

Brain Mind Institute
Extraordinary seminar

Monday, September 25th, 2017 - 09:00 AM

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**“SLC6A15, a novel stress vulnerability candidate, regulates anxiety
and depressive like behavior through the glutamatergic system”**

SLC6A15, a neutral amino acid transporter predominantly expressed in neurons, has been recently suggested to play a role in the aetiology of major depressive disorder. The purpose of this study was to explore a putative mechanism of action of the transporter in the brain and to characterize behavioural and molecular changes following manipulation of SLC6A15 in mice. Therefore, we analysed hippocampal neurochemistry and behaviour in animals with reduced, i.e. full knockout or acute pharmacological inhibition, or increased levels of SLC6A15, i.e. targeted overexpression in the hippocampus. We furthermore investigated the effects of reduced SLC6A15 levels on glutamate synthesis, mitochondrial function and electrophysiology in primary hippocampal cell culture. Ablation of SLC6A15 reduced tissue levels of several substrate amino acids such as proline and leucine as well as glutamate levels in the hippocampus, while overexpression increased hippocampal glutamate levels. We observed an anxiolytic effect of SLC6A15 KO after chronic stress exposure and of SLC6A15 antagonist treatment under control conditions, an effect that was reversed by hippocampal overexpression of the transporter. Lack of the transporter was furthermore associated with alterations in sensorimotor gating. In neuronal culture, lack or inhibition of SLC6A15 affected neuronal transmission as well as mitochondrial respiration. In summary, our results implement SLC6A15 as a modulating factor for emotional behaviour and stress vulnerability. Our data thereby provide a mechanistic basis for the genetic associations of SLC6A15 polymorphisms with mental disorders and suggest SLC6A15 antagonists as a promising therapeutic intervention strategy.

Host : Prof. Carmen Sandi

Conference Room SV 1717 • EPFL-Lausanne