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Stress, ethanol, and neuroactive steroids

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Abstract

Neurosteroids play a crucial role in stress, alcohol dependence and withdrawal, and other physiological and pharmacological actions by potentiating or inhibiting neurotransmitter action. This review article focuses on data showing that the interaction among stress, ethanol, and neuroactive steroids may result in plastic molecular and functional changes of GABAergic inhibitory neurotransmission. The molecular mechanisms by which stress–ethanol–neuroactive steroids interactions can produce plastic changes in $GABA_A$ receptors have been studied using different experimental models in vivo and in vitro in order to provide useful evidence and new insights into the mechanisms through which acute and chronic ethanol and stress exposure modulate the activity of GABAergic synapses. We show detailed data on a) the effect of acute and chronic stress on peripheral and brain neurosteroid levels and $GABA_A$ receptor gene expression and function; b) ethanol-stimulated brain steroidogenesis; c) plasticity of $GABA_A$ receptor after acute and chronic ethanol exposure. The implications of these new mechanistic insights to our understanding of the effects of ethanol during stress are also discussed. The understanding of these neurochemical and molecular mechanisms may shed new light on the physiopathology of diseases, such as anxiety, in which GABAergic transmission plays a pivotal role. These data may also lead to the need for new anxiolytic, hypnotic and anticonvulsant selective drugs devoid of side effects.

Keywords: Neuroactive steroids; Stress; Ethanol; $GABA_A$ receptor plasticity; $GABA_A$ receptor function; Rat

Abbreviations: ACTH, Adrenocorticotropic hormone; ADX, Adrenalectomized; CRF, Corticotropin-releasing factor; DBI, Diazepam binding inhibitor; GABA, γ-aminobutyric acid; GHB, γ-hydroxybutyrate; HPA, Hypothalamic–pituitary–adrenal; IPSC, Inhibitory postsynaptic current; mIPSC, Miniature IPSC; ORX, Orchiectomized; PBR, Peripheral benzodiazepine receptor; StAR, Steroidogenic acute regulatory protein; TBPS, *t*-butylbicyclophosphorothionate; THIP, 4,5,6,7-tetrahydroisoxazolo-pyridin-3-ol; 3α,5α-THDOC, 3α,21-dihydroxy-5α-pregnane-20-one; 3α,5α-THP, 3α-hydroxy-5α-pregnane-20-one.

Contents

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1. Introduction

In the last twenty years, the study of GABAergic transmission has become one of the most fascinating fields of research in neuropsychopharmacology. Thus, $GABA_A$ receptors, first indicated to be one of the major targets involved in the physiopathology of anxiety disorders are now suggested to play crucial role also in the modulation of those neuronal pathways involved in mental disorders such as depression, schizophrenia and drugs of abuse.

The more recent discovery that endogenous compounds such as steroid derivatives produced by both peripheral organs and brain have the capability to induce, through the activation of $GABA_A$-mediated neurotransmission, behavioral changes indistinguishable from those elicited by anxiolytic drugs suggested that these hormones may play a physiological role in the etiology of some of the above mentioned mental disorders and more in general to stress-associated diseases.

All these findings have suggested that understanding the functional significance of the fluctuations in the brain content of neuroactive steroids induced by physiological, pharmacological and pathological conditions makes an important contribution to clarify the neuroendocrine and neurochemical mechanisms by which regulating the (threshold) the threshold excitability and the functional properties of specific neuronal populations localized in brain areas involved in the modulation of the emotional and affective responses. Previous evidence that acute stress induces parallel but opposite changes in $GABA_A$ receptor function (reduction) and in brain content of neuroactive steroids (increase), together with the more recent data revealing that chronic stressful conditions reduce neuroactive steroid content in plasma and brain, further indicate that these hormones may play a crucial role not only in the physiological modulation of brain homeostasis, but also under environmental, chemical, pharmacological and pathological stressful stimuli associated with changes in the function of different neurons. Consistent with this conclusion different laboratories have recently shown that, like stress, ethanol intake and withdrawal, change the peripheral and central secretion of neuroactive steroids, an effect associated with parallel changes in $GABA_A$ receptor function and gene expression of selective subunits assembled in synaptic and extrasynaptic $GABA_A$ receptors.

Given that stressful conditions able to change neurosteroid brain content and $GABA_A$ receptor function are often associated with long-lasting increases in ethanol intake, we consider it of interest to report recent data obtained by our group and other authors showing the most relevant functional and molecular events involved in the interaction between neurosteroids and $GABA_A$ receptors during stressful conditions, acute and chronic ethanol intake and withdrawal. Mainly, the results reported have indicated that neuroactive steroids synthetized in peripheral organs and brain play a role in modulating the plastic and functional changes elicited by stress and ethanol on $GABA_A$-mediated neurotransmission in a way and through mechanisms similar to those associated to the changes of $GABA_A$ receptor gene