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The Dual-active G9a inhibitor and Histamine H3 Receptor Antagonist A-366 Ameliorates Autism-Like Phenotypes, Neuroinflammation and Oxidative Stress in BTBR T+tf/j Mice

Autism spectrum disorder (ASD) is a prevalent combination of complex neurodevelopmental disorders characterized by repetitive stereotyped behaviours and impaired social communication. Although both epigenetic alterations and neurotransmitter imbalance are reported to contribute to ASD onset, almost no therapies targets both aspects simultaneously. This study investigated A-366, a selective histone H3K9 methyltransferase G9a inhibitor with additional histamine H3 receptor (H3R) antagonist properties, in BTBR T+tf/J mice. Chronic administration of A-366 (0.5, 1, or 2 mg/kg, i.p.) reduced repetitive behaviors, improved cognitive flexibility, and enhanced sociability and social novelty, with the highest dose restoring performance to near control levels. Enzymatic activity assays confirmed G9a inhibition in cerebellum and hippocampus, which was unaffected by coadministration with the H3R agonist RAMH. At dose 2 mg/kg, A-366 also significantly lowered cerebellar and hippocampal levels of TNF-α, IL-6, and IL-1β, and normalized oxidative stress by reducing malondialdehyde (MDA) and restoring superoxide dismutase (SOD) activity. Compared to the reference H3R antagonist Pitolisant, A-366 showed broader behavioral and biochemical improvements. Partial reversal of A-366's observed effects by coadministration with the centrally acting and selective H3R agonist RAMH indicated that H3R antagonism contributes to its mechanism of action, while G9a inhibition remained unaffected. These results suggest that A-366's dual modulation of epigenetic chromatin remodeling and G-protein coupled histamine H3 receptor signaling simultaneously addresses key pathological features of ASD. Although further pharmacological refinement is needed, the pharmacophore of A-366 offers a promising structural basis for the design of next-generation multi-target therapeutics for neurodevelopmental disorders.

Keywords
A-366, Autism spectrum disorder, G9a inhibitor, Histamine, H3R antagonist, BTBR mice.

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Biography

Bassem Sadek is Full Professor in the Department of Pharmacology & Therapeutics, College of Medicine & Health Sciences, United Arab Emirates University. He received his Bachelor of Pharmacy and later my PhD in Drug Design and Preclinical Drug Development from the Free University of Berlin/Germany. He is a member of several scientific societies, including European Histamine Research Society (elected society officer), German Society of Pharmacology and Toxicology, and German Pharmaceutical Society. Prof Sadek is an editorial board member of numerous peer-reviewed journals. His work in the field of drug design, pharmacological, and preclinical evaluation of ligands targeting cognitive as well as behavioral disorders has resulted in more than 110 publications in in the most prestigious journals in the world including Neuropharmacology, European Neuropsychopharmacology, Frontiers in Pharmacology, Behavioural Brain Research, Scientific Reports, Medicinal Research Reviews and many others. Also, his work is well recognized and as a result he is currently appointed as an honorary Research Associate in the Institute of Pharmaceutical and Medicinal Chemistry, Heinrich Heine University Düsseldorf, Germany.

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