Ruprecht-Karls-Universität Heidelberg

Medizinische Fakultät Mannheim

Dissertations-Kurzfassung

Gene environment interactions in transgenic mice with serotonergic modulations

Autor: Sergej Kutscherjawy
Institut / Klinik: Zentralinstitut für Seelische Gesundheit Mannheim (ZI)
Doktorvater: Prof. Dr. D. Bartsch

Depression and anxiety disorders are the most common psychiatric diseases worldwide. Despite recent advances, the neurobiological mechanisms underlying individual differences in susceptibility to anxiety and affective disorders still remain elusive.

The serotonergic system plays an important role in the modulation of central nervous system processes that appear to be dysregulated in psychiatric disorders. Therefore, study of gene variants of the tryptophane hydroxylase 2(Tph2), the rate-limiting enzyme of serotonin (5-HT) synthesis in the brain with a significant impact on the functionality of the brain serotonergic system is of interest. In humans, several *Tph2* polymorphisms and their haplotypes have been found to be associated with a variety of neuropsychiatric diseases, ranging from affective disorders to Tourette syndrome or personality disorders.

Identified in the coding region of the mouse *Tph2* gene, the functional single nucleotide polymorphism (SNP) C1473G leads to reduced 5-HT synthesis in tissue culture. Inbred mouse strains homozygous for the 1473G allele show a lower 5-HT concentration in several brain regions when compared to inbred strains homozygous for the 1473C allele. In parallel, these different mouse strains also showed differences in emotional behavior, stress reactivity and sensitivity to drugs modulating serotonergic neurotransmission. However, attempts to correlate this polymorphism with behavioral phenotypes were not conclusive, since behavioral differences might be determined by other components within the different genetic background.

Within the scope of this thesis, the biochemical and behavioral consequences of the functional SNP C1473G of *Tph2* were determined in congenic mice of C57BL/6N background, carrying either a homozygous 1473C or 1473G allele. The *in vivo* assessment of Tph2 activity in frontal cortex and hippocampus revealed a reduction of synthesis rate by ~27% and ~33%, respectively, in mice homozygous for 1473G allele. However, this reduced synthesis rate was not reflected in reduced steady state 5-HT concentration in these brain regions, suggesting compensating changes in response to synthesis deficiency. In behavioral experiments, 1473G mice showed increased anxiety-like behavior, but didn't display altered depression-related behavior compared to 1473C mice. Additionally, increased anxiety of 1473G mice was accompanied by a higher aggression.

In attempt to determine whether the presence of 1473G allele of *Tph2* gene causes increased vulnerability to stress-related anxiety or depressive-like behavior, mice were subjected to a chronic mild stress procedure. 1473G mice as well as wild type mice showed increased locomotor activity but did not change their anxiety and depression-related behavior following stress.

Chronic medication with a selective-serotonin reuptake inhibitor, effective in treatment of mood and anxiety disorders, attenuated the increased anxiety-like behavior measured in 1473G mice to the same level as treated 1473C mice.

These data suggest that in C57Bl/6N mice the reduced Tph2 activity leads to compensatory changes in serotonergic neurotransmission, resulting in increased anxiety and higher aggression. However the increased anxiety has no predisposing effect on the animals to higher vulnerability to stress and doesn't support the hypothesis of positive correlation between lower genetically based Tph2 activity and predisposition to depression. The C57Bl/6N mouse substrain carrying *Tph2* 1473G allele is a useful animal model for the identification of changes caused by lower Tph2 activity in humans and for the development of treatments for pathological anxiety and exaggerated aggression.