NEUROINFLAMMATORY REACTIONS IN EXPERIMENTAL GASTRIC ULCER: TARGET FOR MUCOSAL PROTECTION

K. GYIRES
Department of Pharmacology, Semmelweis University of Medicine, Nagyvárad tér 4, H-1089 Budapest, Hungary

ABSTRACT

The effect of different opioids receptor agonists - morphine, DAGO (µ-agonists), DADLE, DPDPE and deltorphin II (δ-agonists) - on gastric mucosal damage induced by either acidified ethanol or acidified aspirin was studied following subcutaneous (sc) administration of these agonists. The results indicate that both µ and δ receptors are involved in gastroprotection. Morphine, DAGO and DADLE, injected intracerebroventricularly, were also effective in both ulcer models. This suggests that gastric cytoprotection can be induced also be central action, since gastric acid secretion is not involved in the pathomechanism of mucosal damage induced by acidified ethanol. Interaction between the opioids and α2-adrenoceptors in gastroprotection is suggested by the findings that the gastroprotective effect of clonidine (0.09 μmol/kg orally) was antagonized by opioid antagonists. As both naloxone (1.38 μmol/kg sc) and naltrindole (12 μmol/kg sc) exerted antagonist effects, both µ and δ receptors are likely to be involved in presynaptic α2-receptor-mediated gastroprotection.

Keywords: opioids, α2-agonists, gastric mucosal defence

INTRODUCTION
Dual mechanisms involving both inhibition of aggressive factors (gastric acid secretion) and stimulation of the defensive mechanism, are involved in gastric mucosal protection. Antagonism of the well-defined receptor populations comprising muscarinic, histaminic and gastrinergic systems mediate inhibition of gastric acid secretion. On the other hand, there are only few data which refer to the involvement of receptors in gastroprotection, or cytoprotection as defined by Robert et al. [1]. Contradictory data have been published on the gastroprotective effect of antisecretory drugs. Thus, for example, the histamine H2-receptor antagonists were found to be effective against gastric mucosal damage induced by necrotizing agents [2,3]. However, others failed to confirm the cytoprotective effect of H2-receptor blocking drugs [3–5]. The muscarinic M1 receptor antagonist, pirenzepine, was reported to be effective against acid-dependent and acid-independent ulcer models at doses that failed to influence gastric acid secretion [6]. The gastrin receptor antagonist, proglumide, exerts its antiulcer effect partly by its antisecretory, and in part by its cytoprotective activities [7]. Moreover, the proton pump inhibitor, omeprazole, protected the gastric mucosa against necrotizing agents after oral administration [8]. Its protective effect was not due to an antisecretory action, since, given intravenously in doses which completely
suppressed gastric acid secretion, no gastroprotection was observed. However, neither of these studies analysed whether the gastroprotective effect of the above-mentioned antisecretory agents is a receptor-mediated process or whether their mucosal protective effect is independent of their actions at receptors.

Possible involvement of receptors in gastroprotection is suggested by the results of Bertaccini et al. [9] who found that histamine H3-agonist inhibited gastric damage induced by 100% ethanol, an effect which was reversed by the H3-receptor antagonist, thioperamide. This indicates that H3-receptors are likely to mediate gastroprotection. Others found that opioids exerted a gastroprotective effect against different types of gastric mucosal damage [10–16]. The effects of these opioids could be abolished by different opioid antagonists, suggesting that opioid receptors might mediate gastroprotection. Analysis of the opioid-receptor types involved in gastroprotection indicates that µ [10,11,15] and δ [13,15] receptors may be involved in mucosal protective effect of opioids against HCl-, ethanol- or stress-induced gastric mucosal damage. Involvement of κ and σ receptors was suggested by Bálint and Náfrádi [16]. The role of opioids in maintaining gastric mucosal integrity is supported by the finding of µ and δ opioid-receptor binding sites in the mucosa and submucosal plexus of rat and guinea pig [17].

However, data from the literature suggest that opioids, beside having protective effects can cause aggravation of mucosal lesions [18–20]. The contradictory findings cannot be satisfactorily explained. However, it is worth noting that opioids, depending on the doses, have a dual role also on sensory neurons: they can exert excitatory and inhibitory activities [21]. As a result of excitation of sensory neurons, neuropeptides (like calcitonin gene-related peptide [CGRP]) may be released [22], which are likely to be involved in maintaining gastric mucosal integrity [23]. In contrast, inhibition of the activity of sensory neurons may result in a decreased release of gastroprotective peptides, leading to aggravation of mucosal lesions.

The site of opioid-induced gastroprotection might be either central or peripheral. Both central and peripheral effects may be involved in gastroprotective action of opioids against stress- or pylorus-ligation-induced mucosal lesions [15,24,25]. However, gastric acid secretion is involved in the pathomechanism of both ulcer models. Since opioids exert inhibitory activity on gastric acid secretion injected either intracerebroventricularly (icv) or peripherally [24,26], the question was raised whether the antiulcer activity of opioids following icv administration is due to their antisecretory activity or whether their gastroprotective effect is independent of their antisecretory property. Therefore, in the present experimental series, we examined how opioids influence gastric lesions following icv administration in an ulcer model, where gastric acid secretion is not involved in the development of gastric mucosal lesions. Also, we compared the gastroprotective effect of selective agonists of different opioid receptors against acidified ethanol and acidified aspirin-induced mucosal lesions following peripheral and central administration.

In the second part of the present experimental series, we analysed whether there is an interaction between the opioid system and presynaptic α2-adrenoceptors. It has been proposed that there are interactions between these two endogenous systems. For example, clonidine-induced analgesia is likely to be mediated by the release of endogenous opioid-like substance [27]. Likewise, cross-tolerance between morphine