

Environmental stimulation during development modulates individual behavioural and neurochemical responses to cannabinoid agonists in mice: a ¹H MRS study

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Introduction – Clinical and experimental studies indicate that adverse environmental conditions may favor the onset of emotional disturbances and increase the vulnerability towards the effects of the consumption of psychoactive drugs. Conversely, stimulating environmental conditions may exert a protective or compensatory role. Neurobiological systems such as the hypothalamic-pituitary-adrenal (HPA) and the endocannabinoid system (ECS) interact to modulate the expression of emotions. Here we analysed by ¹H MRS and behavioral tests in adulthood how exposure to stimulating environments during development (childhood and adolescence) modulates individual response to the administration of an ECS agonist during adolescence.

Methods - Newborn (postnatal days, PND, 1-8) CD1 mice were exposed to a moderate dose of corticosterone (LC, 33.3 mg/l) supplemented in the maternal drinking water; an independent group of mice were housed in environmentally enriched (EE) conditions (physical and social stimuli were provided) between weaning and adulthood. Adolescent mice (PND 23-33) were administered an ECS agonist (JWH-018, 0.3 mg/kg) or vehicle 0.9% saline (99%), and ethanol (1%). ¹H MRS experiments were performed at adulthood (PND>120) 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 sagittal images (TR/TE=3000/70 ms, 13 consecutive slices of 0.8 mm thickness, FOV=20 x20 mm², matrix of 128x128, ns=2)s were acquired to localise the regions of interest. ¹H localised MR spectra (PRESS sequence, TR/TE = 4000/23ms, ns=256 or 512) were collected from the hippocampus (11.7 µl) and prefrontal cortex (5.9 µl). According to a quantitative protocol (1), which includes water T2 measurements, spectra were analysed by using LCModel fitting program (2) and the unsuppressed water signal for metabolite quantification. Data were analysed through multivariate analysis of variance (MANOVA) including metabolites as dependent variables and corticosterone exposure, environmental enrichment and JWH-018 administration as independent variables.

Results - Water T2 analyses confirmed that no changes occurred in the T2s. Alterations in brain metabolite concentrations have been found between the groups in both regions.

Here we consider the effect of LC administration and EE with respect to the adolescent treatment (JWH-018) separately.

For the first effect (LCxJWH-018) in the PFC we find a combined effect for total choline (tCho, p=0.02): each treatment increases the metabolite level, but their interaction is not additive. Regarding glutamine and glutamate pool (Glx) we find a significant increase (p=0.01) in the JWH-018 group (due mainly to a Glu increase) but no interactions with LC are detected. In Hip we find an interaction effect for the total NAA (tNAA, p=0.05): JWH-018 increase the level of total NAA and LC revert this effect (LC administration alone significantly decreases the level of NAA (p=0.03)).

For the other interaction (EExJWH-018) in PFC we find interaction effects for the following metabolites: tCho (p<0.0001), tNAA (p=0.003) and total creatine (tCr, p=0.01). For all these metabolites EE reverts the effect of the JWH-018 treatment. Also in Hip tNAA shows the same trend (p=0.04) while the Glu significantly increases in JWH-018-treated animals (p=0.01).

Exposure to JWH-018 during adolescence is associated, in the short-term, with hypomotility, analgesia and reduced body temperature; in the long-term, adolescent exposure to JWH-018 is associated with anhedonia, anxiety and increased rearing.

Discussion and Conclusion – Beside exerting independent behavioural and metabolic effects, exposure to stimulating environments contrasts some of the consequences of JWH-018 administration on behavior (hypolocomotion during adolescence and increased anxiety in adulthood) and brain metabolic profiles. These data support the hypothesis that moderate neonatal stress, environmental enrichment and pharmacological stimulation of the ECS contribute to the expression of emotions throughout the entire course of development.

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References

- 1) Canese et al NMR Biomed 2012.
- 2) Provencher Magn Reson Med 1993.

