

The dual-acting AChE inhibitor and H₃ receptor antagonist UW-MD-72 reverses amnesia induced byscopolamine or dizocilpine passive avoidance paradigm in rats

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Both the acetylcholine esterase (AChE) and the histamine H₃ receptor (H₃R) are involved in the metabolism and modulation of acetylcholine release and numerous other centrally acting neurotransmitters. Hence, dual-active AChE inhibitors (AChEIs) and H₃R antagonists hold potential to treat cognitive disorders like Alzheimer's disease (AD). The novel dual-acting AChEI and H₃R antagonist UW-MD-72 shows excellent selectivity profiles over the AChE's isoenzyme butyrylcholinesterase (BChE) as well as high and balanced *in vitro* affinities at both AChE and hH₃R with IC₅₀ of 5.4 μM on hAChE and hH₃R antagonism with K_i of 2.54 μM, respectively. In the current study, the effects of UW-MD-72 (1.25, 2.5, and 5 mg/kg, i.p.) on memory deficits induced by scopolamine (SCO) and dizocilpine (DIZ) were investigated in a step-through type passive avoidance paradigm in adult male rats applying donepezil (DOZ) and pitolisant (PIT) as reference drugs. The results show that acute systemic administration of UW-MD-72 significantly ameliorated the SCO- and DIZ-induced amnesic effects. Furthermore, the ameliorating activity of UW-MD-72 in DIZ-induced amnesia was partly reversed when rats were pretreated with zolantidine, but not with the H₁R antagonist pyrilamine. Moreover, ameliorative effect of UW-MD-72 in DIZ-induced amnesia was strongly reversed when rats were pretreated with a combination of ZOL and SCO, indicating that these memory enhancing effects were partly observed through histaminergic H₂R as well as muscarinic cholinergic neurotransmission. These results demonstrate the ameliorative effects of UW-MD-72 in two *in-vivo* memory models and provide evidence for the potential of dual-acting AChEI and H₃R antagonists to treat cognitive disorders.

Biography:

Dr Bassem Sadek is Associate Professor of Pharmacology in College of Medicine and Health Sciences, UAE University. He received his B. Pharm. in 1994 from The Free University of Berlin (FUB), Germany, and PhD in Medicinal Chemistry, Drug Design and Development in 1999 from FUB University (Germany). Over the years, he has developed innovative research projects which focused on the identification and manipulation of brain signaling regulating psychiatric as well as neurodegenerative disorders such as Alzheimer, addiction, depression, epilepsy, anxiety, and stress. Dr Sadek is a member of editorial board and a peer-reviewer to many international journals.