ETHANOL WITHDRAWAL AND $GABA_A$ RECEPTOR PLASTICITY

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The subunit composition of native $GABA_A$ receptors plays an important role in defining their function in the physiological and pharmacological modulation of neuronal excitability and associated behaviour. The pattern of $GABA_A$ receptor gene expression is affected by environmental stimuli, physiological processes, and drugs that modulate $GABA_A$ receptor-mediated neurotransmission. $GABA_A$ receptors have been indicated as a major target site for ethanol and neurosteroids. Prolonged exposure to and subsequent withdrawal of ethanol and neurosteroids are associated with marked and specific changes in $GABA_A$ receptor subunit gene expression as well as in receptor function and pharmacological sensitivity in cultured rat neurons. Here, we focused our study on the effects of either exposure to chronic ethanol or progesterone and their subsequent withdrawal on the expression of the δ subunit of the $GABA_A$ receptors in cultured rat hippocampal neurons. $GABA_A$ receptors containing δ subunit are preferentially extrasynaptic, are responsible for the tonic inhibition and possess greater sensivity to the agonist THIP, to the neurosteroid allopregnanolone as well as to low concentrations of ethanol. Immunocytochemical and confocal microscopy studies showed that δ subunit is preferentially expressed on the dendrites in hippocampal neurons. Long-term ethanol exposure increased δ subunit mRNA and peptide levels in hippocampal neurons. In contrast ethanol withdrawal was associated to a time related return of δ mRNA and protein to values found in untreated cells. Progesterone exposure increased both δ subunit mRNA and protein during the first 24h but produced a marked decrease in the amount of the both mRNA and protein after 6 days of treatment. During withdrawal, the abundance of δ subunit mRNA and protein was increased at 9h and 12h when compared to untreated cells. This effect on mRNA and protein returned to control level by 12h and 24h, respectively. Prevention of allopregnanolone synthesis by the 5α-reductase inhibitor finasteride prevented the changes in both mRNA and protein levels of δ subunit elicited by progesterone. The molecular events observed during ethanol or progesterone treatment and following withdrawal were also accompanied by parallel changes in the function of $GABA_A$ receptor. The changes in gene expression and function of $GABA_A$ receptor containing the δ subunit induced by chronic exposure and withdrawal of ethanol and progesterone are opposite in hippocampal cells. These results suggest complex and distinct mechanisms of regulation of the expression of δ subunit of $GABA_A$ receptors.