CHANGES IN THE ENDOCANNABINOID SYSTEM UNDERLIE THE ALTERED SOCIAL BEHAVIOR OBSERVED IN A RAT MODEL OF AUTISM SPECTRUM DISORDERS

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Autism spectrum disorders (ASD) are characterized by impaired social interaction and communication and repetitive patterns of behavior. To date, no effective and specific treatments are yet available for ASD. Given the multifactorial etiology of ASD, the use of animal models is essential to dissect the role of genetic and environmental factors in the pathogenesis of this disease, to unravel the relationships between altered brain function in ASD and behavior and to test new pharmacological options. The endocannabinoid system has been shown to modulate socio-emotional behaviors, and several components of the endocannabinoid system have been found altered in genetic and environmental animal models of ASD. In this study, we investigated the role of the endocannabinoid system in the altered social behavior observed in the rat valproic acid model of ASD. In particular, the present study had a three-fold aim: 1) investigate whether VPA prenatal exposure alters social behavior both in the adolescent and adult rat offspring; 2) study the activation of CB1 receptors in brain areas involved in socio-emotional functioning; 3) test the possibility that pharmacological manipulation of the endocannabinoid system may correct the behavioral deficits found in VPA-exposed animals. Wistar pregnant rats were treated intraperitoneally with VPA (500mg/Kg/2ml) (Servadio et al., 2016), or the same volume of saline solution (SAL) at gestational day 12 (GD12). After delivery, the male offspring was tested in the social play behavior test in adolescence (post natal days (PND) 30-35), and in the 3-chamber test both in adolescence and adulthood (PND 70-80). Furthermore, the phosphorylation of CB1 receptors was analyzed both during adolescence and adulthood by western blot in the following brain areas: prefrontal cortex, dorsal striatum, ventral striatum, hippocampus, amygdala and cerebellum. In the last part of the study, the effects of URB597, that inhibits the hydrolysis of the endocannabinoid anandamide, were tested in rats prenatally exposed to either VPA or vehicle. Animals prenatally exposed to VPA responded less to play solicitation compared to SAL-exposed animals ($p<0.05$). In the 3 chamber test, both during adolescence and adulthood, VPA-exposed animals spent less time approaching the stimulus compared to SAL-exposed animals (adolescence: $p<0.01$; adulthood: $p<0.01$). Furthermore, the western blot experiments revealed that the phosphorylation of CB1 cannabinoid receptors was decreased in the hippocampus and increased in dorsal striatum both in adolescent (hippocampus: $p<0.01$; dorsal striatum: $p<0.001$) and adult (hippocampus: $p<0.001$; dorsal striatum: $p<0.001$) VPA-exposed animals, and decreased in the amygdala only at adulthood ($p<0.05$). Interestingly, URB597 corrected the altered social behavior displayed by VPA-exposed animals at adolescence and adulthood. Altogether, these findings reveal that prenatal exposure to VPA provides a good model for specific aspects of ASD. In particular, we observed altered social behavior in VPA-exposed rats both during adolescence and adulthood. Furthermore, the altered activation of CB1 cannabinoid receptors in different brain areas involved in socio-emotional functioning, together with the positive effect of pharmacological

manipulation of the endocannabinoid system, suggests a possible involvement of this neurotransmitter system in the symptomatology and etiology of ASD.

Servadio et al. (2016). Translational Psychiatry 6(9):e902.