P.297

PERIPUBERTAL TREATMENT WITH CANNABIDIOL REVERSES BEHAVIORAL ALTERATIONS IN Δ9-THC ANIMAL MODEL OF SCHIZOPHRENIA

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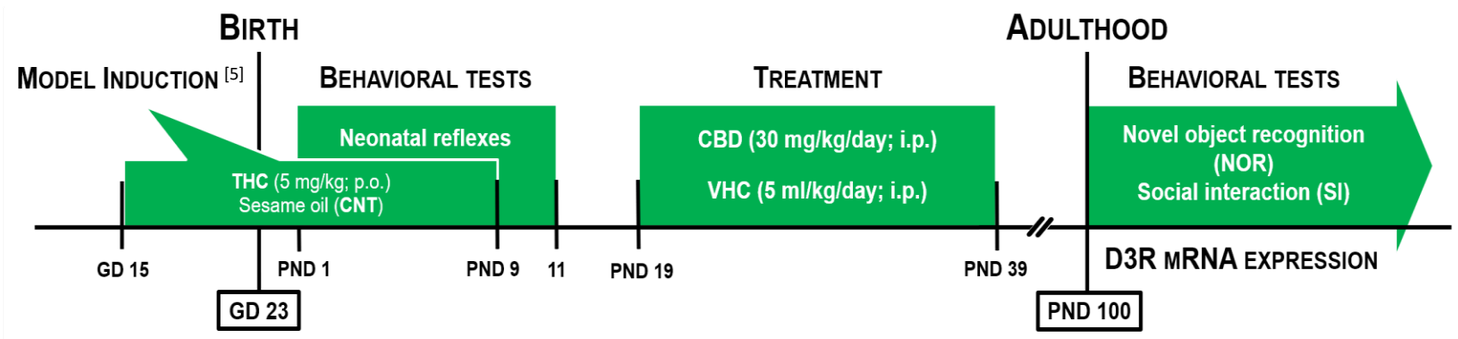
INTRODUCTION

Several studies suggest that disturbances in the neurodevelopment could lead to schizophrenia (SCZ), a psychiatric disorder with severe symptoms in cognitive and social domains [1]. While a variety of studies emphasize the role of the endocannabinoid system (ECS) in the neurodevelopmental dysregulation during perinatal and adolescent periods, mostly arising from well-known long-lasting negative effects of delta-9-tetrahydrocannabinol (Δ^9-THC, the main psychoactive compound of *Cannabis sativa*) [2,3], very little attention is dedicated to the positive potential of the ECS modulation in these sensitive periods as a preventive intervention. Given that preventive antipsychotic treatment seems to reduce the risk of transition to psychosis in vulnerable individuals [4], we hypothesized early modulation of ECS could be a potential novel therapeutic strategy.

AIMS OF THE STUDY

- To assess the effects of perinatal administration of Δ^9-THC on
  - the development of neonatal reflexes as marker of neurological maturation.
  - the development of behavioral phenotype resembling schizophrenia at adult age
  - mRNA expression of D3 receptors (D3R) in prefrontal cortex (PFC)
- To assess the potential of peripubertal treatment with cannabidiol to reverse Δ^9-THC induced alterations

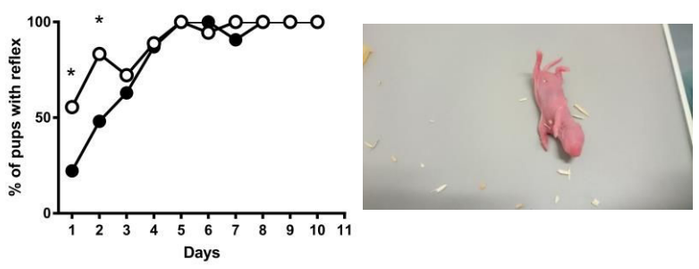
EXPERIMENTAL DESIGN



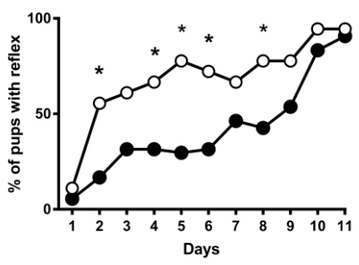
RESULTS

NEONATAL REFLEXES

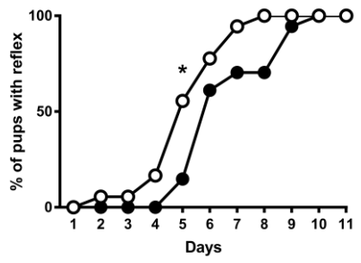
Righting



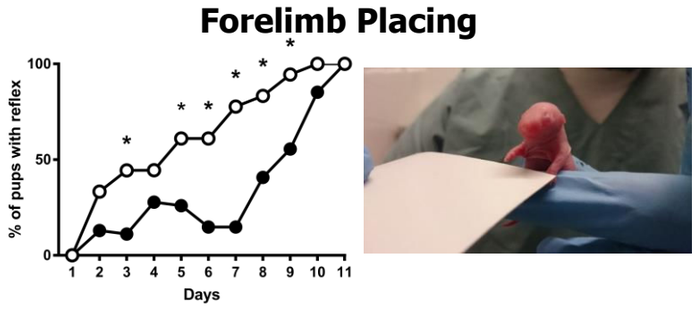
Cliff Aversion



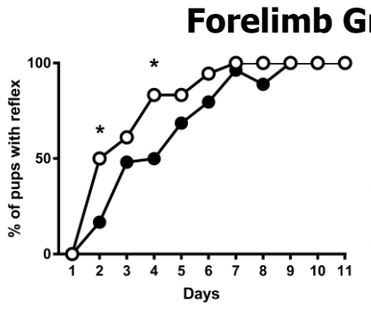
Bar Holding



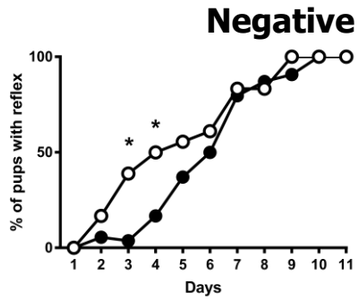
Forelimb Placing



Forelimb Grasping



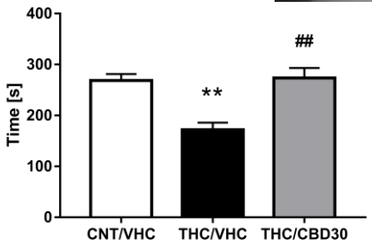
Negative Geotaxis



ADULT BEHAVIORAL PHENOTYPE

Social Interaction

- **Negative-like symptom**
- Each animal was allowed to freely explore unfamiliar congener for 10 min.

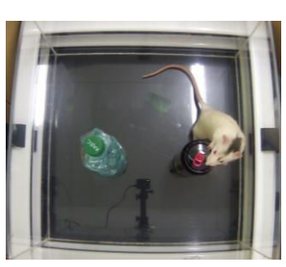


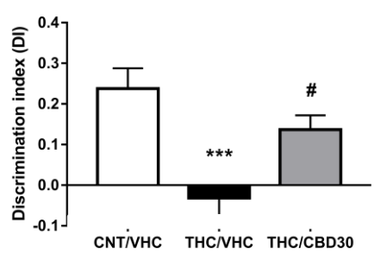
One-way ANOVA: p=0,0002; *post-hoc:* Tukey's MCT: ** p<0,01 vs CNT/VHC; ## p<0,01 vs THC/VHC

Novel Object Recognition

- **Cognitive deficit**
- familiarization (5 min)
- inter-trial (3 min)
- test (5 min)

$$DI = \frac{(Tn - Tf)}{(Tn + Tf)}$$



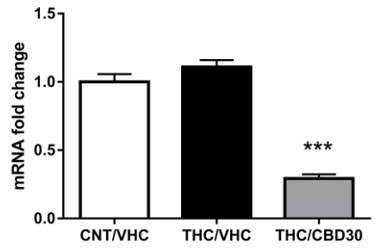


One-way ANOVA: p=0,0006; *post-hoc:* Tukey's MCT: *** p<0,001 vs CNT/VHC; # p<0,05 vs THC/VHC

ADULT PREFRONTAL CORTEX

D3 receptors (D3R)

- **Antagonism** at prefrontocortical D3 receptors improves performance in Social novelty discrimination and Novel object recognition [6].
- **Agonism** at prefrontocortical D3 receptors impairs performance in Social novelty discrimination and Novel object recognition [6].



One-way ANOVA: p=0,0001; *post-hoc:* Tukey's MCT: *** p<0,001 vs CNT/VHC

CONCLUSIONS

- Perinatal exposure to Δ9-THC delayed the development of neonatal reflexes in pups as marker of impaired brain maturation.
- Perinatal exposure to Δ9-THC induced schizophrenia-like phenotype at adult age.
- These abnormalities do not seem to be related to altered D3Rs gene expression in prefrontal cortex of Δ9-THC-exposed animals.
- Early pharmacological intervention with cannabidiol could be a promising therapeutic approach to prevent the development of social and cognitive aspects of schizo-affective disorders.

ACKNOWLEDGEMENTS

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REFERENCES

[1] Jones, C.A., Watson, D.J.G., Fone, K.C.F. (2011). Animal models of schizophrenia. *Br. J. Pharmacol*. 164, 1162–1194.

[2] Higuera-Matas, A., Ucha, M., & Ambrosio, E. (2015). Long-term consequences of perinatal and adolescent cannabinoid exposure on neural and psychological processes. *Neuroscience and Biobehavioral Reviews*, 55, 119–146. https://doi.org/10.1016/j.neubiorev.2015.04.020.

[3] Renard, J., Rushlow, W. J., & Laviolette, S. R. (2016). What Can Rats Tell Us about Adolescent Cannabis Exposure? Insights from Preclinical Research. *Canadian Journal of Psychiatry. Revue Canadienne De Psychiatrie*, 61(6), 328–334. https://doi.org/10.1177/0706743716645288.

[4] McGorry, P. D., Killackey, E., & Yung, A. (2008). Early intervention in psychosis: concepts, evidence and future directions. *World Psychiatry: Official Journal of the World Psychiatric Association (WPA)*, 7(3), 148–156.

[5] Campolongo, P., Trezza, V., Cassano, T., Gaetani, S., Morgese, M. G., Ubaldi, M., … Cuomo, V. (2007). Perinatal exposure to delta-9-tetrahydrocannabinol causes enduring cognitive deficits associated with alteration of cortical gene expression and neurotransmission in rats. *Addiction Biology*, 12(3–4), 485–495. https://doi.org/10.1111/j.1369-1600.2007.00074.x.

[6] Watson, D. J. G., Loiseau, F., Ingallinesi, M., Millan, M. J., Marsden, C. A., & Fone, K. C. F. (2012). Selective blockade of dopamine D3 receptors enhances while D2 receptor antagonism impairs social novelty discrimination and novel object recognition in rats: a key role for the prefrontal cortex. *Neuropsychopharmacology*, 37(3), 770–786. doi: 10.1038/npp.2011.254