Vesicular glutamate transporters as circuit-based therapeutic target for depression: evidence from a

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Depression is a stress-related psychiatric disorder twice as prevalent in women as in men, whose therapeutic needs are largely unmet (Marcus et al, 2005; Rush et al., 2006).

Altered neuroplasticity of excitatory synapses in the nucleus accumbens (NAc) is a key pathophysiological feature of susceptibility to stress (Christoffel et al., 2015), but the contribution of distinct glutamatergic inputs to the NAc is still unclear.

Here we employ the sub-chronic variable stress (SCVS) paradigm of depression with the aim of evaluating glutamatergic plasticity in the NAc underpinning gender-related vulnerability to stress. SCVS induces a vulnerable behavioural phenotype in female mice, whereas males are resilient (Hodes et al., 2015). It consisted of a 6-day exposure to unpredictable stressors, including footshock, tail suspension and restraint, in female and male mice. SCVS effects on glutamatergic synapses in the NAc were evaluated by using the different isoforms of the vesicular glutamate transporter (VGLUT) as pre-synaptic markers of input-specific synapses (Fremeau et al., 2004). In particular, VGLUT-1- and VGLUT-2-positive axon terminals, together with post-synaptic density protein PSD95, were targeted and quantified by immunofluorescence and confocal microscopy. Then, the specific contribution of the thalamo-striatal glutamatergic pathway, a relevant subcortical afferent bearing VGLUT-2 (Fremeau et al., 2004), was tested by circuit-specific optogenetic stimulation on behavioural reactivity, anxiety- and depression-like behaviour.

Our results show that SCVS induced circuit-specific pre-synaptic alterations in the NAc of susceptible animals. In particular, SCVS decreased VGLUT-1 immunoreactivity and increased VGLUT-2 puncta only in susceptible female mice, in the absence of post-synaptic alterations of PSD95, spine density or type (Brancato et al., 2017). Moreover, in vivo optogenetic stimulation of the thalamo-striatal circuit increased latency to eat in the novelty suppressed feeding test, showed a trend in decreasing sucrose consumption in the sucrose preference test, while it did not exert significant alterations of behavioural reactivity in the open field and elevated plus maze. Taken together, these data suggest a role for VGLUT-2-positive subcortical excitatory projections to the NAc in inducing a susceptible behavioural phenotype. Moreover, they point at VGLUTs as novel therapeutic targets for circuit-based, gender-oriented pharmacological treatment of depression.

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