

MEETING ABSTRACTS

7-METHOXYDERIVATIVE OF TACRINE IS A ‘FOOT-IN-THE-DOOR’ BLOCKER OF GluN1/GluN2 AND GluN1/GluN3 NMDA RECEPTORS

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N-methyl-D-aspartate receptors (NMDARs) are glutamate-gated ion channels that mediate excitatory neurotransmission in the mammalian central nervous system (CNS), but their dysregulation results in the aetiology of many human CNS disorders. Several NMDAR modulators including memantine have been used successfully in clinical trials. Indeed, 1,2,3,4-tetrahydro-9-aminoacridine (tacrine; THA) was the first approved drug for Alzheimer's disease (AD) treatment. 7-methoxyderivative of THA (7-MEOTA) is less toxic and showed promising results in patients with tardive dyskinesia. Here, we employed electrophysiological recordings in HEK293 cells and rat neurones to examine the mechanism of action of THA and 7-MEOTA at the NMDAR. We showed that both THA and 7-MEOTA are “foot-in-the-door” open-channel blockers of GluN1/GluN2 and GluN1/GluN3 NMDARs and that 7-MEOTA is a more potent but slower blocker than THA. Furthermore, the inhibitory potency of 7-MEOTA at synaptic and extrasynaptic hippocampal NMDARs was similar, and 7-MEOTA exhibited better neuroprotective activity in rats exposed NMDA-induced lesions in hippocampus when compared with THA and memantine. Finally, intraperitoneal administration of 7-MEOTA attenuated MK-801-induced hyperlocomotion in rats. We conclude that 7-MEOTA is a promising candidate for the treatment of diseases associated with the dysfunction of NMDARs.

Keywords: glutamate receptor; patch-clamp technique; inhibitor; excitotoxicity

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