EFFECTS OF STEROIDS WITHDRAWAL ON $GABA_A$ RECEPTOR δ SUBUNIT GENE EXPRESSION AND RELATED FUNCTION

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Type A receptors for γ-aminobutyric acid ($GABA_A$ receptors) that contain the δ subunit are implicated in modulation of neuronal excitability through tonic inhibition. The experimental observation that mice lacking the δ subunit became markedly less sensitive to neuroactive steroids suggested that the δ subunit-containing $GABA_A$ receptors could play a pivotal role in the modulatory action of neuroactive steroids on the GABAergic transmission. This notion is currently supported by a plethora of evidences making δ-containing $GABA_A$ receptors good candidates to be the preferential target of action of endogenous neuroactive steroids. In this study we examined the effects of chronic exposure to and subsequent withdrawal of progesterone or its metabolites allopregnanolone (AP) and THDOC on the gene expression of the δ subunit of $GABA_A$ receptors and on receptor function in cultured rat cerebellar granule cells. RNase protection assays revealed that exposure of cultures of cerebellar granule cells to 1 μM progesterone for 1 to 5 days did not significantly modify the abundance of the mRNA encoding for the δ subunit of the $GABA_A$ receptor, whereas 5 days of treatment significantly decreased of about 21% the abundance of the corresponding δ subunit peptide. The decrease in δ subunit peptide induced by chronic progesterone treatment was comparable to that induced by AP and THDOC. In addition, progesterone withdrawal drastically reduced δ subunit mRNA abundance at any tested day of exposure in a range between 32 and 47% and this decrease was accompanied by a reduction of about 46% of the corresponding peptide. These effects were time dependent and abolished by finasteride. Using whole-cell patch-clamp electrophysiological recordings we found that chronic progesterone exposure slightly reduce the modulatory effect of 1 μM AP (144% potentiation) on THIP-evoked Cl^- current compared with that apparent in control cells (187%). However, withdrawal of progesterone was associated with a significant decrease (51% potentiation) in AP efficacy. These data well correlate with the progesterone withdrawal-induced down-regulation of the δ subunit and are consistent with the notion that progesterone metabolites play a key role in modulation of GABAergic synapses and that fluctuations in their concentrations observed in physiological and patho-physiological conditions, or induced by pharmacological treatments, could play a major role in the temporal pattern of expression of various subunits of the $GABA_A$ receptor with related changes in their function.