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

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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 tissue. Subsequently, immunohistochemical studies revealed a wide distribution of enkephalin in the gastrointestinal tract and pancreas, both in endocrine cells and in peripheral nerves. In a previous study met-enkephalin was found to enhance submaximal pentagastrin-stimulated acid secretion in man without affecting serum gastrin levels. Naloxone, an opiate receptor antagonist, inhibits basal and meal-stimulated gastric acid secretion, without affecting serum gastrin concentration in man. 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.

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.

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 (31Cr-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 $4.8 \pm 0.6$ mmol/l H$^+$/15 min (Fig. 1). The addition of naloxone did not alter pentagastrin stimulated gastric acid secretion, output being $4.3 \pm 1.7$ 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 ± SEM.](image)

![Fig. 2: Gastric acid secretion and serum gastrin concentration during stimulation with pentagastrin and infusion of naloxone. Mean ± SEM.](image)

**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,$^4$ suggests that met-enkephalin participates in the physiological acid response. This accords with our previous
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 feeding but inhibits meal-stimulated acid secretion, renders it probable that met-enkephalin participates in the gastric phase of acid secretion.

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References


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