CHANGES IN NEUROACTIVE STEROIDS LEVELS, $GABA_A$ RECEPTOR PLASTICITY AND SENSITIVITY TO ANXIOLYTIC DRUGS INDUCED BY NEONATAL EXPOSURE TO ESTROGEN

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Neuroactive steroids are steroids that, independently of their peripheral or central origin, exerts a rapid, non genomic, effect on excitability of neurons through a direct modulation of the activity of membrane receptors. The progesterone reduced metabolites, allopregnanolone and THDOC, are potent positive modulators of the type A receptor of gamma-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the brain which is involved in the regulation of neuronal excitability. The observation that these compounds are selective modulators of GABAergic transmission suggests that endogenous changes in plasma and brain concentrations of these compounds induced by physiological conditions (estrus cycle, pregnancy, menopause) might affect the activity of $GABA_A$ receptors. Reproductive aging in female mammals is characterized by a progressive decline in fertility and changes in neuroendocrine axis. Exposure of neonatal female rats to estrogens, has been proposed as an early animal model of reproductive senescence. Administration of estradiol benzoate (10 μg/50μl/rat, s.c.) on day of birth results in a decrease of cerebral cortical and hippocampal concentrations of progesterone (-79% and -76%, respectively) and allopregnanolone (- 90% and - 47%, respectively), measured 60 days after birth. The plasma concentrations of these steroids are also reduced but by smaller extent. On the contrary, THDOC levels were not significantly modified in both brain areas. The decrease in brain allopregnanolone levels are associated by increased expression of specific subunits (α1 and γ) of $GABA_A$ receptors in both brain areas. Moreover, in the elevated plus-maze test, diazepam (0.5-2 mg/Kg i.p.) induced a greater increase of the time spent in the open arms in neonatally estrogenized females with respect to control females suggesting an increased sensitivity to the anxiolytic action of this drug. The evidence that the persistent decrease in the plasma and brain concentrations of progesterone and allopregnanolone induced by estrogen administration to neonate female rats is associated with a plastic adaptation of $GABA_A$ receptor gene expression in brain and changes in the sensitivity to GABAergic drugs, suggests that this treatment might represent an useful experimental model in which to further investigate the physiological role of these steroids in the modulation of GABAergic transmission.