Prenatal influences facilitate the precipitation of a schizophrenia-like phenotype: Assessing the role of the endocannabinoid system

T. Štark[1], J. Kučerová[1], V Pekařík[1], F. A Iannotti[2], T. Aveta[2], K. Tabiová[1], F. Drago[3], V. Di Marzo[2], A. Sulcova[1], V. Micale[1,3]

[1]CEITEC (Central European Institute of Technology), Masaryk University, Brno, Czech Republic
[2]Endocannabinoid Research Group, Institute of Biomolecular Chemistry, Consiglio Nazionale delle Ricerche, Pozzuoli, Naples, Italy
[3]Dept. of Biomedical and Biotechnological Science, Section of Pharmacology, University of Catania, Catania, Italy

Several clinical data suggest that prenatal perturbations such as hypoxia, maternal infection, and malnutrition could be one of the causes of schizophrenia (SCZ), which leads to severe personal and social dysfunctions. Even though the symptoms and brain morphological changes resulting from this detrimental neuronal development remain relatively dormant until the psychosis in adulthood is manifested, a possible identification of certain premorbid neurodevelopmental signs has been suggested [1]. Among the prenatal influences, early cannabis use has been suggested to play a role in the genesis of SCZ in predisposed subjects. A variety of animal and human studies found a dysregulation of the endocannabinoid system (both in term of cannabinoid receptors CB1 or CB2 and endocannabinoid ligands anandamide or 2-arachidonoylglycerol) in psychosis; thus, the pharmacological manipulation of the endocannabinoid system could be a novel approach for treating SCZ [2]. In the present study, we aimed to investigate the potential effects of prenatal administration of the mitotoxin methylazoxymethanol acetate (MAM) on early neurophenotypic presentations using a battery of behavioral tests [3]. We also measured the brain expression of endocannabinoid receptors and metabolic enzymes (such as FAAH and MAGL) and the levels of the endocannabinoids anandamide and 2-arachidonoylglycerol. Timed-pregnant Sprague Dawley rats were treated with MAM (22 mg/kg) or vehicle (VHC) intraperitoneally on gestational day 17 (GD17). To assess the development of neonatal behavior, starting on postnatal day 1, newborn pups were observed for neonatal reflexes (i.e.: righting, cliff aversion, forelimb placing, bar holding, forelimb grasping, negative geotaxis) as an index of brain maturation, until the maximal appearance of these signs was scored (i.e. 100% of the brood was found to exhibit the full repertoire of reflexes). During adolescence, the offspring was submitted to different behavioral tests such as the social interaction test or the novel object recognition and the Y-maze tests to assess negative-like symptoms or various cognitive aspects, respectively. At birth, neonatal reflexes had a delayed onset (i.e. percent of appearance) in prenatally MAM-exposed rats, as compared to the control group ($P<0.05$; $P<0.01$; $P<0.001$). At adolescent age, prenatally MAM exposed rats engaged in less social behavior as suggested by the reduced time of interaction ($P<0.05$). No difference in the number of episodes, as index of locomotor activity, was found. In the novel object recognition test prenatally MAM-exposed rats showed an impaired cognitive performance, as described by the decreased discrimination index ($P<0.001$). By contrast, spatial recognition memory was not affected by prenatal MAM-exposure since no difference between the two groups of rats (MAM vs VHC) was found in the Y-Maze test. Interestingly, the behavioral alterations were correlated with both decreased expression of FAAH and MAGL ($P<0.05$) and with enhancement of anandamide and 2-arachidonoylglycerol levels ($P<0.05$) in prenatally MAM-exposed rats. These results suggest that behavioral abnormalities resulting from a MAM environmental challenge, which resemble a SCZ-like phenotype, could be due to abnormalities in the endocannabinoid tone.