ELECTROPHYSIOLOGICAL INVESTIGATION OF THE REWARD SYSTEM IN THE VALPROIC ACID MODEL OF AUTISM

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Introduction: Autistic Spectrum Disorder (ASD) is a heterogeneous set of neurodevelopmental disabilities. ASD is characterized by altered social interaction, compromised verbal and nonverbal communication, stereotyped and repetitive behaviours, often associated with comorbid features, such as social and generalized anxiety. Both genetic and environmental factors are involved in the etiology of ASD. Many of the ASD-associated genes are involved in brain development, cortical organization, synaptogenesis and neurotransmission. Among the environmental causes, valproic acid (VPA) exposure during pregnancy is the main risk factor. In fact, results from animal models and clinical data show that exposure in pregnancy is associated with autistic-like signs in the offspring which include reduced sociability and stereotyped behaviors. The most important brain areas involved in reward and reward-related learning are the ventral tegmental area (VTA), the nucleus accumbens (NAc), and the prefrontal cortex (PFC), which are inter-connected in complex ways. Dopaminergic neurons projecting from VTA to NAc form the mesolimbic pathway (MLP) which is involved in motivation and reward-related behavior. The main goal of this research is to test the existence of mesolimbic circuit dysfunctions that could lead to altered reward processing in the VPA rat model of ASD.

Materials and methods: We investigated the consequences of VPA prenatal exposure on the reward system with brain slice electrophysiology. On gestational day 12.5, females Wistar rat received a single intra-peritoneal dose of 500 mg/kg either VPA or saline (SAL). ASD-like phenotype was assessed by means of standard behavioral tests including homing behavior (HB), social interaction (SI) and elevate plus maze (EPM), carried out on the male offspring. Afterwards, animals were used for whole-cell patch clamp recordings from medium spiny neurons (MSNs) of the Nucleus Accumbens (NAc) in brain slices.

Results: VPA rats exhibit a decrease maternal attachment, social interaction and increase in anxiety-like behavior, compared to age-matched control animals. Brain slices recordings indicate that VPA prenatal exposure changes basic electrical proprieties (input resistance and resting membrane potential) and enhances intrinsic somatic excitability of VPA-MSNs compared to CTRL-MSNs. Moreover, preliminary data show a reduction in inwardly rectifying potassium current in VPA-MSNs.

Discussion and conclusion: Collectively, our data suggest that VPA-induced ASD involves functional defects in key elements of the reward system, supporting the hypothesis that alterations in the MCL circuit may be involved in the expression of autistic-like behavior, thus providing a mechanistic link between single neuron properties and behavioral abnormalities in ASD.