INVESTIGATIVE NUCLEAR MEDICINE

A Study of Gastrointestinal Opiate Receptors: The Role of the Mu Receptor on Gastric Emptying: Concise Communication

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Animal and in vitro experiments suggest that opiates exert their actions by interaction with possibly five different subtypes of opiate receptors, identified as mu (μ), kappa (κ), sigma (σ), delta (δ), and epsilon (ϵ). As yet there is no conclusive evidence for their existence in man. Our experiments on morphine and the enkephalin analog DAMME have suggested at least two types of opiate receptors involved in gastric secretion. In this study we have used the very powerful and nonselective opiate agonist etorphine to stimulate as many of the different opiate receptors as possible. We have then attempted to block selectively the μ receptor by administering a small dose of naloxone. Etorphine delayed gastric emptying whereas naloxone alone had no effect. In combination, the inhibitory effect of etorphine on gastric emptying was incompletely prevented while the subjective effects of etorphine were completely abolished. These results may indicate that μ receptors are important in the regulation of gastric emptying, but that other (non-μ) receptors are also involved. The radionuclide study of gastric emptying, as used here, is a potentially powerful tool in physiological research on the gastrointestinal tract.

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Animal and in vitro experiments suggest the existence of at least three, and possibly five, subtypes of opiate receptors (*1–4*). These have been identified by the varying affinities and effects of opiate agonists and antagonists on various biological systems (*5–9*). The receptors are identified as μ (mu), κ (kappa), σ (sigma), δ (delta), and ϵ (epsilon). Morphine is a prototypic agonist for the mu receptor, ketocyclazocine for the kappa receptor, and SKF-10,047 for the sigma receptor (*2,4,7,8*). The delta receptor has high affinity for the enkephalins (*6*), whereas the epsilon receptor shows preference for the beta endorphine (*5*). The tissue distribution of these receptors is not uniform from species to species, or even from strain to strain (*2*). Opiate receptors are found not only in the central nervous system; (*1,2*) there is at least indirect evidence that some of these receptors exist in animal gastrointestinal tract (*4,9*). With immunoreactivity and immunohistochemical methods (*10–13*), enkephalin-like and endorphine-related peptides have been found in the gastrointestinal tract. As yet there is no conclusive evidence for the existence of different opiate-receptor subtypes in man, but our own experiments on inhibition of gastric function by morphine and the enkephalin analog (DAMME) (*14–19*) suggest that there may be at least two types of opiate receptor involved in the regulation of gastric secretion. In this study we report the effects of etorphine, the most powerful opiate agonist discovered to date, (*19*) on gastric emptying. We studied etorphine with and without the opiate antagonist naloxone (*20*) in an attempt to identify the type of opiate receptor involved in gastric motility.

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METHODS

Radionuclide studies of gastric emptying were performed on seven healthy volunteers (ages 22–35; 60–80

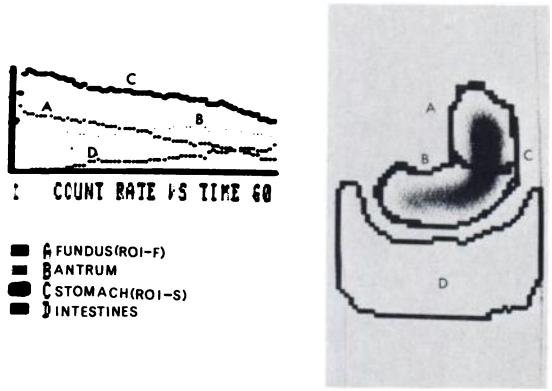

FIG. 1. Regions of interest selected for this study. (ROI-F) represents fundus and part of body of stomach. C (ROI-S) represents entire stomach. Curves illustrate raw data of dynamic part of study (first 60 min) of volunteer before processing of curves. Note that fundus and entire-stomach curves typically follow similar emptying pattern.

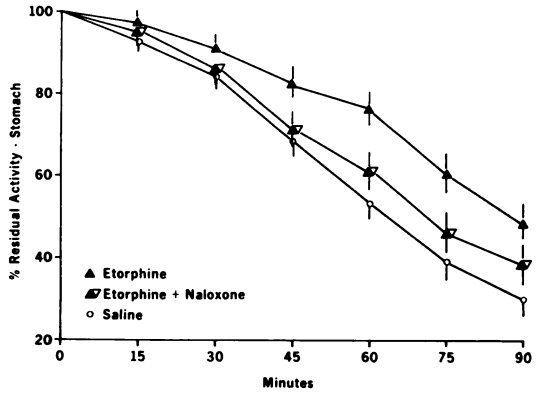

FIG. 3. Effects of etorphine on gastric motility are compared with combined effect of etorphine and naloxone. There was definite difference in individual cases as well as in group as whole but statistically insignificant. The combination brought gastric motility back to level close to that produced by saline injection.

kg). Informed consent was obtained from each subject and the study was approved by Health Sciences Standing Committee on Human Research at our institution. Each volunteer was studied on four occasions, at least a week apart. After an overnight fast, a test meal consisting of an egg salad sandwich and 150 ml of orange juice was ingested over 3 to 5 min. The sandwich consisted of two slices of white bread, one medium-sized egg, and 30 ml of mayonnaise. Upon completion of the meal the volunteers received one of the following four intravenous injections in random order: (a) naloxone 4 μg/kg, (b) etorphine 0.125 μg/kg, (c) etorphine plus naloxone in combination and in above doses, or (d) a saline placebo in equivalent volume.

Anterior scintigrams were made with the subjects supine. Counts were collected for 90 min using a standard gamma camera with diverging collimator and online computer. The first 60 min provided a dynamic study with 1-min frames; then two static images were made at 75 and 90 min, again using 1-min frames. The patients remained supine on a stretcher throughout the 90 min.

The two static images (at 75 and 90 min) were added to the first 60 points to give a continuous curve through 90 min. Each point was corrected for physical decay of Tc-99m. The counts at 15, 30, 45, 60, 75, and 90 min were expressed as a percentage of the maximum count. Two regions of interest were analyzed; ROI-S for the whole stomach, and ROI-F is for the fundus, although it also includes a portion of the body of the stomach (Fig. 1). Statistical analysis was by paired Student's t-test.

RESULTS

None of the patients had distressing symptoms from etorphine, and all experienced mild euphoria and a brief period of vertigo without nausea. Naloxone completely prevented all of the etorphine symptoms. There was a significant prolongation of gastric emptying time by the etorphine (Fig. 2). The effect was similar on the stomach as a whole (ROI-S) as well as the fundus (ROI-F). The inhibitory effects of etorphine on gastric motility were completely counteracted by naloxone in three of the

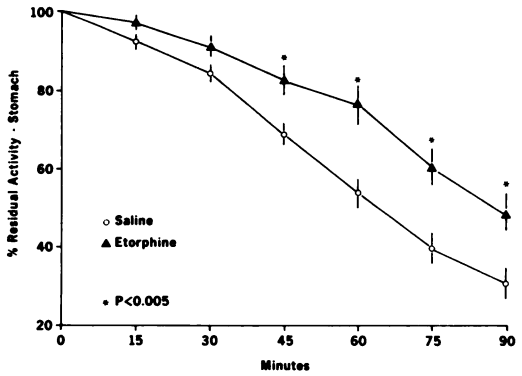

FIG. 2. Means for seven patients (with s.e.m.) were used to produce these curves, representing total stomach. (ROI-S). Etorphine is compared with saline. Significant inhibitory etorphine effect on gastric motility was established by paired Student's t-test.

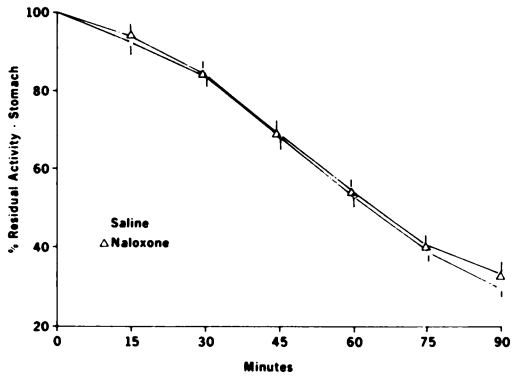

FIG. 4. Naloxone by itself had no inhibitory or excitatory effect on gastric emptying compared with intravenous saline.

seven subjects, and partially in four of the seven. The means and s.e.m. of all the seven subjects are represented in Fig. 3. Naloxone by itself did not significantly affect gastric emptying (Fig. 4). The effects of all of the four injections were similar on both ROI-S and ROI-F.

DISCUSSION

The presence of opiate receptors in the gastrointestinal tract (*1–9*), and of substances with opiate activity (*10–13*), strongly suggest that endogenous opiates are involved in regulating gastrointestinal function. In addition, exogenous administration of opiate substances—either into the central nervous system or the peripheral circulation—may affect the gastrointestinal motility and secretion (*2,24*). In previous studies of healthy volunteers we have shown that both morphine and the enkephalin analog DAMME inhibit gastric motility (*14–16*) as well as gastric acid secretion (*17,18*). The effect of morphine was completely reversed by naloxone (*17*), but naloxone did not reverse the inhibitory effects of the enkephalin analog (*18*). This raised the possibility that several subtypes of central or peripheral opiate receptors might be involved in gastric secretion. In this study we have attempted to ascertain whether multiple opiate receptors might also be involved in the regulation of gastric emptying. Unfortunately, receptor-specific narcotic agonists are not available for human use, although morphine in low doses is relatively μ-receptor specific (*2,9*). Receptor-specific narcotic antagonists are not available for human use. Naloxone is an antagonist for all five receptors, but its efficacy in blocking the activity of different opiate substances at different opiate receptors is not uniform (*4,6,20*). Naloxone is at least ten times as potent as a μ antagonist relative to its antagonistic effect on κ (pA_2 = 8.81 compared with 7.58) (*4*). It is also a poor antagonist for the δ receptor, and much larger doses are required to reverse the effects of enkephalin on the δ receptor. In this study we have used the very powerful, nonselective, and short-acting opiate agonist etorphine (*2,8,25*) to stimulate as many of the different opiate receptors as possible. Etorphine is approximately 500 times as potent as morphine on a weight basis, therefore the doses used in this study are equivalent to approximately 5 mg of morphine (*25*). We have then attempted to block selectively the effect of etorphine on the μ receptor by administering a dose of naloxone that is more than sufficient to reverse an equivalent dose of morphine, and that we found from preliminary studies to be approximately twice the minimum dose of naloxone required to eliminate or block completely all the subjective effects of etorphine. Etorphine and naloxone have approximately the same duration of effect (*20,25,26*). Following simultaneous bolus injection of etorphine and naloxone, the blood levels will gradually decrease; however, the molar ratio of the drugs at the opiate receptor will remain relatively constant, and there should be uniform blockade of the μ receptor with time. We hoped by these maneuvers to block the effect of etorphine on the μ receptor but allow continued effect of etorphine on other opiate receptors. We found that etorphine delayed gastric emptying while naloxone itself had no effect. In combination, naloxone only partially blocked the effect of etorphine on gastric emptying, but completely abolished the central subjective effects of etorphine. These results suggest that μ receptors are important in the regulation of gastric emptying, but other non-μ receptors are involved as well. Since etorphine and naloxone both act on the central nervous system, and peripherally on the gastrointestinal tract, this study cannot establish whether the μ receptors and the non-μ receptors involved are central or peripheral.

As more opiate agonists and antagonists that are specific for the receptor subtypes become available for clinical use, the nature of the different central and peripheral opiate receptors involved in the functions of the human gastrointestinal tract will become clearer. The radionuclide gastric emptying study (*21–23*) is potentially a powerful tool in the physiological studies of the gastrointestinal tract.

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