GASTROPROTECTIVE EFFECTS OF THE SELECTIVE HISTAMINE H_3 RECEPTOR AGONISTS METHIMEPIP AND IMMETHRIDINE

[1]Adami Maristella, [1]Guaita Elena, [2]de Esch Iwan JP, [2]Leurs Rob, [3]Stark Holger and [1]Coruzzi Gabriella

[1]Department of Human Anatomy, Pharmacology and Forensic Medicine, University of Parma, Italy;
[2]LACDR, Department of Medicinal Chemistry, Vrije Universiteit Amsterdam, The Netherlands;
[3]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 H_3 receptor agonists immepip and imetit. Moreover, it was recently observed that H_4 receptor antagonists mediate protective effects against gastric lesions induced in the rat by indomethacin (2). Since both immepip and imetit behave as mixed H_3/H_4 receptor agonists, in the present study we investigated the effects of the highly selective H_3 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 H_3 receptor antagonist UCL-2138 (4) (30 mg/kg sc). In conclusion, the use of selective H_3 receptor ligands confirmed that the activation of H_3 receptors mediate protective effects against gastric damage induced by necrotizing agents. Pharmacokinetics of H_3 receptor agonists and/or their affinity at H_4 receptors may explain the discrepancies observed across the experimental assays.

(1) Morini G., Timmerman H., Schunack W., and Grandi D. (2002) Inflamm. Res. 51 (Suppl 1): S75-S76.
(2) Gabriella C., Adami M., Guaita E., de Esch I.J.P., and Leurs R. (2006) 35th EHRS meeting, Delphi, Greece: 69.
(3) Kitbunnadaj R., Hashimoto T., Poli E., Zuiderveld O.P., Menozzi A., Hidaka R., de Esch I.J., Bakker R.A., Menge W.M., Yamatodani A., Coruzzi G., Timmerman H., and Leurs R. (2005) J. Med. Chem. 48: 2100-2107.
(4) Cowart M., Altenbach R., Black L., Faghih R., Zhao C., and Hancock A.A. (2004) Mini Rev. Med. Chem. 4: 979-992.