SLC6A15, a novel stress vulnerability candidate, modulates anxiety and depressive-like behavior: involvement of the glutamatergic system.

Abstract:
Major depression is a multifactorial disease, involving both environmental and genetic risk factors. Recently, SLC6A15 - a neutral amino acid transporter mainly expressed in neurons - was proposed as a new candidate gene for major depression and stress vulnerability. Risk allele carriers for a single nucleotide polymorphism (SNP) in a SLC6A15 regulatory region display altered hippocampal volume, glutamate levels, and hypothalamus-pituitary-adrenal axis activity, all markers associated with major depression. Despite this genetic link between SLC6A15 and depression, its functional role with regard to the development and maintenance of depressive disorder is still unclear. The aim of the current study was therefore to characterize the role of mouse slc6a15 in modulating brain function and behavior, especially in relation to stress as a key risk factor for the development of mood disorders. We investigated the effects of slc6a15 manipulation using two mouse models, a conventional slc6a15 knock-out mouse line (SLC-KO) and a virus-mediated hippocampal slc6a15 overexpression (SLC-OE) model. Mice were tested under basal conditions and following chronic social stress. We found that SLC-KO animals displayed a similar behavioral profile
to wild-type littermates (SLC-WT) under basal conditions. Interestingly, following chronic social stress SLC-KO animals showed lower levels of anxiety- and depressive-like behavior compared to stressed WT littermates. In support of these findings, SLC-OE animals displayed increased anxiety-like behavior already under basal condition. We also provide evidence that GluR1 expression in the dentate gyrus, but not GluR2 or NR1, are regulated by slc6a15 expression, and may contribute to the difference in stress responsiveness observed between SLC-KO and SLC-WT animals. Taken together, our data demonstrate that slc6a15 plays a role in modulating emotional behavior, possibly mediated by its impact on glutamatergic neurotransmission.