

The Role of Sex-differentiated Variations in Microbiota, Stress Hormones, Antioxidants, and Neuroimmune Responses in Relation to Social Interaction Impairment in a Rodent Model of Autism

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Abstract

Autism spectrum disorder (ASD) is a neurodevelopmental disorder (NDD) that presents a male bias particularly regarding the prevalence, with a ratio of up to four males to one female. However, the mechanisms underlying such male susceptibility have not been fully elucidated. In our study, we used a well-established propionic acid (PPA) rodent model of autism to study sex differences in microbiota, stress hormones, antioxidants' status, and the neuroimmune response that may contribute to increasing the risk of autism in males. An equal number of both sexes of Sprague Dawley rats were divided into two groups, the control group (received normal saline), and the PPA-treated group (received PPA; 250 mg/kg). Fecal samples were collected once a week throughout the study. A three-chambered social test was performed to test social interaction in both sexes. The Animals were euthanized at the end of the study and the brain samples were collected directly. Biomarkers related to microbiota (total bacteria, total fungi, Clostridium cluster IV, Clostridium perfringens) were measured in animals' feces. Selected biomarkers representing oxidative stress (glutathione (GSH), glutathione S-transferase (GST), ascorbic acid (AA), malondialdehyde (MDA)), stress hormones (adrenocorticotropin (ACTH), corticosterone), cytokines (Interleukin-6 (IL-6), Interleukin-10 (IL-10), Interferon gamma (IFN γ)), and oxytocin were analyzed in the brain homogenates of animals. The results revealed less social interaction in PPA-male treated animals than PPA- treated females. In addition, PPA- treated male animals had a significantly increased abundance of fecal C. perfringens with a concomitant decrease in Clostridium cluster IV. Female rats showed higher immune tolerance to PPA neurotoxicity. These findings reflect the protective role of female gut microbiota composition, contributing to early intervention strategies that might help to control the increasing prevalence of this disorder.