NOCICEPTIN/ORPHANIN FQ PREVENTS GASTRIC DAMAGE INDUCED BY ACUTE STRESS IN THE RAT BY ACTING IN THE PERIPHERY

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Stress induced by acute exposure to cold alters gastrointestinal functions and mucosal integrity in the rat. Present study was aimed to assess the ability of nociceptin/orphanin FQ (N/OFQ) to protect the rat gastric mucosa against damage by cold restraint stress.
Macroscopically visible hemorrhagic lesions in the glandular part of the stomach were observed in rats placed in semi-restraining cages and exposed to cold for 3 and 4 hours, with a time-dependent increase in the severity and incidence of lesions. Intraperitoneal administration of N/OFQ dose dependently decreased lesion formation in the range 0.03 to 1 μg/kg/h. Its effect was reversed by the concurrent administration of the selective NOP receptor antagonist, [Nphe^{1}Arg^{14}Lys^{15}]N/OFQ-NH_2 (UFP-101), 30 μg/kg/h ip. The selective NOP receptor agonist [(pF)Phe^{4}Aib^{7}Arg^{14}Lys^{15}]N/OFQ-NH_2 (UFP-112), 0.01 to 0.3 μg/kg/h ip, similarly reduced the formation of gastric lesions, displaying a higher potency as compared with N/OFQ. Microscopic examination revealed that stress causes edema and superficial lesions, with a time-dependent increase in the percentage of damaged mucosa. Deeply extending lesions were rare and the overall thickness of the mucosa was not modified in comparison with non-stressed controls. Stress also cause a decrease in production of mucosubstances by surface mucous cells, as also evidenced by scanning electron microscopy. Treatment with N/OFQ effectively restored the integrity of the mucosa and the production of mucus. In stressed animals the number of toluidine blue positive connective tissue mast cells was significantly increased, as compared with non-stressed controls. The density of mast cells significantly decreased in N/OFQ treated rats, probably representing the loss due to cell degranulation.
In summary our results demonstrate that N/OFQ prevents the development of stress-induced gastric lesions and preserves the protective mechanism of mucus secretion and/or production. Mast cells are likely to participate in its activity. Present results also provide pharmacological evidence that NOP receptors are involved in gastric mucosal protection exerted by N/OFQ.