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The h3r Antagonist E159 Alleviates Neuroinflammation and Autistic-Like Phenotypes in BTBR T+ tf/J Mouse Model of Autism

Authors : Shilu Deepa Thomas, P. Jayaprakash, Dorota Łazewska, Katarzyna Kieć-Kononowicz, B. Sadek

Abstract : A large body of evidence suggests the involvement of cognitive impairment, increased levels of inflammation and oxidative stress in the pathogenesis of autism spectrum disorder (ASD). ASD commonly coexists with psychiatric conditions like anxiety and cognitive challenges, and individuals with ASD exhibit significant levels of inflammation and immune system dysregulation. Previous Studies have identified elevated levels of pro-inflammatory markers such as IL-1β, IL-6, IL-2 and TNF-α, particularly in young children with ASD. The current therapeutic options for ASD show limited effectiveness, signifying the importance of exploring an efficient drugs to address the core symptoms. The role of histamine H3 receptors (H3Rs) in memory and the prospective role of H3R antagonists in pharmacological control of neurodegenerative disorders, e.g., ASD, is well-accepted. Hence, the effects of chronic systemic administration of H3R antagonist E159 on autistic-like repetitive behaviors, social deficits, memory and anxiety parameters, as well as neuroinflammation in Black and Tan BRachyury (BTBR) mice, were evaluated using Y maze, Barnes maze, self-grooming, open field and three chamber social test. E159 (2.5, 5 and 10 mg/kg, i.p.) dose-dependently ameliorated repetitive and compulsive behaviors by reducing the increased time spent in self-grooming and improved reduced spontaneous alternation in BTBR mice. Moreover, treatment with E159 attenuated disturbed anxiety levels and social deficits in tested male BTBR mice. Furthermore, E159 attenuated oxidative stress by significantly increasing GSH, CAT, and SOD and decreasing the increased levels of MDA in the cerebellum as well as the hippocampus. In addition, E159 decreased the elevated levels of proinflammatory cytokines (tumor necrosis factor (TNF-α), interleukin-1β (IL-1β), and IL-6). The observed results show that H3R antagonists like E159 may represent a promising novel pharmacological strategy for the future treatment of ASD.

Keywords : histamine H3 receptors, antagonist E159, autism, behaviors, mice
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