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Social deficiency and alterations of cholinergic activity in the medial prefrontal cortex in adult rat prenatally exposed to vaproic acid

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Introduction: The present study was designed to investigate the expression level of the cholinergic ($\alpha 7$ nACh and M1) receptors and acetylcholinesterase (AChE) activity in the medial prefrontal cortex (mPFC) in the behaviorally characterized rat prenatally exposed to vaproic acid (VPA).

Methods: Experiments were carried out on male offspring prenatally exposed to vaproic acid (VPA) at the age of 6 month. Sociability and preference for social novelty in VPA treated and control rats were evaluated in a three-chambered social interaction test. At the end of the behavioral experiments half of rats from each group were used in the immunohistochemical (n = 6) and half in immunoblotting (n = 6) studies.

Results: The results of the sociability test showed that both groups spent more time in the compartment with an unfamiliar rat compared to an empty wire cage ($P < 0.001$). The results of the social novelty phase showed that the control rat spent more time in the compartment with an unfamiliar rat compared to familiar rat ($P < 0.001$). The preference for the social novelty in VPA treated rats was not statistically significant ($P = 0.377$). Immunoblotting studies revealed that the mean level of cholinergic ($\alpha 7$ nACh and M1) receptors in the mPFC is significantly higher in VPA treated group as compared to control group ($p < 0.05$). An immunohistochemical evaluation revealed that the number of AChE positive neurons in the PFC of VPA treated rats significantly higher vs. control group ($P < 0.05$).

Summary: Our results for the first time demonstrate that deficit of social behavior in the VPA induced rat model of autism is accompanied by significant changes in cholinergic activity in the mPFC and reinforce the importance of this model for the preclinical investigation of new therapeutic drugs.

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Key Words: Autism spectrum disorder, valproic acid, prefrontal cortex, social behavior, rat According to the data obtained by the Beritashvili Center for Experimental Biomedicine, in 2021, the concentration of cadmium in soils in Bolnisi, Kazreti and Didi Dmanisi will increase in almost all samples compared to the maximum allowable concentration. According to these data, Cd pollution was equal to the 2021 mark. Bullets are increased in Didi Dmanisi and Bolnisi. Beritashvili's experimental studies clearly show a tendency to increase toxic metals. Cadmium (Cd) is a highly toxic heavy metal that accumulates in the housing system and, as such, is currently one of the most important occupational and environmental pollutants. Cd reaches the environment through anthropogenic mobilization and it is absorbed as a result of tobacco consumption or the ingestion of contaminants. Its extremely long biological half-life (about 20-30 years in humans) and low rate of excretion from the body lead to cadmium storage mainly in soft tissues (primarily liver and kidneys), with a variety of toxic effects such as nephrotoxicity, hepatotoxicity, and redox. Moreover, Cd-dependent neurotoxicity was also associated with neurodegenerative diseases such as Alzheimer's and Parkinson's diseases. Based on the above, we can say that the health of people living in the region we studied is at risk.

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