NEUROSTEROID-MEDIATED INCREASE OF GABAergic TONIC INHIBITION IN RAT DENTATE GYRUS GRANULE CELLS BY ETHANOL

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γ-aminobutyric acid type A ($GABA_A$) receptors are responsible for mediating the fast component of the inhibitory neurotransmission in the central nervous system, and are considered sensitive targets for the actions of ethanol (EtOH). Recent evidence has accumulated to suggest that certain pharmacological effects of EtOH may result from an increased brain concentrations of neuroactive steroids such as 3α,5α-THProg, a potent and efficacious positive modulator of $GABA_A$ receptors. Our lab has also suggested that EtOH may stimulate hippocampal steroidogenesis independently from the activity of the HPA axis, an effect that results in an increased synaptic $GABA_A$ receptor function in CA1 pyramidal neurons. Given that extrasynaptic $GABA_A$ receptors containing the α4 and δ subunits, such as those expressed in dentate gyrus granule cells (DGGCs), are particularly sensitive to 3α,5α-THProg, in the present study we examined the effect of EtOH on tonic GABAergic currents in DGGCs and determined the role of hippocampal steroidogenesis. Whole-cell patch clamp recording of GABAergic tonic currents was performed in DGGCs (V_{hold} = -65 mV), present in coronal hippocampal slices prepared from Sprague-Dawley rats, before, during, and after perfusion of EtOH (50 -100 mM) for 30 min. EtOH increased tonic current noise variance in DGGCs in a time-dependent manner, with an onset of about 20-30 min. Perfusion for 30 min of 100 mM EtOH resulted in a 15 ± 2.5% increase ($p < 0.05$; $n = 19$) over the EtOH pre-exposure basal level. On the other hand, we found no significant change in tonic current noise variance during the initial 10 min of EtOH exposure (6 ± 2.1% change). In addition, EtOH did not alter tonic current shift produced by the exposure of 20 μM bicuculline at any time point. EtOH-induced increase in tonic current noise variance was completely prevented by the co-application of the 5α-reductase inhibitor finasteride (1 μM). These results demonstrate that exposure of hippocampal slices to EtOH for 30 min results in the stimulation of local neurosteroid concentration at relevant levels to modulate the function of DGGC extrasynaptic $GABA_A$ receptors.

Supported by INIA-Stress Consortium - NIAAA