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Mediators of synaptic activity in anxiety- and depression-related behaviors

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ABSTRACT

Depression and anxiety are leading causes of years lost to disability, despite antidepressants being among the most prescribed medications. Most of the prescribed antidepressants were found serendipitously rather than from an understanding of the biological mechanisms underlying depression. Recent evidence supports the antidepressant efficacy of glutamate-targeting drugs, such as ketamine, which promote plastic changes in synaptic structure and function in various brain regions.

Here we employed pharmacological and genetic approaches to study the role of various molecules known to mediate synaptic activity and plasticity in baseline depression- and anxiety-related behaviors and antidepressant-like effects in mice. Specifically, we examined voltage-gated potassium channels (Kv4.2) known to regulate dendritic excitability, a molecule of the postsynaptic density (PSD-95), and glutamatergic receptors, including the GluA1 subunit of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and its phosphorylation sites, and the GluN1, GluN2B, and GluN2A subunits of *N*-methyl-D-aspartate (NMDA) receptor. We employed traditional assays for murine depression-related behavior, including the forced swim test (FST), and a novel test for responses to repeated swim stress.

We found that mice with constitutive deletions to GluA1, GluN2A and PSD-95 showed reduced depression-related behaviors in the FST, but similar behavioural effects were not observed in mice with a conditional cell-type specific knockout of NMDAR subunits. However, pharmacological blockade of GluN2B, via administration of Ro 25-6981, reduced depression-like behavior in the FST. This antidepressant-like effect was replicated by microinfusion of Ro 25-6981 into the medial prefrontal cortex (mPFC). By contrast, neither lentiviral-mediated knockdown of GluN2B nor conditional GluN2B deletion in forebrain pyramidal neurons or interneurons was sufficient to reduce depression-like behavior in the FST. Pharmacological GluN2B antagonism via Ro 25-6981 similarly reduced despair-like behavior during a repeated swim stress, and, unlike spontaneous swim measures, this effect was replicated by genetic deletion of GluN2B on pyramidal cells, but not interneurons. Collectively, these results suggest that multiple synaptically-expressed molecules mediate depression-related behavior. The GluN2B-containing NMDARs play a role in mediating depression-related behaviors during acute and repeated stressors, depending upon the pharmacological or genetic manipulations used, cell-type and brain region localization.

Together this suggests that multiple synaptic proteins are important in depression-related behavior. However, reduction of GluN2B receptors does not per se lead to changes in depression-related behaviors. Here we suggest that it is the NMDAR-antagonist induced rise in extracellular glutamate and subsequent increase in synaptic transmission, such as through AMPARs, that is necessary for an antidepressant-like response and is lacking in the genetic deletions of GluN2B. In the repeated stress procedure our data supports a role of GluN2B transmission selective to pyramidal cells in mediating the behavioural alterations that lead to despair-like behavior. This would fit with previous data showing systemic NMDAR antagonism reduced atrophy in these same cell types, and suggests that it is the pyramidal cell NMDARs that mediate the morphological and behavioural effects of repeated stress. ISBN 978-91-7457-764-8