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The College of Graduate Studies and the College of Medicine and Health Sciences Cordially Invite You to a

PhD Dissertation Defense

Entitled

THE ROLE OF HISTAMINE H3 RECEPTOR ANTAGONISTS IN MODULATING AUTISTIC BEHAVIORS AND ALTERED CENTRAL INFLAMMATORY RESPONSES IN DIFFERENT MOUSE MODELS OF AUTISM SPECTRUM DISORDER

by

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Date & Venue

1:00 PM
Wednesday, 12 June 2019
Fatima Theater, College of Medicine and Health Sciences, 2nd floor lecture theater (Female side)

Abstract

Autistic spectrum disorder (ASD) represents a neurodevelopmental disorder characterized by impairment of social communication and restricted/repetitive behavior patterns or interests. Brain histamine and acetylcholine play a crucial role in cognitive functions. Considering this, the effects of systemic sub-chronic treatment with H3R antagonist DL77 (5, 10, or 15 mg/kg) on autistic-like behavioral parameters, oxidative stress, and neuroinflammation in male Tuck-Ordinary (TO) and C57BL/6 (C57) mice, prenatally exposed to valproic acid (VPA, 500 mg/kg), were investigated. Moreover, the effects of dual-active H3R antagonist and balance acetylcholinesterase inhibitor E100 (5, 10, or 15 mg/kg) on autistic-associated abnormalities of VPA- exposed male C57 mice as well as BTBR T+tf/J (BTBR) mice were assessed. The results showed that VPA-exposed mice exhibited significantly lower sociability and social novelty preference compared to VPA-exposed TO and C57 mice pretreated with DL77 (10 mg/kg) or (15 mg/kg), respectively. Moreover, the same doses of DL77 attenuated repetitive/compulsive behaviors of both strains, without appreciable effects on disturbed anxiety and hyperactivity when compared to the reference drug donepezil (1 mg/kg). The amelioration in autistic-like phenotypes by DL77 were accompanied by the restoration of oxidative stress by increasing glutathione and decreasing malondialdehyde levels, and attenuation of proinflammatory cytokines interleukin-1β, interleukin-6 and tumor necrosis factor-α in VPA-exposed mice brain tissues. Comparing the results observed for DL77, the dual-active E100 (10 mg/kg) showed significantly higher improvement of autistic behavioral alterations in VPA-exposed C57 mice, and significantly palliated disturbed anxiety levels. In addition, E100 attenuated several pro-inflammatory cytokines and inflammatory mediators through the suppression of upregulated NF-κB signaling. Immunofluorescence analysis showed significant reduction in ionized calcium-binding adaptor molecule-1 increased expression in VPA-exposed C57 mice by E100, demonstrating inhibition of activated microglia. Similarly, oxidative stress status was also mitigated by E100 in brain tissues. The promising effects of E100 on autistic features in C57 mice were further comprehended with the results observed with E100 (5 mg/kg) in BTBR mice as idiopathic model of ASD. These results provide evidence that simultaneous modulation of brain histaminergic and cholinergic neurotransmissions may have therapeutic efficacy for core symptoms of ASD. Further preclinical investigations are still necessary to corroborate and expand these observed data.

Keywords: ASD, mouse models, histamine H3 receptor antagonists, autistic-like behaviors, neuroinflammation, oxidative stress.