Stress during gestation and exposure to an indirect cannabinoid agonist during adolescence alter brain metabolism in mice

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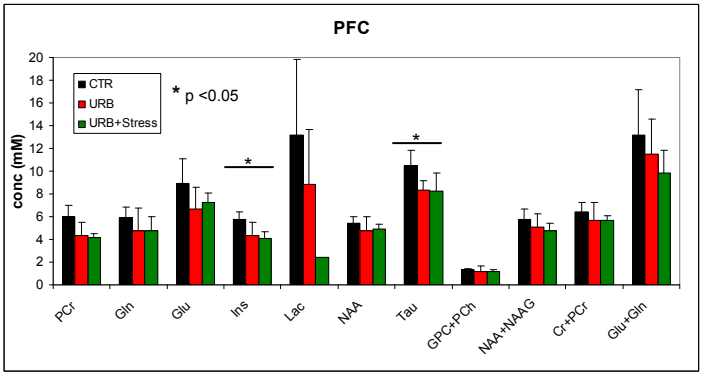
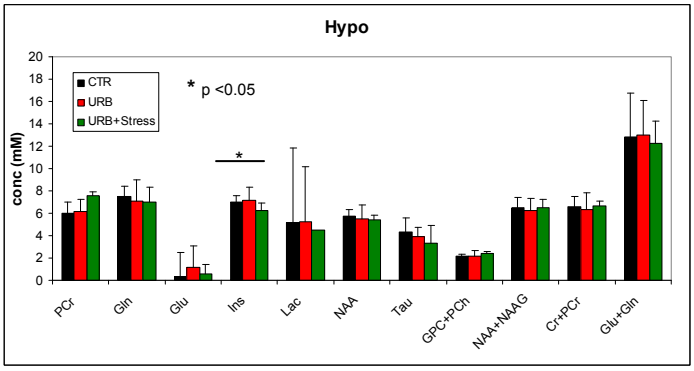
Introduction -
Current evidence indicates that the endocannabinoid system (ECS), the set of endocannabinoids (anandamide and 2-AG) and their receptors, is directly involved in the perception of emotions (1). Specifically, the levels of endocannabinoids have been shown to fluctuate in response to both positively and negatively salient events. Additionally, the ECS has been proposed to persistently regulate the individual reactivity to environmental stimuli. Stress during embryonic development, in the form of repeated maternal daily restraint, has been shown to upregulate hormonal stress reactivity and to increase indices of behavioural fearfulness in adult rodents (2, 3). Altered brain metabolism has also been detected in prenatal-stressed adult rodents (4).
Here, we investigated whether prenatal stress, combined with a pharmacological modulation of the endocannabinoid system during adolescence influenced adult mouse behaviour and metabolism by in vivo ^{1}H MRS.

Methods -
To mimic pre-natal stress, we exposed pregnant CD1 mice to elevated levels of corticosterone (100 mg/kg) during the last week of gestation. Adolescent mice thereon generated were exposed during adolescence (i.e. between postnatal day, P, 29-39) to an indirect cannabinoid agonist (daily URB597, 0.4 mg/kg). Three groups of animals have been analysed by MRI/MRS: adolescent URB exposed (n=7), adolescent URB exposed and prenatally stressed (n=7) and controls (n=7).
MR examinations were performed on a VARIAN Inova MRI/MRS system operating at 4.7 T, by using a volume coil as transmitter and a surface coil constructed for mouse head as receiver (RAPID Biomedical). Multislice fast spin echo (TR/TEeff = 3000/70 ms, ns = 2, slice thickness 1 mm, matrix 128 x 256) sagittal images were acquired to localise the regions of interest. Single voxel localised ^{1}H MR spectra (PRESS, TR/TE = 4000/23 ms, ns = 256) were collected from: prefrontal cortex (PFC), 6.8 μl; dorsal striatum (STR), 16 μl, hippocampus (Hip), 11.7 μl and hypothalamus (Hypo), 8.8 μl. Spectra were analysed by using LCModel fitting program (5). The unsuppressed water signal was used for metabolite quantification. Statistical analyses were performed through sequentially rejective Bonferroni t-tests. Such statistical test strategy was needed in order to sequentially investigate the main effect of URB597 exposure and then whether prenatal stress further affected the observed phenotype.

Results -
During adolescence, both prenatal stress and pharmacological modulation of the ECS resulted in reduced locomotion, evaluated through automated infrared photobeams in the home-cage during a single 5-hr session. In adulthood, maternal stress during gestation also resulted in increased behavioural anxiety measured in a 0-maze test. Finally, while URB597 resulted in a long term reduction in inositol and taurine concentration in the prefrontal cortex [t (1,10)=6.4, P=0.03, t (1,11)=13.3, P=0.004, respectively], prenatal stress apparently reduced inositol concentrations in the hypothalamus [t (1,18)=5.63, P=0.03].





Discussion and Conclusion –
Present data further corroborate the view that stress during gestation and pharmacological activation of the endocannabinoid system during adolescence persistently modify the emotional regulations in adult mice. Thus, we also observed persistent alterations in brain metabolism putatively related to emotional disturbances. Specifically, whereas taurine has been associated with the onset of schizophrenia and depression (6, 7) inositol has been shown to modulate anxiety-related responses (8). The present study indicates that prenatal stress might affect emotional regulations and individual responses to pharmacological stimulation of the ECS.

References

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