Excessive aggression, ADHD- and ASD-like phenotypes in TPH2- and brain ganglioside-deficient mice

Impact

Neurodevelopmental disorders include, for example, attention-deficit/hyperactivity disorder (ADHD) with prevalence estimates ranging from 5 to 12% and autism spectrum disorders (ASD) with estimated prevalence from 0.6 to 2.3%. Marked aggression is one of the common symptoms: according to epidemiological research, the prevalence of abnormal aggression is estimated in the range from 5.7% in ADHD to about 68% in ASD. The World Health Organization categorizes aggression and violence among the top 20 causes of disability, so there is an evident need to understand the neurobiology of aggressive behavior with a view to developing new treatments.

In the present study, we aimed to investigate the impact of environmental adversities on neurobiological correlates of two experimental genetic animal models and study the validity of these models as models of gene × environment interaction in neurodevelopmental disorders. Genes affected in these models were shown to be the risk factors for neurodevelopmental disorders.

The interaction of an individual's genetic background with adverse environmental experiences (gene × environment interaction) is one of the main pathogenic factors for these disorders, but not many models are available to mimick this situation experimentally.

We used mice with a genetic decrease in neuronal serotonin, a model of gene × environment interaction in male aggression. Mutation in the gene, which is partially inactivated in these mice, was associated with neurodevelopmental disorders, including ADHD and ASD. We showed

that in these mice emotional stress-related aggression is accompanied by substantial changes in the brain neurochemistry of the regions crucial for aggressive, emotional, and social behavior. For these mice, no data on the behavior of females was previously available. Surprisingly, although aggression is thought to be outside of the natural behavioral repertoire of female mice, we found aggressive behavior in female mice with deficiency of brain serotonin after emotional stress.

This behavior was accompanied by prominent changes in brain molecular markers, which were previously shown to be involved in aggression and depressive behavior. One of these markers is also implicated in inflammation. Notably, in both male and female mice with a serotonin deficiency we found signs of alteration in myelination, a neurodevelopmental process ensuring proper signal propagation in the nervous system, and, thus, functional connectivity, which was shown to be affected in many psychiatric disorders.

Secondly, for the first time, we studied the social behavior of mice with a genetic deficit of major brain gangliosides — ubiquitous molecules playing various roles in the CNS. In humans, lack of brain gangliosides leads to devastating neurodevelopmental deficits, accompanied by severe intellectual disability, growth retardation, and seizures. These mice, however, do not mirror these deficits completely due to compensatory mechanisms. Thus, these mice are considered as a model of more subtle neurodevelopmental anomalies linked to brain gangliosides. Genetic variants of one of the genes involved in brain ganglioside synthesis were found to be associated with ADHD and ASD.

In ganglioside-deficient mice we have found aberrant social and dominant behaviors, as well as signs of repetitive behaviors, which are reminiscent of ASD-like syndrome. These findings were complemented by increased inflammatory markers, which are also known to be increased in patients with ASD. Additionally, as in the case with the first mouse model, we found signs of altered myelination in both sexes of ganglioside-deficient mice. We also found an altered response to inflammatory stress accompanied by increased aggression and aberrant social behavior in these mice, thus underpinning the importance of gene × environment interaction in the pathogenesis of excessive aggression.

Thus, in both mouse lines we found abnormal aggression and other alterations in social behavior as a consequence of environmental stressors, which suggests them as promising models for studies of the gene × environment interaction in ADHD and ASD.

Our work also offers a new model of female aggression. Such models are very scarce, and female aggression demonstrated in serotonin-deficient mice may also prove itself useful as a tool for studies of gene × environment interaction in female aggression.

We also are the first to report signs of alterations in myelination in these models. Myelination and neuroinflammation are interrelated processes, and with our results we may set the direction for further investigations, as the data on the role of alterations in myelination and brain connectivity in neurodevelopmental disorders such as ADHD and ASD are scarce. Overall, we assume that our work provides further addition to the idea that the interaction between various genetic and

environmental factors may affect converging mechanisms leading to neurodevelopmental pathologies such as ADHD and ASD.

We consider our primary target group to be researchers working in the field of neurobiology of aggression and neurodevelopmental disorders; however, our results are relevant also for the medical community, as they provide data for the development for new pharmacological treatments. The data will be published in peer-reviewed journals and presented at national and international conferences.