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Sex and stress steroid modulation of GABA mediated chloride ion flux in rat CNS

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Abstract

Background: Sex and stress steroids are metabolized to 3α-hydroxy-pregnane-steroid metabolites such as allopregnanolone (Allo) and tetrahydrodeoxycorticosterone (THDOC). Allo and THDOC are neuroactive steroids that are metabolized in the brain and act in brain as potent positive $GABA_A$ receptor function modulators. Allo as well as THDOC levels increase during stress. Allo has been associated with a number of symptoms and malfunctions such as impaired memory function and negative mood symptoms in a subgroup of individuals both for animals and humans. Pregnane steroids with 3β-hydroxy-configuration (3β-steroids) have been shown to reduce the Allo enhanced GABA effect.

Aims: The aims for the present thesis were to investigate the effect of 3β-steroids on the GABA mediated $GABA_A$ receptor function in presence of positive $GABA_A$ receptor modulators. Further, the regional variances between the 3β-steroids as well as the mechanism of the effect were studied. Finally, the effect of stress steroid metabolites on the $GABA_A$ receptor function was investigated.

Results: 3β-OH-5α-pregnane-20-one reduced the Allo enhanced GABA mediated chloride ion uptake into cortical microsacs. The 3β-isomer reduced the efficacy of Allo without shift the concentration response curve. It is therefore suggested that the 3β-isomer has a non-competitive effect. Further, it was shown that the 3β-isomer reduced the Allo effect in a selective way since the 3β-isomer did not interact with other positive modulators or with GABA itself. Five tested 3β-steroids reduced the Allo enhanced GABA mediated chloride ion uptake in cerebral cortex and hippocampus as well as the Allo prolongation on spontaneous inhibitory postsynaptic currents (sIPSCs) in preoptic nucleus. In cerebellum on the other hand the 3β-steroids showed to have weaker or no effect compared to the other tested regions. Interestingly, in absence of Allo, two of the 3β-steroids positively modulated the GABA stimulated $GABA_A$ receptor function. In absence of Allo, 5β-pregnane-3β,20(R)-diol increased the desensitization rate of current response. In contrast to the reducing effect on the Allo induced prolongation on sIPSCs, the effect of the 3β-steroid on GABA application, was not altered in presence of Allo. The mechanism of the 3β-steroid is therefore suggested being desensitization dependent in contrast to Allo, which has been suggested to decrease the GABA unbinding rate. In contrast to the enhanced effect of Allo, glucocorticoid metabolites reduced the GABA mediated chloride ion uptake in a concentration dependent way. The results in present thesis indicate that both sex and stress steroid metabolites interact with the $GABA_A$ receptor function. The knowledge that diversity of endogenous steroids interact with the $GABA_A$ receptor function is of importance for further understanding of different sex and stress steroid related symptoms and syndromes.

Keywords: Allopregnanolone, chloride ion uptake, patch-clamp, 3β-steroids, kinetic parameters, rat brain