The impact of stress on the glutamate system: relevance for psychopathology and treatment

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Stressful life events impact on memory and cognition and are known to precipitate mood and anxiety disorders. The outcome of stress may range from plasticity enhancing effects, associated with improved cognition, to noxious effects, associated with impaired function or triggering of neuropsychiatric disorders. Half a century after the monoamine hypothesis, it has become increasingly acknowledged that maladaptive changes in the structure and function of excitatory/inhibitory circuitry (representing the vast majority of neurons and synapses in brain) have a primary role in the pathophysiology of mood and anxiety disorders, particularly major depression.

Clinical neuroimaging studies showed consistent volumetric changes in brain areas where glutamate neurons and synapses predominate. In parallel, rodent studies have shown that stressors induce dendritic atrophy, reduction of synapses number and volumetric reductions resembling those observed in patients with mood and anxiety disorders. A major role in this process is attributed to elevation of glucocorticoid hormones by stressors, which enhance glutamate release/transmission, in turn inducing retraction of dendrites. Converging evidence from various groups, including ours, has shown that enhancement of glutamate release/transmission in cortical/limbic areas, in turn induced by stress and glucocorticoids, is crucial for these structural/functional changes (1). We have shown that acute stress rapidly enhances glutamate release/transmission in prefrontal and frontal cortex (PFC/FC), mediated by glucocorticoid/mineralocorticoid receptors (GR/MR) (2). We have now evidence that acute stress rapidly enhances glutamate vesicles mobilization, through activation of synaptic GR/MR-mediated non-genomic mechanisms. Our results suggest that rapid (non-genomic) synaptic action of corticosterone is necessary, but not sufficient, to increase glutamate release/transmission in PFC/FC, which requires activation of delayed, genomic, mechanisms.

Additional support for the role of glutamate in mood and anxiety disorders comes from studies showing that antidepressants prevent the enhancement of glutamate release induced by acute stressors, and may partly reverse the maladaptive changes in synapses/circuitry of chronically stressed rodents. Furthermore, recent compelling evidence showed rapid and sustained antidepressant action of glutamate receptor antagonists (e.g., ketamine) whose rapid action has been linked to a burst of glutamate release/transmission (3). However, the nature and direction of changes in the glutamate system, in pathophysiology and during treatment, is not clear. While acute stressors enhance glutamate release and transmission, repeated stressors seem to bring about destabilization of neuronal architecture and loss of synaptic connections in some pathways, with diffuse alterations in areas and circuits mediating cognitive and emotional behaviors (e.g., hippocampus, prefrontal cortex). A main target for research is the identification of specific effectors mediating the destabilizing effects of repeated stress.

References

1. M. Popoli, Z. Yan, B.S. McEwen, G. Sanacora, *Nat. Rev. Neurosci.* 13, 22 (2012).
2. L. Musazzi et al., *PLoS ONE.* 18, 1413 (2012).
3. R.S. Duman, G.K. Aghajanian, *Science* 338, 68 (2012).