Time-dependent structural, functional and behavioral changes induced by acute stress at excitatory synapses in prefrontal and frontal cortex. Implications for therapy of stress-related disorders

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Dysfunction of the glutamatergic system has been associated with the pathophysiology of stress-related neuropsychiatric disorders (Popoli et al., 2012). Clinical neuroimaging studies on patients with mood disorders have shown volumetric changes in brain areas where glutamate neurons are predominant. In parallel, preclinical studies on rodent models showed that stress and its mediators cause enhancement of glutamatergic release/transmission and structural changes in cortical/limbic areas. Nevertheless, the mechanisms whereby stress affects neurotransmission are still largely unknown.
Chronic stress has been shown to induce reduction of density of synapses and dendrites within the prefrontal cortex, with concomitant impairments in neuronal activity and cognitive functions. Instead, the early and rapid effects of acute stress on synaptic function and plasticity are often opposite (Yuen et al., 2011), with enhancement of glutamate release/transmission, increased number of spines and synapses and enhancement of synaptic strength (Treccani, Musazzi et al., 2014; Nava et al., 2014). However, the delayed effects of acute stress have not been investigated, although this could give crucial information on the time-dependent changes in the brain stress response.
Main aim of the present work was to analyze the effects of acute footshock stress in the prefrontal and frontal cortex of rats at different times after the stress protocol. We found that acute stress induced early increase of the ready releasable pool (RRP) of vesicles in excitatory perforated synapses, and of the number of non-perforated and axo-spinous excitatory synapses (without changes in vesicle pools). Intriguingly, the increase of the RRP size was sustained over time and the total number of synaptic spines was increased up to 24 h, while apical dendrites showed decreased density 2 weeks after acute stress (with no significant changes at earlier times). In behavioral tests for working memory, acute stress improved performance 2 h after stress and impaired it after 24 h. Changes in glutamate release, RRP, number of synapses and spines are blocked or attenuated by prior chronic treatment with the antidepressant desipramine.
The different glutamatergic modifications in functional and morphological plasticity suggest a biphasic process, during which the stress response within the prefrontal cortex may turn from early excitatory activation into its opposite. Better knowledge of the cellular effectors involved in this biphasic effects of stress may be useful to understand the pathophysiology of stress-related disorders, and open new paths for the development of therapeutic approaches.

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