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Anxiety-like behavior in NL-2 knockouts: a study of the physiological mechanism and modulation by ISMO

NL-2 is a synaptic adhesion molecular that ensures stability and proper functioning of inhibitory synapses via interactions with the postsynaptic protein machinery. Deletion of NL-2 in mice leads to impairment in inhibitory synaptic transmission in vivo. NL-2 knockout mice show an increase in anxiety-like behavior during an open field test. Here, we investigated the mechanisms by which deletion of NL-2 leads to augmentation of anxiety in mice. We studied cFOS activation in brain structures involved in anxiety processing and showed that basal amygdala is highly activated in knockouts as compared to wild types, while medial orbital cortex shows reduced activity. We also report a marked reduction of inhibitory postsynaptic scaffolding protein gephyrin at perisomatic synapses in basal amygdala of NL-2 knockouts. Deletion of ISMO, a protein that was recently described as a postsynaptic partner of NL-2, leads to distinct phenotype in mice and appears to modulate anxiety-like behavior in double NL-2 -/- ISMO-/- knockouts. Based on these findings we propose a model in which NL-2 deletion leads to impairment of inhibitory circuits in basal amygdala causing an increased behavioral response to anxiogenic stimulus. In addition, our findings expand current knowledge on the physiological role of ISMO in mice.