Relationship between brain oxidative stress and autistic behaviors in autism spectrum disorder rats

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[Background] Autism spectrum disorders (ASD) belong to neurodevelopmental diseases characterized by social deficits, repetitive behaviors, and learning disability. Although ASD are pathogenetically heterogeneous and complex as the causes are diverse genetically and environmentally, oxidative stress and mitochondrial dysfunction are associated with ASD brain pathology. We here addressed whether oxidative stress and mitochondria in the brain could be targets for ASD therapeutics, using prenatal valproic acid (VPA)-exposed rats. **[Methods]** After prenatal exposure to VPA (600 mg/kg, p.o.) on embryonic day 12.5, rats were subjected to behavioral tasks to assess social behaviors, learning and memory at adolescence. Then the dorsal hippocampus was collected and oxidative damage and mitochondrial function were measured. **[Results]** Social behaviors, spatial reference memory, and object recognition were impaired in VPA-exposed rats like ASD patients. Immunohistochemical analyses using 4-hydroxy-2-nonenal antibody revealed that oxidative stress is increased in the dorsal hippocampus of VPA-exposed rats, and this was accompanied by aberrant enzymatic activities of mitochondrial transport chain and reduced ATP levels. Chronic treatment of intranasal oxytocin (12 μg/kg) improved these ASD-like behaviors but not oxidative stress or mitochondrial dysfunction. In contrast to oxytocin, oral 5-aminolevulinic acid (5-ALA; 30 mg/kg), a mitochondrial heme precursor, attenuated not only ASD-like behaviors but also oxidative stress and mitochondrial dysfunction seen in VPA-treated rats. **[Conclusion]** Oral 5-ALA treatment improves ASD-like behaviors like intranasal oxytocin administration. These results indicate that 5-ALA could ameliorate ASD symptoms through amelioration of oxidative stress and mitochondrial dysfunction, of which mechanisms are different from oxytocin.