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Abstract :

Background Animal models can be used to mimic human conditions of psychopathology, and also as pre-clinical models to evaluate candidate drugs. With hormonal treatment it is possible to produce behavior in the rat which corresponds to the mental symptoms of pre-menstrual syndrome (PMS), and pre-menstrual dysphoric disorder (PMDD). PMS affects 25-30 % of all women in fertile age and 3-8% are diagnosed with the more severe condition PMDD. The cardinal mental symptoms are; irritability, mood-swings, depression, anxiety, fatigue, insomnia, difficulties with concentration and memory and learning difficulties. The symptoms of PMS/PMDD occur in the luteal phase in conjunction with increasing concentrations of progesterone (P4) and P4-metabolites. In anovulatory cycles the symptoms are absent. The hormones which produce the monthly reoccurring negative symptoms on mood are foremost the neuroactive metabolites; allopregnanolone (ALLO) and tetrahydrodeoxycorticosterone (THDOC). ALLO is produced by the corpus luteum, but can also be synthesized in the brain, both ALLO and THDOC can also be released from the adrenal cortex during stress. These steroids are active on the inhibitory GABA neurotransmitter system through the GABA_A receptor, and the effects are similar to that of alcohol and benzodiazepines. These steroids have strong sedative and hypnotic effects. A paradox is that some individuals seem to react with negative mood on sex steroids while all fertile women

have the cyclical steroid changes during the menstrual cycle. Some individuals are more sensitive to neuroactive steroids with influences of personality, heritability and stress factors.

Aims The thesis aims were to develop pre-clinical animal models of PMS/PMDD and to investigate induction of ALLO tolerance, individual sensitivity to neurosteroids and the interactions between chronic social stress and neurosteroids.

Methods In these studies male and female Wistar rats were used to test steroid hormone effects on learning and memory and behaviors analogous to negative mood symptoms. This was accomplished through hormonal treatment and a subsequent withdrawal period from P4 (P4) + estradiol (E2) (PEWD), or ALLO. To assess tolerance, memory and learning in the Morris water maze (MWM) was studied. Anxiety-like behaviors were tested with the elevated plus maze (EPM), open field test (OFT), and the intruder test (IT). The EPM or OFT was used to classify the rats as high or low responders on risk-taking and explorative behavior (HR/LR). For social ranking order assessment the tube test (TT) and food competition test (FCT) were used. Chronic social stress was accomplished through co-habituation with two older rats (chronic subordination stress). In female rats the estrous cycle followed using staining of vaginal smears. Concentration of corticosterone (CORT) was measured by radio-immuno-assay (RIA).

Results In the MWM ALLO pre-treatment produced tolerance to the acute negative ALLO effects. Both male and female rats showed behavioral correlations between the EPM and OFT tests, and correlations were also seen in CORT levels. Individuals with the stable trait of high risk-taking and explorative behavior (HR) were more sensitive to PEWD induction of anxiety-like behavior. These animals also showed decreased CORT levels during withdrawal. Chronic subordination stress enhanced the response to PEWD on measures of locomotor activity and social anxiety-like behavior.

Conclusions It is possible to induce tolerance to the negative ALLO effects on learning and memory. The animal models of anxiety-like behavior show an individual PEWD response profile where HR rats are more sensitive. Exposure to chronic social stress enhanced the PEWD response. Hence there are both inherent and environmental factors behind the behavioral response to steroid hormones in rats.