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Master Thesis Defense

Entitled

Effects of ST713 with simultaneous histamine H3 and dopamine D2/D3 receptor antagonist properties on cognitive impairments and autism-like behaviors in BTBR T+TF/J mice

By

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Date & Venue

At 1 PM

Wednesday, 16th of March 2022

Conducted online and accessed via the attached link

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Abstract

Autism Spectrum Disorders (ASD) is a multifactorial neurodevelopmental disorder characterized by two core symptoms which are impairments in social interaction and communication, repetitive and restricted behaviors. Dopamine (DA) and histamine (HA) are two neurotransmitters that are proposed to be involved in several brain disorders including schizophrenia, depression, anxiety, and narcolepsy, all of which are comorbid with ASD. Thus, the palliative effects of the novel multiple-active histamine H3 receptor (H3R) antagonist and dopamine D2/D3 receptor (D2/D3R) antagonist ST-713 with its high H3R antagonist affinity and balanced inhibitory effects on both dopaminergic receptor subtypes D2R and D3R on ASD-like behaviors in male BTBR T+tf/J mice model of ASD were evaluated. Chronic systemic administration of ST-713 (2.5, 5, and 10 mg/kg, i.p.) dose-dependently mitigated social deficits of BTBR mice and significantly reduced the repetitive/compulsive behaviors of tested BTBR mice. Additionally, ST-713 modulated disturbed anxiety levels but failed to balance hyperactivity parameters. Moreover, the ST-713-provided effects on social parameters were entirely reversed by co-administration of the H3R agonist (*R*)-α-methylhistamine or the anticholinergic drug scopolamine (SCO, 0.3 mg/kg, i.p.). Furthermore, ST-713 (5 mg/kg) attenuated the increased levels of hippocampal and cerebellar protein expressions of Tumor necrosis factor (TNF-α), Interleukins-1β (IL-1β), and IL-6 in treated BTBR mice brains (all $P <$

0.01). The obtained in vivo results demonstrate the effectiveness of a potent multiple-active H3R and D2R/D3R antagonist/inverse agonist against ASD-like phenotype, signifying the potential role of such multiple-active compounds for the therapeutic management of neuropsychiatric disorders, such as ASD.

Keywords: Autistic spectrum disorder, BTBR mice, histamine H3 receptor antagonist, dopamine D3/D3 receptor antagonist, social deficits, stereotyped repetitive behavior, anxiety, neuroinflammation.