Altered social behavior and increased anxiety in the rat valproic acid model of autism: role of the endocannabinoid system

M. Servadio[1], F. Melancia[1], F. De Fulvio[1], F. Picerno[1], V. Cartocci[1], V. Pallottini[1], V. Trezza[1]

[1]Dept. of Science, Roma Tre University, Rome, Italy

Autism spectrum disorders (ASD) are characterized by impairment in social interactions, altered communication and repetitive behaviors, often accompanied by 'associated symptoms' (e.g., anxiety, epilepsy, cognitive deficits). No effective and specific treatments are yet available for ASD. Prenatal exposure to valproic acid (VPA) has been proposed as a rodent model of ASD, on the basis of clinical studies reporting a higher incidence of ASD in children exposed 'in utero' to this anticonvulsant drug. The first purpose of this study was to investigate whether VPA prenatal exposure induces behavioral abnormalities that resemble the core and associated symptoms of ASD both in the adolescent and adult rat offspring.
It has been shown that the endocannabinoid system modulates socio-emotional behaviors, and that several components of the endocannabinoid system are altered in VPA-exposed rats. Therefore, the second purpose of this study was to analyze possible biochemical alterations of the endocannabinoid system in brain areas involved in the regulation of cognitive and emotional processes of VPA-exposed animals, and to test if pharmacological manipulations of the endocannabinoid system can revert the behavioral alterations found in VPA-exposed rats. Female Wistar pregnant rats were treated intraperitoneally with VPA (Schneider and Przewlocki, 2005)or the same volume of saline solution (SAL) at gestational day 12 (GD12). After weaning, the adolescent and adult male offspring was tested in the social interaction and elevated plus maze (EPM) tests. In the social interaction test, two rats from the same experimental group were placed together in a neutral arena and the social behaviors, both related and unrelated to play, were scored. Furthermore, the 50-kHz ultrasonic vocalizations (USVs) emitted during the social encounter were registered. The adolescent and adult offspring was also tested in the EPM test, that is the most common animal model of anxiety and it is based on the innate fear of rodents for open and elevated spaces.
At adolescence, VPA-exposed animals showed altered social play behavior and USV emission during the social encounter compared to SAL-exposed rats. The altered social behavior and USV emission persisted into adulthood. Furthermore, both adolescent and adult VPA-exposed animals showed an anxious phenotype in the EPM test.
In the second part of the study, we analysed by Western blot the phosphorylation level of CB1 cannabinoid receptors in prefrontal cortex, amygdala, hippocampus, dorsal striatum, ventral striatum and cerebellum of VPA- and SAL-treated rats. Then, we tested the ability of the anandamide hydrolysis inhibitor URB597 to correct the behavioral abnormalities displayed by VPA-treated rats. The Western blot experiments revealed a different phosphorylation level of CB1 cannabinoid receptors between VPA- and SAL-exposed rats in amygdala, hippocampus and dorsal striatum. Furthermore, treatment with URB597 reverted the altered behavior displayed by adolescent and adult VPA-exposed animals in the EPM test. Ongoing experiments are evaluating the effects of URB597 on the altered social behavior displayed by VPA-exposed rats.
Altogether, these findings reveal that early embryonic exposure to VPA in rats provides a good model for specific aspects of ASD and is a valuable tool to explore pathophysiological hypotheses and to evaluate potential new treatments.

Schneider and Przewlocki (2005). *Neuropsychopharmacology* 30: 80-89