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Neurophysiology 2020: Changes in the GABAergic signalling in the prefrontal cortex of mice model of posttraumatic stress disorder- Arina Serbina, Immanuel Kant Baltic Federal University/School of Life Sciences

Arina Serbina

Immanuel Kant Baltic Federal University/School of Life Sciences, Russia

It has been suggested that the neurons of prefrontal cortex, along with the hippocampus & amygdala, can undergo morphological & molecular remodeling during the development of stress-related disorders, such as PTSD. Pathological remodeling of the GABAergic inhibitory signaling during stress disorders might bring significant contribution to impairment of synaptic plasticity & cognition. In this work we have used an experimental model of PTSD in mice, based on a single prolonged stress protocol & studied alteration in the synaptic transmission & long-term synaptic plasticity in the pyramidal neurons of prefrontal cortex. The stress state in the animals was evaluated with the aid of open field & elevated cross-maze behavioral tests. We have found an increase in the quantal amplitude of GABAergic spontaneous inhibitory synaptic currents in the neurons of prefrontal cortex of stressed animals. There was also elevation in the frequency of neurons of the stress-group vs control group. These results demonstrate that that exposure to stress can cause an up-regulation of the GABAergic inhibitory system in the prefrontal cortex. In the experiments on long-term potentiation of field postsynaptic potentials, we have observed that the amplitude of LTP induced by the theta-burst stimulation in the prefrontal cortex synapses of stressed mice was much lower than in the control group. The data obtained suggest that stress-induced up-regulation of inhibitory signaling can affect long-term synaptic plasticity in the prefrontal cortex & thereby contribute to cognitive impairment.

The prefrontal cortex plays a central role in stress adaptation, & impaired circuitry & function of PFC sub regions are pathological features of many psychiatric illnesses. Clinical research has consistently reported that depression & other stress-related illnesses are associated with decreased volume, neuronal atrophy, & altered connectivity of PFC. These findings in humans are supported by rodent studies demonstrating that chronic stress exposure produces several alterations in the PFC, including dendritic atrophy & synapse loss, as well as loss of neurotropic factor support. These core features of rodent stress studies have led to the hypothesis that reductions in neurotropic factor expression result in neuronal & synaptic morphological deficits observed in human subjects. A related hypothesis suggests that an imbalance in excitatory & inhibitory neurotransmission occurring directly through deficient GABAergic inhibitory signaling in the PFC could account for the outcomes observed in human subjects & rodent models.

In this paper, we review the literature & evidence demonstrating GABA dysfunction in human depression as well as in preclinical rodent stress studies. Recent examples from researches in transgenic mice that shed light on how GABA interneuron subtypes can balance cortical transmission & ultimately shape top down control of depression & anxiety-like behaviors. Finally, based on recent studies, we propose how intra-cortical GABA inhibition in the PFC can provide important therapeutic targets for the treatment of depression & other psychiatric illness.

From early development to adulthood GABA interneurons play crucial role in assembling the micro circuitry & orchestrating the activity of the cerebral cortex. Impairments in the function of the cortical GABAergic transmission exert a strong influence on brain function, including cognitive, learning, mood & behavior. Here, we highlight recent findings that are beginning to delineate how changes in various components of the PFC GABAergic microcircuit are casually linked to stress & depression. Indeed, the studies of ketamine & scopolamine have generated considerable excitement, pointing to a vital role of GABAergic transmission in the effects of rapid acting antidepressants & in the development of next-generation therapeutics.

Despite intensive research, we are left with several significant gaps in our understanding of GABA/glutamate balance in the pathophysiology of depression & other stress related illnesses. One problem that has hindered the complete understanding of the underlying cause of depression is the lack of techniques to selectively manipulate each interneuron subtype. This is now being addressed with advances in optogenetics, chemo genetics, micro endoscopy, & imaging technology; these approaches will allow studies to determine the influence of stress on the activity of GABA interneuron subtypes & the effects of activation or inhibition of specific GABA cell populations on neighboring GABA & principle neurons, as well as behavior. Moreover, analysis of sex specific differences in stress-induced effects on GABA interneuron populations are surprisingly incomplete & could lead to improved treatments for women who suffer higher rates of depression compared to men. Progress & new insights in these areas will help us to generate alternative & more efficacious therapeutic strategies & eventually prevention of stress related illnesses such as depression.

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