AUTISTIC-LIKE BEHAVIORAL ABNORMALITIES OBSERVED IN FEMALE RAT PRENATALLY EXPOSED TO VALPROIC ACID.

1)Schiavi S.. 2)Servadio M.. 3)Melancia F.. 4)Trezza V..

Roma Tre University

Autism spectrum disorders (ASD) are characterized by impaired social interaction, reduced social communication and repetitive patterns of behavior often accompanied by “associated symptoms” (e.g., anxiety, cognitive deficits). One of the most important findings in ASD research is the higher rate of ASD diagnosis in males than in females, with a ratio of about 1 female for every 4 males diagnosed. Considering the multifactorial etiology of ASD, animal models are essential to dissect the role of genetic and environmental factors in the pathogenesis of this disease. In humans, prenatal exposure to valproic acid (VPA) is a risk factor for ASD. Accordingly, prenatal exposure to VPA in rodents has been proposed as a preclinical model of ASD capable to mimic in laboratory animals the majority of the behavioral alterations described in human autism. Therefore, the main goal of the present study was to reveal the presence of ASD-like symptoms in female rats prenatally exposed to VPA to better understand the validity of this model in female rodents and the influence of gender in ASD. We focused on core and comorbid behavioral traits that are frequently impaired in ASD and that have been found aberrant in male VPA rats (Servadio et al., 2016): (1) social communication at infancy through the analysis of isolation-induced ultrasonic vocalizations (USVs); (2) locomotor and repetitive/stereotypic-like activity, (2) anxiety, (3) social behavior and (4) emotional memory. 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). At infancy, when isolated from the nest, the USV rate of female rats prenatally exposed to VPA did not differ from SAL-exposed animals. At adolescence, female rats prenatally exposed to VPA responded less to play solicitation compared to SAL-exposed animals (frequency of partial rotation $p<0.01$; frequency of evasion $p<0.05$), without showing any impairment in locomotor activity, neither repetitive/stereotypic-like behaviors nor anxiety. At adulthood, female VPA-exposed rats displayed repetitive/stereotypic-like behaviors in the hole board test ($p<0.001$), and an atypical locomotor activity in the elevated plus maze test (frequency of close entries $p<0.05$; frequency of total entries $p<0.01$) compared to SAL-exposed animals. Furthermore, VPA-exposed rats showed deficits in emotional memory assessed in the inhibitory avoidance test ($p<0.05$).

Altogether, these findings highlight the potential role of prenatal VPA exposure in female rats as a preclinical model of ASD. In particular, our results show that female rats are somehow less vulnerable to the deleterious effects of prenatal VPA exposure on social communication and emotional reactivity than their male counterpart. Conversely, similarly to what happens in male rats, prenatal VPA exposure induces deficits in social behavior, stereotypies and changes in emotional memory in the female offspring.

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