Acute stress induces time-dependent modulation of AMPA/NMDA receptor subunits and changes in working memory

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A growing number of studies strongly suggests the dysfunction of glutamate neurotransmission as a core feature of stress-related neuropsychiatric disorders. Indeed, clinical studies on patients with mood and anxiety disorders have shown alterations in levels, clearance, and metabolism of glutamate, and consistent volumetric changes in brain areas involved in emotion and stress response, such as amygdala, hippocampus and prefrontal and frontal cortex (FC and PFC). Moreover, preclinical studies on rodent stress-based models of depression showed that stress deeply affects glutamatergic transmission in the same brain regions. Intriguingly, modifications of the glutamatergic system induced by stress within the FC and PFC seem to be biphasic: while the fast response to acute stress enhances synaptic transmission and plasticity, long-term adaptive changes induced by stress has been shown to induce opposite effects. The analysis of time-dependent changes induced by stress could be crucial for a better comprehension of the mechanisms involved in this switch.
We have previously found that acute footshock (FS)-stress rapidly enhances depolarization-evoked glutamate release in FC and PFC, an effect prevented by the chronic treatment with different antidepressants. Moreover, several lines of evidence showed that acute behavioral stressors significantly potentiate glutamatergic synapses, increasing glutamate receptors trafficking to synapses and activation.
Main aim of the present study was to analyze the time-dependent changes in NMDA and AMPA receptor subunit expression and phosphorylation levels induced by acute FS-stress in total homogenate and post-synaptic spine membranes (purified as triton-insoluble fraction, TIF) of rat FC and PFC. Our results show that acute stress rapidly increases the levels of post-synaptic GluN1 and the ratio of GluN2A/GluN2B NMDAR subunits. We also observed a fast decrease in post-synaptic expression of GluA2, a subunit involved in the regulation of Ca^{2+} permeability and receptor trafficking, together with an increase in GluA2 phosphorylation at S880 after stress, suggesting increased internalization of the receptor, which may represent a compensatory response to the enhanced glutamatergic transmission.
We also performed the delayed alternation T-maze test, a well-established behavioral protocol for PFC-mediated working memory, on rats at different times after the stress protocol completion. Our results show that acute stress exerts a biphasic effect on working memory, which results to be enhanced 2 h after FS stress, and impaired 24 h after the stress session. Interestingly, chronic treatment with the antidepressant desipramine attenuates both the positive and negative behavioral effects seen after FS-stress.
Further investigation of the mechanisms involved in this biphasic action of stress, at both molecular and behavioral level, may be useful to understand the pathophysiology of stress-related disorders and their treatment with antidepressants.