GASTROPROTECTIVE EFFECT OF DIZE, AN ACTIVATOR OF ACE II: ROLE OF ANG (1-7)/MAS, IN MODELS OF GASTRIC INJURY IN MICE

Introdução: Peptic ulcer disease is a disorder of gastrointestinal tract that have been described as a leading cause of morbidity and mortality in adults. In current research, the route of the Angiotensin Converting Enzyme II (ACEII) was related to several beneficial effects in the body, including the gastroprotection. Recently, Diminazene Aceturate (DIZE), a trypanosomicide used in animals, was described as activator ACEII. Materiais e Métodos: To assess the gastroprotective effect of DIZE against ethanol-induced acute injury, mice (25-30g) were pretreated orally with saline (control), DIZE (0.7, 7 and 20 mg/kg) or omeprazole (10mg/kg). After one hour ethanol 50% (0.5ml/25g) was administered. One hour after animals were sacrificed, the stomach removed and immediately opened for analysis. Gastric damage was measured (Image J®). To evaluate the role of ACEII/Ang(1-7)/MAS pathway, animals were pretreated with A-779 (antagonist MAS receptor; 5mg/kg, i.p.) and after 30 minutes DIZE (7mg/kg) or saline were administered. The others steps were similar to those described above. Tissue samples were removed for microscopic analysis, MDA and GSH. Mucus and gastric secretion tests were performed. For analysis of DIZE effects in wound healing against acetic acid-induced chronic damage, animals were anesthetized and laparotomy was performed, the stomach was exposed and the acetic acid 40% (100 µl/1min) was administered in the serous. Treatment with saline, DIZE, A-779, A-779 + DIZE or OMP was performed the 2nd to 7th day after the injury. The animals were sacrificed of the seventh day and the stomach removed and opened for analysis. Samples were removed for histological analyzes, MPO activity and concentration of Ang(1-7) measured using ELISA. Resultados e Discussão: Ethanol-induced damage was reversed by DIZE pretreatment (20 and 7 mg/kg, inhibition of 90 and 94%, respectively), as well as OMP (88% inhibition) (P<0.0001). A-779 reversed the protective effect of DIZE. DIZE (7 mg/kg, better dose) elevated GSH levels and decreased the MDA concentration when compared with untreated group (403.3 ± 23.9; 187.8 ± 13.3 mg/NPSH/g and 166.4 ± 9.9; 327.0 ± 44.8 nmol/g, respectively). A-779 administration reversed these biochemical parameters when compared with control group (279.9 ± 9.1, 382.2 ± 38.7 mg/NPSH/g, and 481.1 ± 39.0, 169.4 ± 7.4 nmol/g, respectively). DIZE elevated mucus levels (58.9 ± 3.3 alcian Blue µg/g), decreased gastric secretion (p<0.0001) and decreased MPO activity (2.3 ± 1.7 U/mg). DIZE, also, decreases acetic acid-induced gastric injury and A-779 reversed this
effect (64%; 0% inhibition, respectively) (P<0.0001). The pre-treatment and treatment with DIZE decrease inflammatory cell infiltration, edema formation and loss of epithelial cells. Furthermore, DIZE elevated Ang(1-7) levels in both injury models (P<0.0001). Conclusão: Thus, the DIZE could become a future drug gastroprotective.