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Restoration by ketamine of stress-induced maladaptive changes in synaptic function and brain architecture

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Stressful events represent a major risk factor for neuropsychiatric disorders. Whereas the effects of chronic stress have been widely investigated in animal models, the long-term consequences of acute stressors have been little studied, despite it is known that even a single trauma may induce a disorder in humans (e.g., PTSD).

Recently, we have dissected the destabilizing effects of acute stress on the excitatory glutamate system. Acute inescapable footshock stress induced a rapid and sustained (at least up to 24 h) enhancement of depolarization-evoked glutamate release/transmission in the prefrontal cortex (PFC). Acute stress also dramatically increased the total number of excitatory synapses in PFC, while at the same time caused a significant atrophy of apical dendrites, measured already 24 h after stress exposur,e and sustained for at least 14 days. Intriguingly, both prior chronic treatment with traditional antidepressants (2 weeks), and single administration of ketamine (KET; 10 mg/kg) 24 h before stress blocked the enhancement of glutamate release. To dissect adaptive and maladaptive mechanisms underlying acute stress response, we are now using sucrose intake (SI) test, a standard behavioral test for anhedonia, allowing to identify animals resilient/vulnerable towards acute stress.

We are also using the Chronic Mild Stress (CMS) model of depression to look at the effects of chronic stress and of the antidepressant mechanism of KET. Rats were subjected to CMS for 5 weeks. Sucrose Preference Test (SPT) was used to distinguish stress-resilient (CMS-R) from vulnerable (CMS-V) rats. KET was acutely administered to CMS-V 24 hours before sacrifice. A decrease in basal and depolarization-evoked glutamate release was measured in synaptosomes from the hippocampus of CMS-V. In situ hybridization showed reduced dendritic trafficking of BDNF mRNA in CA1 and CA3 of CMS-V. Morphological analysis of CA3 pyramidal neurons showed a reduction in total length and branching of apical dendrites. KET reversed most of these CMS- induced changes in CMS-V.

Overall, our results showed that both acute and chronic stress induce a functional and structural remodeling of excitatory synapses, while acute ketamine restores most of the maladaptive changes induced by stress.