

INFLUENCE ON NEUROACTIVE STEROIDS AND GABA_A RECEPTOR PLASTICITY AND FUNCTION BY CHRONIC STRESS

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We have previously demonstrated that social isolation of rats immediately after weaning is associated to a reduction in the cerebrocortical and plasma concentrations of progesterone and its metabolites $3\alpha,5\alpha$ -TH PROG and $3\alpha,5\alpha$ -THDOC. In socially isolated (SI) rats the level of α_2 , α_4 and δ subunits immunoreactivity was found to be increased, while the amounts of α_1 and γ_2 were decreased, throughout the hippocampus compared with that apparent in group-housed (GH) rats. The functional response of the HPA axis to acute stimuli (foot shock stress or acute i.p. injection of ethanol, ETH) is markedly increased in SI rats. Moreover, acute administration of ETH in SI rats increases the level of $3\alpha,5\alpha$ -TH PROG to a greater degree in the cerebral cortex than in plasma. ETH also increased the amplitude of GABA_A receptor-mediated miniature inhibitory postsynaptic currents (mIPSC) recorded from CA1 pyramidal neurons with a greater potency in hippocampal slices prepared from SI rats than in those from GH, an effect inhibited by finasteride, an inhibitor of the 5α -reductase. Accordingly, the ability of ETH to inhibit isoniazid-induced convulsions is greater in SI rats than in GH animals an effect prevented by treatment with finasteride. Voluntary ETH consumption, that is increased during social isolation, abolished both the reduction of the brain and plasma concentrations of $3\alpha,5\alpha$ -TH PROG and the enhanced potency of ethanol on mIPSC recorded from CA1 pyramidal neurons. However, the amplitude of GABA_A receptor-mediated tonic inhibitory currents in granule cells of the dentate gyrus, greater in hippocampal slices from SI rats than in those from GH animals, was further increased in SI animals. Voluntary ETH consumption was associated with small, but significant, further enhancement of the amount of δ subunit immunoreactivity throughout the hippocampus and an increase in α_1 subunit. At variance, this treatment did not further modify the hippocampal level of α_2 , α_4 and γ_2 subunits in SI rats. These observations and the finding that SI rats are more sensitive to the effects of ethanol on the brain concentrations of $3\alpha,5\alpha$ -TH PROG and $3\alpha,5\alpha$ -TH DOC, both of which possess anxiolytic properties and potentiate the central actions of ethanol, suggest that chronic stress may induce plastic adaptation of neuronal systems that contributes to a vulnerability to alcohol abuse.

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