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Entitled

ANTICONVULSANT AND PROCOGNITIVE EFFECT OF NON-IMIDAZOLE HISTAMINE H3R RECEPTOR ANTAGONISTS /INVERSE AGONISTS IN EXPERIMENTAL ANIMAL MODELS

by

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Abstract

Epilepsy is a common chronic neurological disorder accompanied by cognitive impairment. Available antiepileptic drugs (AEDs) have not been reported to have ameliorative effects on epilepsy-associated memory impairment. The potential of histamine H3 receptors (H3R) in several neuropsychiatric diseases, including epilepsy and Alzheimer's disease, is well recognized. In this study, a series of H3R antagonists (1-16) was screened for in vivo anticonvulsant effect in several acute-induced seizure models in rats. Moreover, the procognitive effect of the most promising H3R antagonist was investigated in dizocilpine (DIZ)-induced amnesic effect applying several behavioral memory tests. Moreover, the most promising H3R antagonist was assessed for its simultaneous anticonvulsant and procognitive effect plus in addition to its antioxidant effect in acute and chronic pentylenetetrazol(PTZ)-induced models and pilocarpine(PLC)-induced status epilepticus (SE) model. Furthermore, the modulatory effect of the most promising H3R antagonist on levels of several hippocampal neurotransmitters and c-fos immunofluorescence were assessed in PTZ model.

The Observed results indicated that H3R antagonist 4 (10 mg/kg i.p.) significantly exhibited high protection in maximum electroshock model (MES) model and full protection in the PTZ-acute induced seizure model, and H3R antagonist 4-provided protections were abrogated with co-administration of CNS-penetrant H3R agonist (R)-α-methylhistamine (RAM) in MES model. Moreover, H3R antagonist 4 (5 mg/kg i.p.) showed a procognitive effect that was abrogated with RAM co-injection in all behavioral memory tests. Additionally, treatment with H3R antagonist 4 showed a simultaneous anticonvulsant and procognitive effect in addition to antioxidant effect in PTZ- acute and -chronic models. Furthermore, chronic treatment with H3R antagonist 4 (5 mg/kg i.p.) modified histamine, acetylcholine, and glutamate release, and reduced hippocampal c-fos activation. In addition, RAM administration reversed the protective effects provided by H3R antagonist 4 in PTZ- chronic model. Moreover, and in PLC-induced SE, systemic administration of H3R antagonist 4 (10 mg/kg i.p.) mitigated severity of SE and exhibited antioxidant effect in the hippocampus of the treated rats, and RAM reversed the observed protective effects. Our findings recommend that the newly developed H3R antagonist 4 provides antiepileptic, memory-enhancing, and antioxidant properties in a PTZ-induced kindling model of epilepsy and provides neuroprotection in a preclinical PLC-induced SE in rats, highlighting the histaminergic system as a potential therapeutic target for the management of epilepsy with accompanied memory deficits.

Keywords: Histamine H3 receptor; antagonist; Epilepsy; Hippocampus; Pentylenetetrazol; Pilocarpine; Oxidative stress; c-fos; Memory impairment; status epilepticus.