds thiamine (vitamin B1), its precursor benfotiamine, and plant extracts and identified them as effective treatments preventing excessive aggression and associated behavioral and molecular alternations, which have the potential to be used in the clinical practice.

We also validated two new mouse models that result in excessive aggression. In the model of ultrasound-induced emotional stress mice are subjected to variable frequencies chosen to mimic natural ultrasonic signals of fear and anxiety without direct physical stressors. This approach enhances its etiological validity, since emotional stress is as a human-specific trait. Mice with partial genetic deficit of TPH2 develop excessive aggression after being subjected to predator, showing similar behavioral profile to that of null mutants, modeling sensitivity to stress of patients with specific TPH2 polymorphisms. Our data suggest that both models can be useful for drug researcher development, as they are effective, etiologicaly relevant and inexpensive.

Target groups

We consider our target group could be patients and individuals with excessive aggression, as well as researchers, working in the field of neurobiology of aggression.

Activity / Products

We proposed new ways of pharmacological management of excessive aggression, based on use of compounds with antioxidant properties. We also validated new aggression models with high etiological validity that could be used in drug researcher development.

Innovation

We have shown for the first time that the expression of 5-HT6 receptor and GluA2 subunit of AMPA receptor was altered

in two different models of aggression, suggesting these molecules as possible pharmacological targets of stress-related aggression. We proposed thiamine compounds and herbal antioxidant as new ways of treatment of excessive aggression and emotional behaviors. Moreover, we established and validated two new mouse aggression paradigms that model both genetic and environmental factors, such as emotional stress and TPH2 deficiency.

Implementation

Our results are relevant for both the scientific and medical communities. They have been or will be published in peer-reviewed journals and presented at national and international conferences.