Effect of naloxone on met-enkephalin-induced gastric acid secretion and serum gastrin in man

P SKOV OLSEN, P KIRKEGAARD, B PETERSEN, AND J CHRISTIANSEN

From Department of Surgery D, Glostrup Hospital, University of Copenhagen, Copenhagen, Denmark

SUMMARY It has previously been demonstrated that met-enkephalin, an endogenous opiate, stimulates gastric acid secretion in man, while naloxone inhibits meal-stimulated acid secretion. In seven healthy subjects the opiate receptor antagonist naloxone was infused in a dose of 10 µg/kg/h during stimulation of gastric acid secretion with pentagastrin 100 ng/kg/h and met-enkephalin 0.1 µg/kg/h. Naloxone had no effect on pentagastrin-induced acid secretion, whereas met-enkephalin-induced acid secretion was completely abolished in both studies without affecting serum gastrin levels, suggesting that the acid inhibitory effect of naloxone is specifically directed towards met-enkephalin-induced acid secretion. The results support the assumption that met-enkephalin participates in the physiological stimulation of gastric acid secretion.

Opiate receptors and enkephalins were originally discovered in brain tissue¹. Subsequently, immuno-histochemical studies revealed a wide distribution of enkephalin in the gastrointestinal tract and pancreas, both in endocrine cells² and in peripheral nerves.^{3,4} In a previous study met-enkephalin was found to enhance submaximal pentagastrin-stimulated acid secretion in man without affecting serum gastrin levels⁵. Naloxone, an opiate receptor antagonist, inhibits basal and meal-stimulated gastric acid secretion, without affecting serum gastrin concentration in man.⁶ These findings indicate that endogenous opiates may participate in the stimulation of gastric acid secretion, a view that also accords with the fact that the great majority of met-enkephalin-containing cells in the gastrointestinal tract are located in the antrum and proximal duodenum.²

The present study was undertaken to investigate whether the inhibitory effect of naloxone on gastric acid secretion is likely to be due only to its action as an opiate receptor antagonist.

Methods

SUBJECTS

Seven healthy subjects, three men and four women, aged 23-58 years, were studied. Informed consent was obtained from all subjects.

*Address for correspondence: John Christiansen, MD, Department of Surgery D, Glostrup Hospital, University of Copenhagen, DK-2600 Glostrup, Copenhagen, Denmark.

EXPERIMENTAL PROCEDURE

Each subject was investigated on three separate days. After an overnight fast a Levin tube was placed in the stomach under fluoroscopic control. Through a thin polyvinyl tube welded to the Levin tube a marker substance was instilled into the stomach (⁵¹Cr-Edta, flow 30 ml/h) in order to determine recovery. After emptying the stomach, basal secretion was collected for two 15 minute periods. The volume of secretion was measured for each 15 minute period and corrected to the actual recovery by way of the marker substance instilled.

On the first day the stability of the acid response during prolonged stimulation with pentagastrin 100 ng/kg/h was ensured in a control study during intravenous infusion of saline.

On the second day pentagastrin in a dose of 100 ng/kg/h was administered as a continuous intravenous infusion for three hours. During the last 1½ hours Naloxone (Endo Laboratories Inc. Garden City, New York) was added in a dose of 10 µg/kg/h.

On the third day pentagastrin in a dose of 100 ng/kg/h was infused for 3½ hours. During the last two hours a synthetic met-enkephalin analogue (synthetic met-enkephalin analogue FK 33824, provided by Sandoz, Basel, Switzerland) was added in a dose of 1.0 µg/kg/h. In the last one hour naloxone in a dose of 10 µg/kg/h was also infused. All infusions were administered at a rate of 12 ml/h.

Laboratory analysis

The concentration of H⁺ was determined by titration

with an autotitrator (Radiometer, Copenhagen) to pH 7.0. ^{51}Cr -Edta was determined in a well-counter. In each gastric sample the concentration of Na^+ was determined by flame photometry and osmolarity by freezing point reduction.

Serum gastrin concentration was measured radio-immunochemically. The gastrin antiserum used (2604) binds component I, II (gastrin 34), and III (gastrin 17) with equimolar potency, while the binding of component IV (gastrin 14) is 60% of that of the larger molecular forms of gastrin.⁷ Detection limit, precision and specificity of the assay have been described in details elsewhere.⁸

Statistical analysis was performed by Student's *t* test for paired observations.

Results

The control study showed a constant secretory rate during pentagastrin infusion, a secretory plateau was obtained corresponding to a mean acid output of 4.8 ± 0.6 mmol/l H^+ /15 min (Fig. 1). The addition of naloxone did not alter pentagastrin stimulated gastric acid secretion, output being 4.3 ± 1.7 mmol/l H^+ /15 min ($P < 0.1$). Serum gastrin was unchanged throughout the study (Fig. 2).

Fig. 1 Gastric acid secretion during infusion of pentagastrin + saline. Mean $\pm$ SEM.

Infusion of met-enkephalin increased gastric acid output from 4.8 ± 0.6 mmol/l H^+ /15 min to 7.8 ± 0.4 mmol/l H^+ /15 min ($P > 0.001$). The subsequent addition of naloxone decreased acid output from 7.8 ± 0.4 mmol/l H^+ /15 min to 3.8 ± 0.3 mmol/l H^+ /15 min ($P > 0.001$). Serum gastrin concentration remained unchanged (Fig. 3).

Fig. 2 Gastric acid secretion and serum gastrin concentration during stimulation with pentagastrin and infusion of naloxone. Mean $\pm$ SEM.

Mean gastric recovery was $87 \pm 4.3\%$, this level being unchanged during the study. Duodenogastric reflux did not occur, as no change in the concentration of Na^+ or osmolarity was found.

Discussion

In the present study it has been demonstrated that naloxone does not affect submaximal pentagastrin stimulated gastric acid secretion or serum gastrin concentration. In contrast, met-enkephalin-induced acid response was inhibited by naloxone, also without change in serum gastrin concentration. Consequently, naloxone seems to interfere only with opiate-induced acid secretion. This observation, together with previously reported findings that basal and food-stimulated gastric acid secretion in man inhibited by naloxone,⁶ suggests that met-enkephalin participates in the physiological acid response. This accords with our previous

Fig. 3 Gastric acid secretion and serum gastrin concentration during stimulation with pentagastrin and infusion of met-enkephalin plus naloxone. Mean $\pm$ SEM.

findings that met-enkephalin seems to be a partial agonist of acid secretion.⁵ As other parietal cell inhibitors, such as H₂-receptor antagonists and atropine, also inhibit opiate-induced gastric acid secretion,⁹ it is possible that the effect of endogenous opiates involves release of histamine and acetylcholine.

Met-enkephalin has been detected in the vagal nerve¹⁰ and it has been suggested that it may play a role in the cephalic phase of gastric acid secretion⁵. However, in contrast with basal and food-stimulated gastric acid secretion, sham feeding-induced acid secretion was not inhibited by naloxone,¹¹ indicating that met-enkephalin is unlikely to participate in the cephalic phase of acid secretion.

In conclusion, this study has shown that the opiate receptor antagonist, naloxone, inhibits met-enkephalin-induced gastric acid secretion but not pentagastrin-stimulated secretion, suggesting that the inhibitory effect of naloxone is specifically directed towards met-enkephalin-induced secretion. This observation, together with the findings that naloxone is without effect on sham feeding¹¹ but inhibits meal-stimulated acid secretion,⁶ renders it probable that met-enkephalin participates in the gastric phase of acid secretion.

This study was supported by grants from the Danish Hospital Foundation for Medical Research, Region of Copenhagen, The Faroe Islands, and Greenland (43/80).

References

- Pert CB, Snyder SH. Opiate receptors: demonstration in nervous tissue. *Science* 1973; **179**:1011-4.
- Polak JM, Bloom SR, Sullivan SN, Facer P, Pearce ACE. Enkephalin-like immunoreactivity in the human gastro-intestinal tract. *Lancet* 1977; **1**:972-4.
- Lundberg JM, Hökfelt T, Nilsson G, Terenius L, Rehfeld J, Elde R, Said S. Peptide neurons in the vagus, splanchnic and sciatic nerves. *Acta Physiol Scand* 1978; **104**:499-501.
- Schultzberg M, Dreyfus CF, Gershon MD, Hökfelt T, Elde RP, Nilsson G, Said S, Goldstein M. VIP-enkephalin-, substance P- and somatostatin-like immunoreactivity in neurons intrinsic to the intestine: immunohistochemical evidence from organotypic tissue cultures. *Brain Res* 1978; **155**:239-48.
- Skov Olsen P, Kirkegaard P, Petersen B, Lendorf A, Christiansen J. The effect of a synthetic met-enkephalin analogue (FK 33-824) on gastric acid secretion and serum gastrin in man. *Scand J Gastroenterol* (in press).
- Feldman M, Walsh JH, Taylor IL. Effect of naloxone and morphine on gastric acid secretion and on serum gastrin and pancreatic polypeptide concentrations in humans. *Gastroenterology* 1980; **79**:294-8.
- Rehfeld JF, Stadil F. Radioimmunoassay for gastrin using immunoosorbents. *Scand J Clin Lab Invest* 1973; **31**:459-64.
- Rehfeld JF. Disturbed islet cell function related to endogenous gastrin release. *J Clin Invest* 1976; **58**:41-9.
- Konturek SJ, Tasler J, Cieszkowski BS, Mikos E, Coy DH, Schally AV. Comparison of methionine-enkephalin and morphine in the stimulation of gastric acid secretion in the dog. *Gastroenterology* 1980; **78**:294-300.
- Lundberg JM, Hökfelt T, Kewenter J, Petersson G, Ahlman H, et al. Substance P-, VIP-, and enkephalin-like immunoreactivity in the human vagus nerve. *Gastroenterology* 1979; **77**:468-71.
- Feldman M, Walsh JM. Endogenous opiates facilitate gastric acid secretion in man (abstract). *Gastroenterology* 1980; **78**:1164.