GASTROPROTECTIVE EFFECTS OF THE SELECTIVE HISTAMINE H₃ RECEPTOR AGONISTS METHIMEPIP AND IMMETHRIDINE

Adami Maristella, Guaita Elena, de Esch Iwan JP, Leurs Rob, Stark Holger and Coruzzi Gabriella

Department of Human Anatomy, Pharmacology and Forensic Medicine, University of Parma, Italy;
LACDR, Department of Medicinal Chemistry, Vrije Universiteit Amsterdam, The Netherlands;
Institut für Pharmazeutische Chemie, J W Goethe-Universität, Frankfurt, Germany

Previous data (1) showed that HCl-induced gastric lesions were reduced by R-(α)-methylhistamine but not by the histamine H₃ receptor agonists immepip and imetit. Moreover, it was recently observed that H₄ receptor antagonists mediate protective effects against gastric lesions induced in the rat by indomethacin (2). Since both immepip and imetit behave as mixed H₃/H₄ receptor agonists, in the present study we investigated the effects of the highly selective H₃ receptor agonist methimepip (3) and immethridine, in comparison with immepip, against the gastric lesions induced by HCl or indomethacin. Methimepip (30 and 100 mg/kg intragastrically, ig) did not modify gastric lesions induced by indomethacin 20 mg/kg subcutaneously, sc, or by 0.6 N HCl ig. However, this compound, administered sc at 30 mg/kg, induced a significant inhibition of HCl-induced lesions; by contrast methimepip (30 mg/kg sc) did not modify indomethacin-induced damage. Immepip (30 and 100 mg/kg, either ig or sc) was inactive against gastric lesions induced by indomethacin or by HCl. Immethridine (30 mg/kg sc) significantly reduced HCl-induced lesions (approximately 62% inhibition) and this effect was prevented by the selective H₃ receptor antagonist UCL-2138 (4) (30 mg/kg sc).

In conclusion, the use of selective H₃ receptor ligands confirmed that the activation of H₃ receptors mediate protective effects against gastric damage induced by necrotizing agents. Pharmacokinetics of H₃ receptor agonists and/or their affinity at H₄ receptors may explain the discrepancies observed across the experimental assays.