Abstract

Activation of the N-methyl-D-aspartate receptor (NMDAR) leads to downstream signaling that modulates structural and functional plasticity, which is crucial for cognitive processes such as learning and memory. Impairments in NMDAR activity are implicated in various mental disorders, including depression and schizophrenia. Despite the growing body of evidence on the effects and potential therapeutic benefits of ketamine and other NMDAR inhibitors, there is still a gap in undestanding the effects of endogenous NMDAR modulators. Specifically, their effects on the neuronal structure and synaptic density is unclear, despite the fact that their levels are dysregulated in patients with mental disorders.

The objective of this study is to elucidate the molecular and cellular changes resulting from endogenous NMDAR modulators and their potential implications in psychiatric disorders. To achieve this, we assessed the morphological and synaptic changes of excitatory and inhibitory neurons induced by the prevalent endogenous NMDAR modulators, including kynurenic acid, pregnenolone sulfate (PS), spermidine, and zinc at various time points.

We measured cell viability using the MTS assay and glutamate release using HPLC. Immunocytochemistry was used to measure dendritic branching and synaptic density. Western blot was used to measure the expression of synaptic proteins, while ELISA for measuring the expression of GABA and BDNF. The study also assessed the antidepressant-like effects of PS in a chronic despair model in mice using the open field test, three chamber test, and forced swim test.

We have not observed any significant changes in glutamate release, neuronal viability or dendritic branching. However, a comparison of the arbor complexity revealed that PS increased distal dendritic arborization, which is consistent with the tendency towards increased expression of BDNF and activation of the TrkB receptor. The density of glutamatergic synapses was consistent across all neuronal groups, except for those treated with PS, which exhibited a reduction in puncta of the scaffolding postsynaptic protein PSD-95. Parvalbumin-positive inhibitory neurons treated with the endogenous NMDAR modulators exhibited a decrease in dendritic branching and arbor complexity, without altering GABA release or expression. Finally, PS was found to reduce anxiety-like behaviour in a chronic despair model in mice.

The observed increase in BDNF release, activation of TrkB receptor and expansion of dendritic fields may contribute to the anxiolytic-like effect observed in mice. Furthermore, the results emphasise the increased sensitivity of parvalbumin-positive neurons to the endogenous NMDAR modulators, providing more insight into their implications in psychiatric disorders.