TIME-DEPENDENT ALTERATIONS OF THE ENDOCANNABINOID SYSTEM AND SYNAPTIC MARKERS FOLLOWING ADOLESCENT Δ9-TETRAHYDROCANNABINOL (THC) ADMINISTRATION IN FEMALE RATS

E. Zamberletti[1], P. Prini[1], M. Gabaglio[1], F. Piscitelli[2], A. Ligresti[2], T. Rubino[1], D. Parolaro[1]

[1] Dept of Functional and Structural Biology, University of Insubria – Busto Arsizio, Italy

[2] Endocannabinoid Research Group, Institute of Biomolecular Chemistry, CNR – Pozzuoli (NA), Italy

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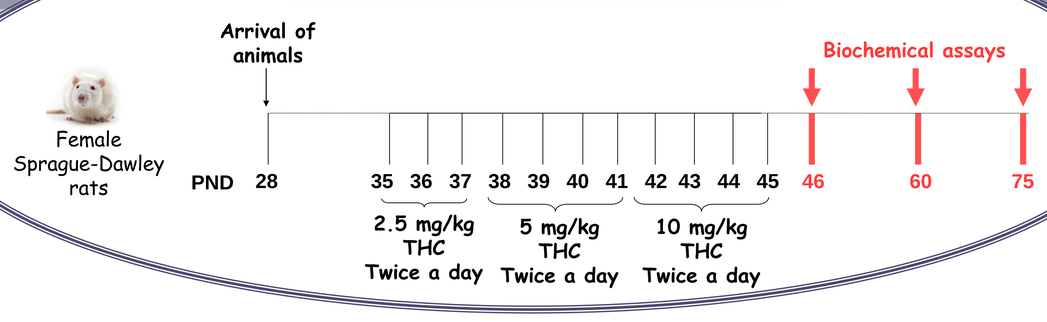
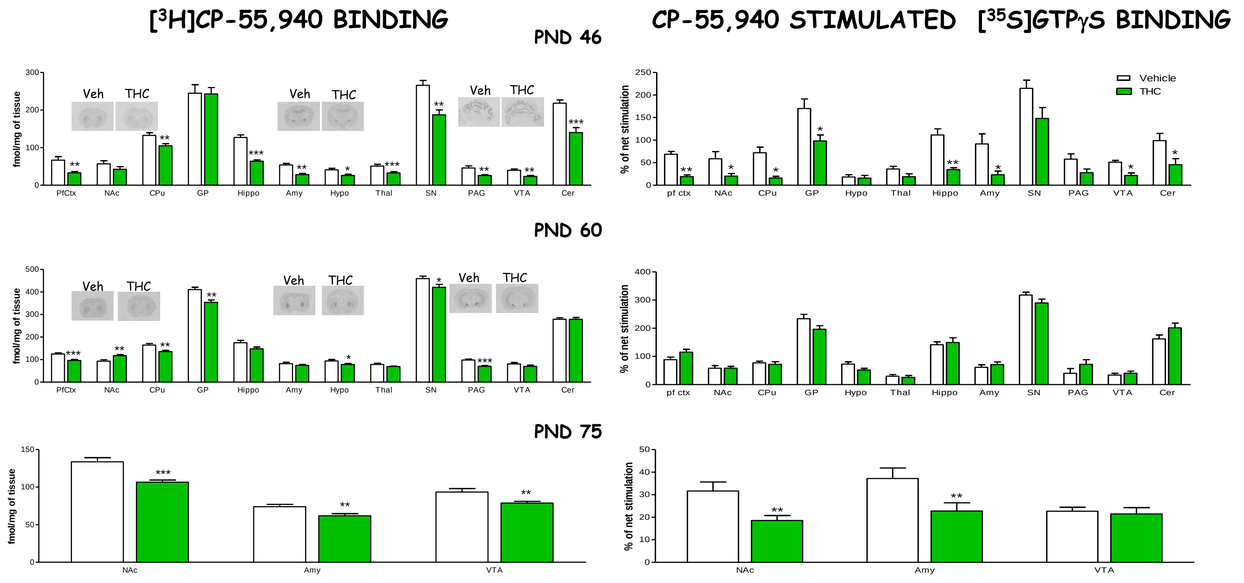
TREATMENT SCHEDULE



CB1 RECEPTOR FUNCTIONALITY



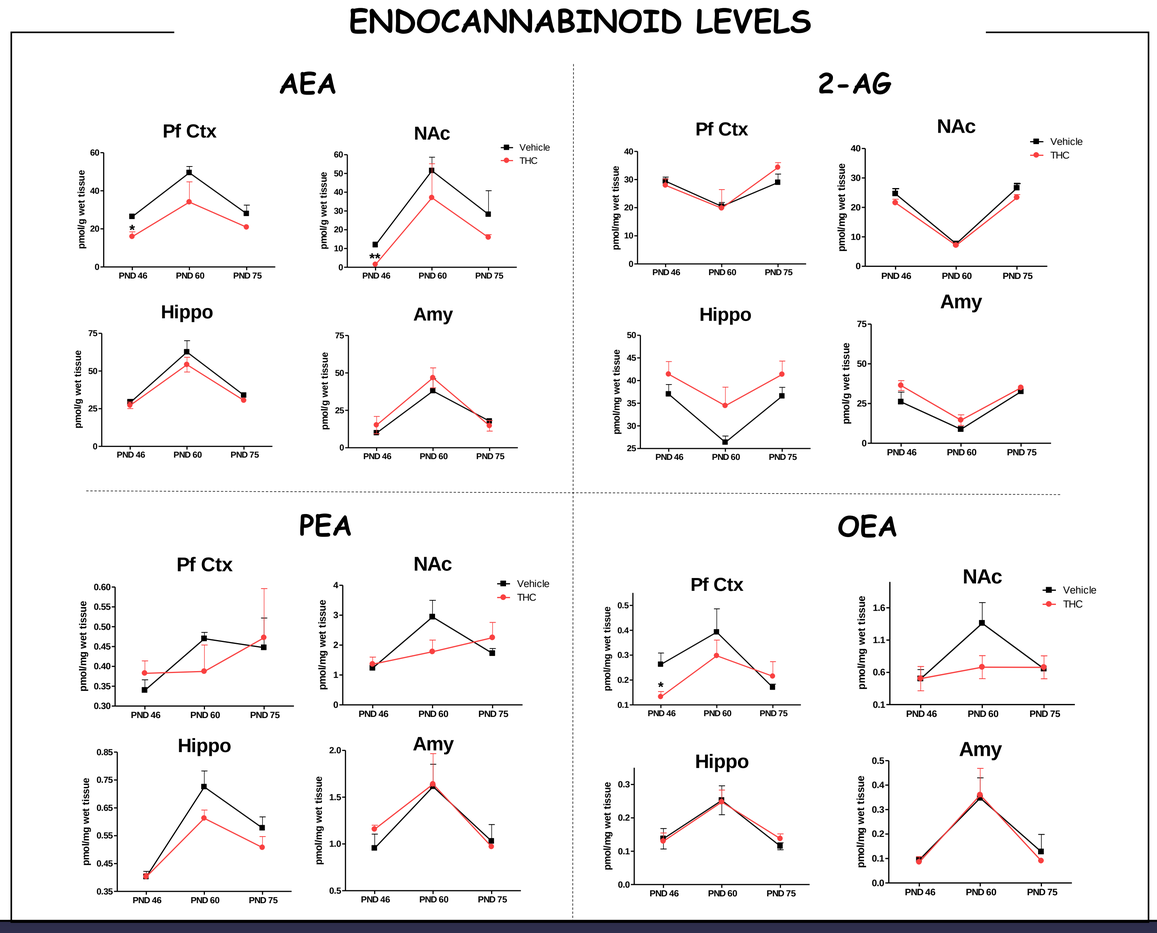
PND 46 → ↓ CB1 receptor density and G protein coupling widespread throughout the brain

PND 60 → ↓ CB1 receptor density (but ↑ in the NAc); no alterations in CB1 receptor/G protein coupling

PND 75 → ↓ CB1 receptor density in the NAc (20%), Amy (16%) and VTA (15%); ↓ CB1 receptor/Gprotein coupling in the NAc (41%) and Amy (38%) of THC-treated rats

THC TREATMENT INDUCED A LONG LASTING DOWNREGULATION IN CB1 RECEPTOR FUNCTIONALITY

ENDOCANNABINOID LEVELS



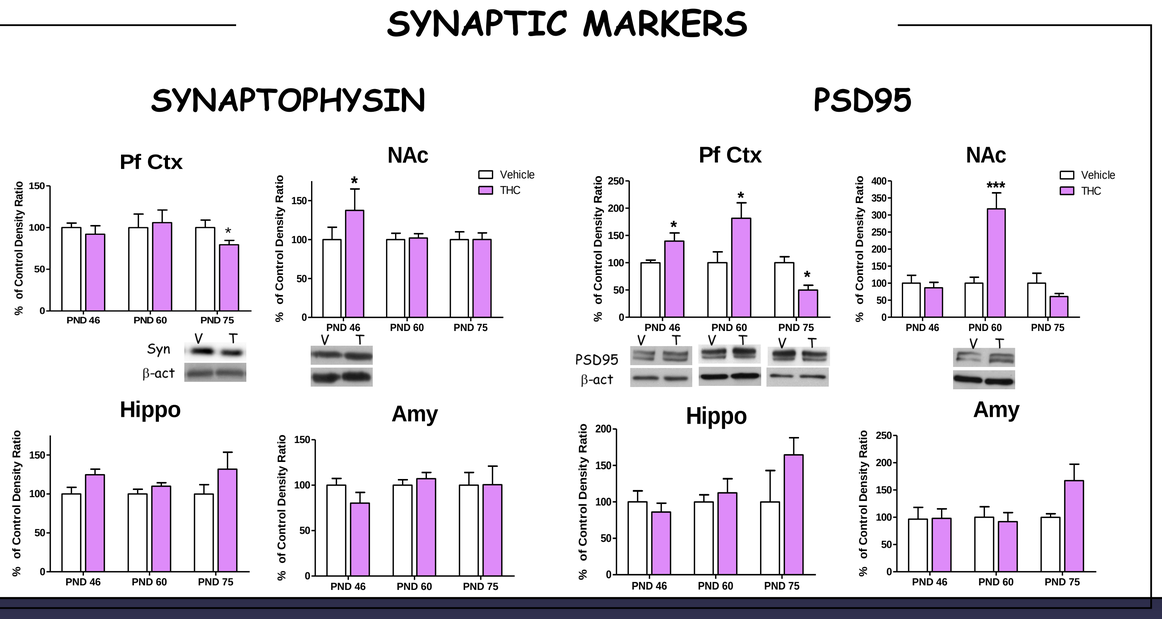
PND 46 → ↓ AEA in the Pf Ctx (40%) and NAc (87%); ↓ OEA in the Pf Ctx (49%)

PND 60 → ↓ AEA in the Pf Ctx (31%) and NAc (28%); ↓ PEA (39%) and OEA (50%) in the NAc

PND 75 → ↓ AEA in the Pf Ctx (25%) and NAc (43%)

THC TREATMENT SIGNIFICANTLY ALTERED THE ENDOCANNABINOID CONTENT DURING NEURONAL DEVELOPMENT COMPARED TO UNTREATED CONTROLS

SYNAPTIC MARKERS



PND 46 → ↑ Synaptophysin in the NAc (21%); ↑ PSD95 in the Pf Ctx (39%)

PND 60 → No alterations in synaptophysin levels; ↑ PSD95 in the Pf Ctx (40%) and NAc (300%)

PND 75 → ↓ Synaptophysin in the Pf Ctx (21%); ↓ PSD95 in the Pf Ctx (51%) and NAc (40%)

THC TREATMENT INDUCED SIGNIFICANT ALTERATIONS IN SYNAPTOPHYSIN AND PSD95 LEVELS IN THE Pf Ctx AND NAc

BACKGROUND

ADULT female rats chronically exposed to THC during adolescence show:

- A COMPLEX DEPRESSIVE-LIKE PHENOTYPE characterized by both emotional and cognitive impairments (Rubino et al., 2008, 2009; Realini et al., 2010);
- A MAJOR VULNERABILITY TO phencyclidine-induced PSYCHOTIC-LIKE SYMPTOMS (Rubino et al., ICRS 2010).

AIM

To clarify the POSSIBLE NEUROBIOLOGICAL CHANGES leading to the behavioural alterations observed in adult THC pre-treated rats, we analysed:

- CB1 RECEPTOR DENSITY AND G-PROTEIN COUPLING;
- ENDOCANNABINOID CONTENTS;
- PSD95 AND SYNAPTOPHYSIN LEVELS, two markers of synaptic plasticity;

…in the prefrontal cortex (Pf Ctx), nucleus accumbens (NAc), hippocampus (Hippo) and amygdala (Amy) of THC-treated and control rats.

…and performed all the biochemical tests AT DIFFERENT TIME-POINTS AFTER DISCONTINUING THC EXPOSURE.

MATERIALS AND METHODS

At each time-point, brains were removed and the following assays were performed.

CB1 RECEPTOR FUNCTIONALITY:

- [3H]CP-55,940 autoradiographic binding;
- CP-55,940-stimulated [35S]GTPγS binding in autoradiography.

ENDOCANNABINOID CONTENTS:

- LC-APCI-MS was performed on lipid extracts.

PSD95 AND SYNAPTOPHYSIN LEVELS:

- western blot on total lysate extracts.

CONCLUSIONS

Adolescent THC treatment induces:

✓ SIGNIFICANT CHANGES IN THE MATURATION OF THE ENDOCANNABINOID SYSTEM coupled with

✓ ALTERATIONS IN MARKERS OF SYNAPTIC PLASTICITY…

…THAT ARE PARTICULARLY EVIDENT IN THE Pf Ctx AND NAc,

brain areas characterized by a strong neuronal remodeling during adolescence since they are involved in processes of decision making and reward.

COULD DEFICITS IN THE MATURATION OF THE ENDOCANNABINOID SYSTEM DURING ADOLESCENCE DIRECTLY IMPACT THE NEURONAL REFINEMENT BY ALTERING SYNAPTOPHYSIN AND PSD95 LEVELS IN SPECIFIC BRAIN AREAS?

However, AN ENDURING FORM OF NEURONAL ADAPTATION IN THESE BRAIN AREAS FOLLOWING ADOLESCENT CANNABINOID EXPOSURE might disrupt normal neuronal development, possibly leading to the development of the behavioural phenotype observed in THC-treated rats at adulthood.

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No potential conflict of interest