Early modulation of the endocannabinoid tone prevents the onset of a schizophrenia-like phenotype

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According to the neurodevelopmental hypothesis of schizophrenia, prenatal stressors (such as maternal infection, malnutrition or hypoxia) interacting with genetic predisposition may lead to a schizophrenic phenotype at adulthood (Jones et al., 2011). Several evidence support a dysregulation of the endocannabinoid system (ECS) in pathophysiology of schizophrenia (Kucerova et al., 2014). Given that preventive antipsychotic treatment seems to reduce the risk of transition to psychosis in vulnerable individuals (McGorry et al., 2008), in the present study we investigated 1) the effects of prenatal administration of the mitotoxin methylazoxymethanol acetate (MAM) on neurophenotypic presentations using a battery of behavioral tests to assess negative-like symptoms and cognitive-like deficits, resembling schizophrenia phenotype 2) the effects of pre/peripubertal pharmacological modulation of the endocannabinoid system on the schizophrenia-like phenotype at adulthood.

Timed-pregnant Sprague Dawley rats were treated intraperitoneally with MAM (22 mg/kg) or vehicle (CTR) on gestational day 17 (GD17) (Lodge and Grace, 2009). From postnatal day (PND) 19 to PND 39 different groups of rats were treated intraperitoneally with the non-psychotropic cannabinoid cannabidiol (10 or 30 mg/kg/day), the CB1 antagonist/inverse agonist AM251 (0.5 mg/kg/day), haloperidol (0.6 mg/kg/day) used as positive control or vehicle. Negative-like symptoms and cognitive-like deficits were evaluated in the social interacton test (SIT) and in the novel object recognition test (NOR), respectively.

In prenatally MAM-exposed rats there was a delayed appearance of neonatal reflexes, as index of impaired brain maturation. At adulthood, the MAM offspring exhibited impaired recognition memory and reduced social interaction as compared to the control group, which were correlated with changes in the ECS elements and in the expression of dopamine D3 receptors in several brain regions. Interestingly, they were reversed by adolescent repeated treatment both with the non-psychotropic phytocannabinoid cannabidiol (30 mg/kg) and with the CB1 antagonist AM251.

These results suggest that early pharmacological modulation of the endocannabinoid signaling could circumvent MAM-induced behavioral and molecular alterations which mimic a schizophrenia-like phenotype at adulthood.

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Jones et al. (2011). Br. J. Pharmacol. 164, 1162–1194.

McGorry et al. (2008). World Psychiatry 7, 148–156.

Kucerova et al. (2014). Recent Pat CNS Drug Discov 9, 13–25.

Lodge and Grace (2009). Behav. Brain Res. 204, 306–312.