Effect of Opiate and Adrenergic Blockers on the Gut Motor Response to Centrally Acting Stimuli

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Labyrinthine stimulation and cold pain inhibit feeding antral pressure activity, delay gastric emptying, and increase blood concentrations of β-endorphin and norepinephrine. Further, labyrinthine stimulation induces, in approximately one-third of healthy individuals, a migrating burst of motor activity in the proximal intestine that interrupts the normal fed pattern. Our hypothesis was that endogenous opiates and catecholamines act as mediators of such disruptive effects of centrally acting stressful stimuli on gut motility. Thus, we studied feeding gastrointestinal pressure activity in healthy volunteers who were exposed to labyrinthine stimulation or cold pressure test, or both (both stimuli being either in their active or in their control forms), while receiving an intravenous infusion of either placebo (saline), or an opioid blocker (naloxone), or a combination of α- and β-adrenergic blockers (phentolamine and propranolol), or all the drugs together. Neither opioid nor adrenergic blockers affected motility during control stimulations. Active stressful stimuli (labyrinthine stimulation, cold pain, or both) significantly inhibited antral feeding activity ($p < 0.05$), but these effects were prevented by concomitant infusion of naloxone ($p < 0.05$). Adrenergic blockade also prevented the antral motor inhibition caused by stress ($p < 0.05$), but it was more effective for cold pain than for labyrinthine stimulation, and, when performed concomitantly with opiate blockade, the preventive effects disappeared. Furthermore, during adrenergic blockade labyrinthine stimulation invariably induced the appearance of a migrating duodenal burst of motor activity. Neither opioid nor adrenergic blockers modified the stress-induced rise of plasma β-endorphin and norepinephrine. Our results suggest that opioids and catecholamines are involved in the mediation of the disruptive effects induced by centrally acting stressful stimuli on postprandial motor activity in the proximal human gut.

Stressful stimuli have been reported to induce important modifications in gastroduodenal motility, initially in anecdotal observations (1), and more recently, using quantitative techniques (2–4). Whereas it is accepted that both neural and humoral pathways link the central nervous system to the gut, little is known about the mechanism by which these centrally acting stimuli exert their perturbing effects on human upper gut.

Evidence for a neural pathway of brain-gut disruption may be found in the existence in the medulla oblongata of centers involved in nausea and emesis (5,6), as well as in some indication that gut motor effects of nauseating stimuli are partially mediated via the vagus nerves (7).

Evidence for humoral pathways includes the release of β-endorphin and catecholamines into the peripheral circulation during some forms of stress (4,8). It has also been noted that opioid receptors are present in the human gut (9) and that administration of exogenous opiates induces gastrointestinal motor disturbances such as inhibition of gastric emptying (10) and bursts of intestinal contractile activity (11). The latter resemble motor activity observed in re-

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sponse to external stimuli and during emesis (3,4,12–14).

Catecholamine receptors (α- and β-subtypes) are also present in the gut (15,16). Adrenergic stimulation is generally felt to exert an inhibitory effect on gut motor activity through both an inhibition of the release of acetylcholine from intrinsic cholinergic neurons and a direct action on smooth muscle cells. Exogenous administration of β-adrenergic agonists induces motor effects resembling those caused by opiates or stress, such as inhibition of gastric emptying (17) and bursts of intestinal motor activity (18). It has been proposed that these effects could be mediated through secondary release of somatostatin (18).

In the present study, we have examined the possible relationship between endogenous opioid and catecholamine release and inhibition of gastric motility in response to stressful stimuli. Naloxone was used as a competitive opioid antagonist, able to interact with variable potency with several subclasses of gut opioid receptors (19). A combination of two nonselective α- and β-receptor antagonists (phentolamine and propranolol, respectively) was used to achieve adrenergic blockade.

Materials and Methods

Subjects

A total of 36 healthy subjects (27 men, 9 women, 20–67 yr old) participated in these studies, which had been previously approved by Mayo Clinic Human Studies Committee. Twelve of them had participated in a previously reported study (4) but were included in the analysis here. General physical and otological examinations were performed in each subject to ascertain suitability for participation in the study. During the tests, the subjects laid supine on a hospital bed, with head end elevated 30° to the horizontal, in a single quiet room.

Motility Recordings

After an overnight fast, each subject swallowed a radiopaque 12-lumen open-tipped tube with side openings located respectively at the tip of the tube and 20, 28, 29, 30, 31, 32, 33, 34, 35, 36, and 37 cm proximally. The overall external diameters were 4 and 5.5 mm. A pneumohydraulic manometric system, as previously described (4), was used to quantify gut pressure activity. The tube was positioned under fluoroscopic control so that some (five to seven) of the 10 most proximal recording sites (1 cm apart) were in the distal antrum and some (three to five) of them in the proximal part of the bulb of the duodenum. The remaining two side openings were located in the second portion of the duodenum and immediately beyond the angle of Treitz. In 4 volunteers, a six-lumen tube with only four manometric sites at the antroduodenal junction was used (4).

Motility was recorded during the fasting period for at least an hour, and then a meal was served. The meal consisted of chicken, potato, butter, tapioca pudding, and 190 ml of water, as used in previous studies (4). Its total caloric value was 504 (fat 36%, carbohydrate 45%, and protein 19%). Recordings were stopped 130 min after the end of the meal.

Blood Samples

Blood samples (20 ml each) were collected before the meal and 5, 11, 13, 15, 17, 20, 40, and 70 min after the end of the meal for determination of circulating levels of β-endorphin and norepinephrine as described previously (4). Because of the expense involved in norepinephrine determinations, only blood samples obtained at 5, 13, and 20 min postprandially were assayed for this substance.

Stressful Stimuli

Ten minutes after the end of the meal, each subject was subjected to two simultaneous stressful stimuli: labyrinthine stimulation to induce vertigo and cold pressor test to produce pain. These stimuli were applied according to standardized techniques previously described in detail (4). The two stimuli were always applied simultaneously unless they were both in the active form. In the latter instance, volunteers were asked to immerse their hand into the cold water as soon as vertigo had started, as it would be quite difficult to induce vertigo by irrigation of the external auditory meatus in a subject already stressed by another stimulus.

Opioid and Adrenergic Blockers

Pharmacologic blockers were infused intravenously into the opposite arm beginning 5 min before application of the stressful stimuli. Subjects received, over a period of 2 min, either (a) saline 0.45%, 10 ml as a placebo (P); (b) naloxone hydrochloride 0.4 mg (Narcan, Du Pont Pharmaceuticals, Garden City, N.Y.) (N); (c) phentolamine mesylate 5 mg (Regitine, CIBA Pharmaceutical Co., Summit, N.J.) and propranolol hydrochloride 5 mg (Inderal, Ayerst Laboratories Inc., New York, N.Y.) (A); or (d) naloxone and phentolamine and propranolol (N-A). Each injection was followed by a 60-min infusion by automatic perfusion pump (Volumette, model 4200, Sigmamotor Inc., Middleport, N.Y.) with the respective combination of drugs, namely (a) placebo (saline) (P); (b) naloxone (N) 40 $\mu g/kg \cdot h$; (c) phentolamine 30 mg/h and propranolol 4.8 mg/h (A); or (d) naloxone and phentolamine and propranolol (N-A) at the same doses.

Choice of the doses of phentolamine and propranolol was based on previous human studies (20,21) in which they were shown to block the metabolic response to epinephrine (blood sugar, glucagon, and free fatty acid increases during epinephrine infusion at 6 $\mu g/min$), without inducing significant side effects. Further, this particular infusion rate of epinephrine (6 $\mu g/min$) has been shown to increase circulating epinephrine levels to values >1000

pg/ml (22), which are above the levels usually achieved in response to cold pain (23).

Ancillary Naloxone Dose-Response Studies

The aim of these preliminary studies was to determine effects of logarithmic increases in the dose of naloxone in individuals exposed to labyrinthine stimulation or cold pain. Five healthy volunteers (2 men and 3 women) received a very high dose of naloxone (0.5 mg/kg over 5 min followed by an infusion of 40 μg/kg · h); 4 of the 5 developed nausea and vomiting that persisted for several hours after the end of the test. Seven other volunteers (6 men and 1 woman) received an intermediate dose of naloxone (4 mg total over 2 min followed by 40 μg/kg · h), and in 3 of the 7 vertigo could not be induced by labyrinthine stimulation. Thus, a 10-fold lower dose of naloxone (0.4 mg over 2 min followed by 40 μg/kg · h), which caused no side effects and allowed vertigo to occur, was finally selected as the optimal dose for subsequent blocking studies.

Extraintestinal Autonomic Responses

To evaluate the individual extraintestinal autonomic response to stressful stimuli and drugs we measured pulse rate and brachial systolic and diastolic pressure levels immediately after each blood sample. We monitored electrical skin conductance levels using a skin dermograph (Autogen 3000, Autogenic Systems, Inc., Berkeley, Calif.) during the study, and the movements of the eyes during the stress period were also recorded by nystagmometry with a differential amplifier (model 2124, DATA, Inc., Fort Collins, Colo.).

Experimental Design

The across-individuals experimental design consisted of 2^4-factorial design (Figure 1) in which 24 subjects (19 men and 5 women) were randomly assigned to one of 16 combinations of four factors (pain, vertigo, naloxone, adrenergic blockers), the four factors each having two levels. Each subject thus received stress consisting of either active or control levels of the stimuli (pain or vertigo) simultaneously with either placebo, naloxone, adrenergic blockers, or all blockers. The factorial design provided an efficient and flexible framework for investigating different factors of interest (in this case four) as well as their possible interactions.

Data Analysis Methods

Antral motor responses. Pressure activity was summarized by counting pressure waves (time of occurrence and amplitude) in the recording channel corresponding to the most distal centimeter of the antrum. This area appeared to be the most active part of the "antral pump," as clearly shown by the accurate motility records that we obtained positioning 10 recording sites 1 cm apart at the antroduodenal junction. As described before (4), a

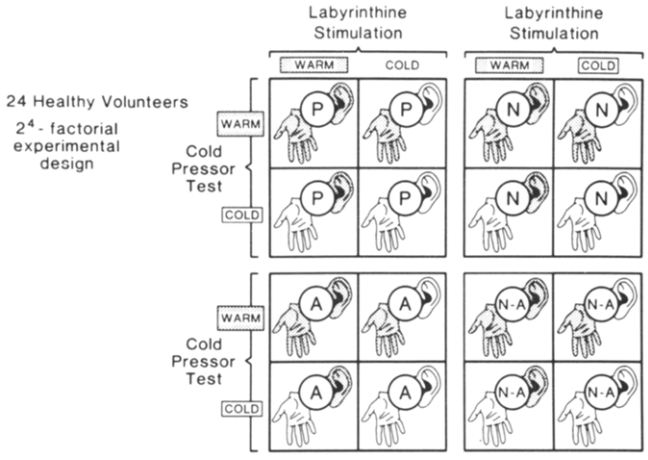

Figure 1. Diagrammatic representation of the experimental design. P, placebo; N, naloxone; A, adrenergic blockers; N-A, naloxone plus adrenergic blockers.

motility index [$\log_e$ (Σ amplitudes * number of contractions + 1)] per 2 min was computed starting 10 min before the end of the meal and continuing for 40 min poststimulus. These 2-min motility indices were then cumulated for each subject. The slope (rate of increase) of this cumulative (log) motility index in each subject was computed separately over time intervals corresponding to the last 10 min of the meal, the 10-min prestimulus period, and for two consecutive 20-min periods poststimulus.

Humoral responses. The log values of β-endorphin at 5 min before application of the stimulus were first subtracted from the log values at sampling times 11, 13, 15, 17, 20, 40, and 70 min (poststimulus samples), thus yielding comparable responses for all patients relative to their initial postprandial (prestimulus) level. The log transformation was used to stabilize the variability in the responses that tended to increase as the level of the response increased. The values in this "relative" (log) response were then cumulated over times 11, 13, 15, 17, and 20 min for each subject, essentially yielding the area under the relative (log) response curve for the first 20 min poststimulus.

For norepinephrine, the relative (log) response at time 20 min was determined by subtracting the log (value at 20 min) from log (value at 5 min).

Extraintestinal autonomic responses. The values of systolic blood pressure, diastolic blood pressure, pulse rate, and skin conductance at 5 min before the administration of the stimulus were subtracted from their corresponding values at 20 min after the meal ended.

Statistical Methods

From previous work (4) it was apparent that the two stimuli, pain and vertigo, induced similar responses alone or in combination. The present data, including the blocker studies, were thus analyzed by defining a factor (stress) with two levels corresponding to the presence of one or both active levels of the stimuli, pain and vertigo. The remaining two factors, presence or absence of adrener-

gic blockers and presence or absence of opiate blocker, could also be viewed as defining a single factor (blocker) with four levels: no blockers (P), just adrenergic (A), just naloxone (N), and all blockers (N-A). In the situation where significant three-factor interactions among stress and the blockers were indicated, the data analysis framework was recast as a 2 × 4-factorial design [stress (two levels) times blocker (four levels)] for easier interpretation. In the case where no three-factor interaction appeared significant, the data were analyzed in the framework of a 2^3-factorial design (stress × adrenergic blockers × naloxone) in order to interpret the responses based on main effects, or at most two factor interactions (24). Specific methods used for analysis of antral motor responses, humoral mediators, and extraintestinal responses are detailed below.

Antral motor responses. These slopes of the cumulative antral motility indices were analyzed via analysis of variance based on a 2 × 4 factorial design. The method used for making multiple posterior tests was based on three groups of comparisons. These involved the comparison of responses for different blocker combinations in the absence of stress (a total of $\binom{4}{2} = 6$ comparisons), in the presence of stress (again $\binom{4}{2} = 6$ comparisons), and comparisons of stress vs. no stress for each blocker combination (4 in this case). The significance level within each group of comparisons was set at $\alpha = 0.05$ divided by the number of comparisons for that group, yielding 0.008, 0.008, and 0.0125, respectively, thus maintaining an overall α-level of 0.05 within each group.

Humoral responses. Areas under relative log β-endorphin responses were analyzed based on a 2^3-factorial analysis of variance (stress × adrenergic blockers × naloxone). For norepinephrine the relative (log) responses at time 20 min were analyzed via analysis of variance based on a 2^3-factorial design (stress × adrenergic blocker × naloxone).

Extraintestinal autonomic responses. Relative differences in pre- and poststimulus systolic and diastolic blood pressure, pulse rate, and skin conductance were analyzed via analysis of variance based on a 2^3-factorial design.

Results

Antral Motility

The statistical analysis of the data on antral pressure activity used a 2 × 4 analysis of variance model. The analysis indicated significant nonadditive effects for the combined influence of stress and blockers (Figure 2). In the absence of stress there was no difference in antral activity during infusion of placebo (no blockers), naloxone, adrenergic blockers, or all blockers combined (Figures 2 and 3).

The results (summarized in Tables 1 and 2) indicated naloxone and adrenergic blockers alone prevented the effects of stress ($p < 0.05$), but the combination of naloxone and adrenergic blockers in the presence of stress was not different from stress without any blockers (Figure 2, compare also Figures 4 and 5). Thus, the combination of both blockers did not appear to alter the antral response to stress. Individual observations suggested that naloxone was effective in preventing the effects of cold pain or labyrinthine stimulation alone (Figure 4), but not quite so effective for cold pain and labyrinthine stimulation combined (Figure 5). The adrenergic blockers were completely effective for cold pain alone but appeared to be less capable of inhibiting the effects of vertigo alone (Figure 6), or of vertigo combined with cold pain.

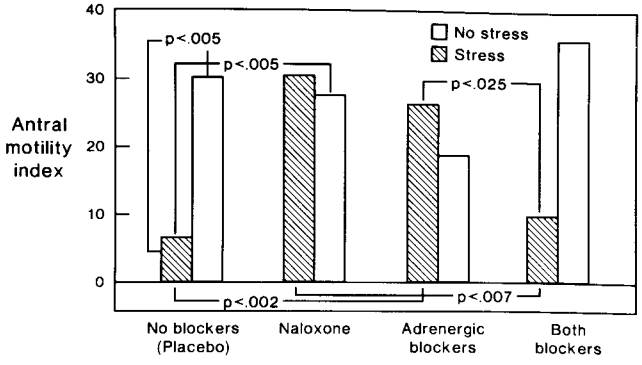

Figure 2. Effects of physical stress on fed antral motility index, in the presence or absence of opioid and adrenergic blockers. Least-squares estimated mean values of antral motility [slope in cumulative (log) motility index] during 10–30 min postprandial for the eight combinations of stress and the two blockers. The comparisons still significant after adjusting for multiple comparisons are described in text.

The analysis of variance results for the second 20 min poststimulus exhibited similar trends but more variability, the test for nonadditive effects being borderline ($p = 0.12$). The adrenergic blockers appeared more effective in blocking the effects of the stress; however, the effect of stress may have diminished by this time as well (Table 2).

Intestinal Motility

Striking effects on intestinal motility were observed during application of stressful stimuli during infusion of blockers. Labyrinthine stimulation *always* interrupted the fed motor pattern and induced the appearance of a phase III-like activity in the duodenum during infusion of adrenergic blockers, whether naloxone was simultaneously infused or not (Figure 6). Furthermore, 1 subject developed a similar intestinal motor activity while exposed to cold pain during the infusion of adrenergic blockers and naloxone (Figure 5). Extraintestinal autonomic responses suggested that a particularly marked adrenergic inhibition with hypotension and bradycardia had occurred in this subject. Table 3 indicates the characteristics of phase III-like intesti-

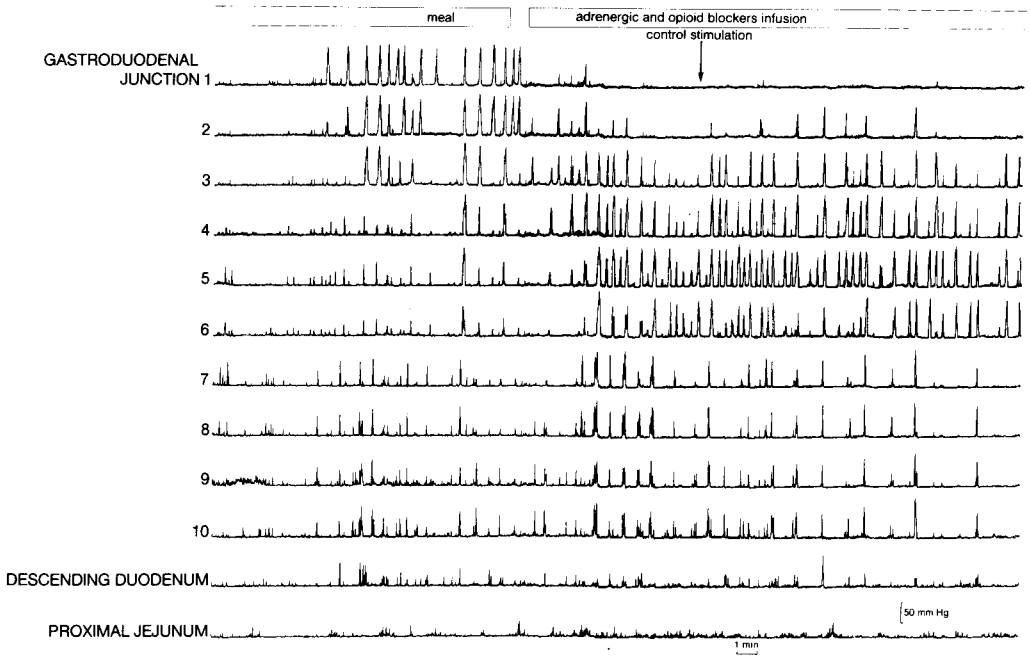

Figure 3. Postprandial gastrointestinal pressure activity during infusion of adrenergic and opioid blockers in a healthy individual. Intense antral motor response to the mixed solid-liquid meal and normal-appearing duodenal fed motor activity are not modified by a combined infusion of naloxone and adrenergic blockers, nor by a control stimulation applied during the infusion of the drugs.

nal motor activity in each instance. Infusion of blockers, alone or in combination, in the absence of stress did not cause any apparent change in the intestinal fed pattern (Figure 3).

Humoral Responses

β-Endorphin. Analysis of variance of the areas under the relative (log) response curve based on 2^3-factorial design indicated significant overall increases in β-endorphin levels ($p < 0.03$) in response to active stress (Figure 7). The increases were similar regardless of whether blockers were infused or not.

Norepinephrine. Analysis of variance of the data indicated significant elevation of norepinephrine levels in the presence of active stress ($p = 0.02$) (Figure 8). This appeared in the presence or absence of either adrenergic blockers or naloxone, although there was the suggestion of greater increment in response to stress in the presence of the opioid blocker.

Table 1. Feeding Antral Pressure Activity During Stress[a] With or Without Infusion of Blockers

			0–10 min		10–20 min		20–30 min		30–40 min		40–50 min	
Stress[a]	Blockers	n	No. waves	ΣA	No. waves	ΣA	No. waves	ΣA	No. waves	ΣA	No. waves	ΣA
Control	Neither	3	2.60 (±0.46)	11.20 (±5.51)	3.27 (±0.24)	8.20 (±4.50)	3.80 (±0.76)	8.20 (±2.21)	3.20 (±0.50)	7.67 (±2.67)	3.80 (±0.72)	9.20 (±2.16)
Active	Neither	9	1.84 (±0.61)	5.53 (±2.24)	0.33 (±0.17)	0.71 (±0.33)	1.20 (±0.42)	2.93 (±1.54)	1.56 (±0.65)	5.64 (±3.04)	1.24 (±0.52)	6.60 (±4.14)
Control	Adrenergic	1	1.00	1.40	2.40	3.00	2.60	4.40	2.40	3.20	2.40	4.80
Active	Adrenergic	3	3.33 (±0.98)	12.13 (±6.10)	2.73 (±1.27)	10.00 (±3.82)	3.67 (±1.39)	11.60 (±3.70)	3.53 (±0.79)	16.40 (±5.52)	4.20 (±0.50)	18.93 (±4.91)
Control	Naloxone	1	1.40	3.00	3.20	7.00	3.20	8.40	2.60	14.20	0.40	2.20
Active	Naloxone	3	3.13 (±0.97)	16.73 (±7.27)	3.87 (±1.11)	10.87 (±1.56)	3.20 (±1.39)	9.93 (±4.04)	3.67 (±0.96)	12.80 (±4.28)	3.53 (±0.64)	11.47 (±2.15)
Control	Both	1	5.20	35.80	4.00	29.80	3.00	16.20	2.80	18.40	3.40	11.00
Active	Both	3	3.33 (±0.85)	13.87 (±3.16)	1.53 (±1.14)	6.07 (±5.57)	1.47 (±0.27)	2.20 (±0.23)	2.00 (±1.31)	7.07 (±4.68)	1.47 (±0.24)	7.40 (±2.05)

Mean (±SE) for the number of contractions (number of waves) and sum of amplitudes (ΣA) per 10-min interval after a solid meal. The number of pressure waves and sum of amplitudes were averaged across subjects for each subcombination listed. [a] Labyrinthine stimulation, cold pressure test.

Table 2. Average Slopes of Cumulative Feeding Antral Pressure Activity During Stress[a] With or Without Infusion of Blockers

Stress[a]	Blockers	n	0–10 min	10–30 min	30–50 min
Control	Neither	3	8.2	30.4	28.6
			(±2.2)	(±1.8)	(±3.2)
Active	Neither	9	5.2	6.6	12.7
			(±1.8)	(±2.6)	(±5.7)
Control	Adrenergic	1	2.0	18.9	20.9
Active	Adrenergic	3	8.9	26.5	37.9
			(±3.7)	(±6.7)	(±4.5)
Control	Naloxone	1	6.0	27.8	11.20
Active	Naloxone	3	11.6	30.7	32.1
			(±2.7)	(±6.4)	(±5.1)
Control	Both	1	16.1	36.2	34.2
Active	Both	3	11.5	9.9	16.9
			(±1.9)	(±3.5)	(±6.5)

Average values (±SE) of the slope of the cumulative (log) motility index over the stated intervals after ingestion of a solid meal are shown. [a] Labyrinthine stimulation, cold pressure test.

Extraintestinal Autonomic Responses

Analysis of the data on blood pressure indicated significant interactions between stress and adrenergic blockers ($p = 0.05$). Inspection of the least-squares estimated mean values indicated that in the presence of stress, significant ($p = 0.001$) differences in the changes (poststimulus minus prestimulus) of both systolic and diastolic blood pressure were detected when comparing adrenergic blockade (decreases) with the absence of adrenergic blockade (increases). In the absence of stress, the blood pressure changes were similar (decreases) irrespective of the presence or absence of adrenergic blockers and were not statistically different from the decreases when stress and adrenergic blockade were both present. Without naloxone, the changes in both systolic and diastolic blood pressure during active stress were significantly different from changes during control stress ($p = 0.04$). In the presence of naloxone the effects of stress could not be detected. Significant interactions were not detected for skin conductance and pulse rate; the overall effect of active stress corresponded to significantly greater increases in skin conductance ($p = 0.03$), but small decreases in pulse rate.

Discussion

We have previously shown that during stress induced by labyrinthine stimulation and cold pain, catecholamine and β-endorphin levels in peripheral blood are elevated while fed antral pressure activity is inhibited (4). Elevation in plasma catecholamine and β-endorphin levels during physical and psychologic stress has been verified by others (8,23,25). The rapid metabolism of epinephrine by peripheral tissues and higher secretion rates result in norepinephrine concentrations in venous blood being higher than epinephrine concentrations (26). It appears on the basis of the present studies that stress-induced elevations in peripheral norepinephrine and β-endorphin levels are not modified by concomitant administration of α- and β-adrenergic blockers or naloxone, or both. Yet, the gut responses to stress may be substantially modified by these blockers.

Naloxone appeared to be particularly effective in blocking the inhibitory effect of either cold pain or labyrinthine stimulation, although the blocking effect seemed to weaken when stress was increased by administering both stimuli together. These results suggest that stress-induced inhibition of antral contractile activity during feeding is at least in part mediated by endogenous opiates. Others have shown similar opiate effects on responses to pain (27), exploratory behavior (28), and pituitary hormone release (29). However, no comparable data exist for the effects in response to active stimulation of the gut by endogenous opioid release.

Antagonism by naloxone is, nevertheless, a neces-

Table 3. Characteristics of Intestinal Phase III-Like Pressure Activity Induced by Stress[a] in the Presence of Adrenergic Blockers

Sex	Age	Stress	Pharmacologic blockers	Vertigo	Nausea	Time from vertigo (s)	Speed of migration $S_{11} \rightarrow S_{12}$[b] (cm/min)	Duration S_{11} (min)[b]	Duration S_{12} (min)[b]	Pattern before complex	Duration postburst quiescence (min)
M	27	CE	A	Yes	No	30	11	6.5	7	Normal fed	12
M	23	CE	N + A	Yes	Yes	60	9	7	11	Normal fed	12
M	22	CH	N + A	No	No	—	10	9	18	Normal fed	17
M	24	CE+CH	N + A	Yes	No	180	($S_{12} \rightarrow S_{11}$)[c] 20	7	7	Normal fed	10
M	26	CE+CH	A	Yes	No	30	7	8	12	Normal fed	12

A, adrenergic; N + A, naloxone plus adrenergic blockers. [a] Labyrinthine stimulation (CE), cold pain (CH). [b] Manometric sites 11 and 12 (intestinal—see Figure 1). [c] Retrograde propagation.

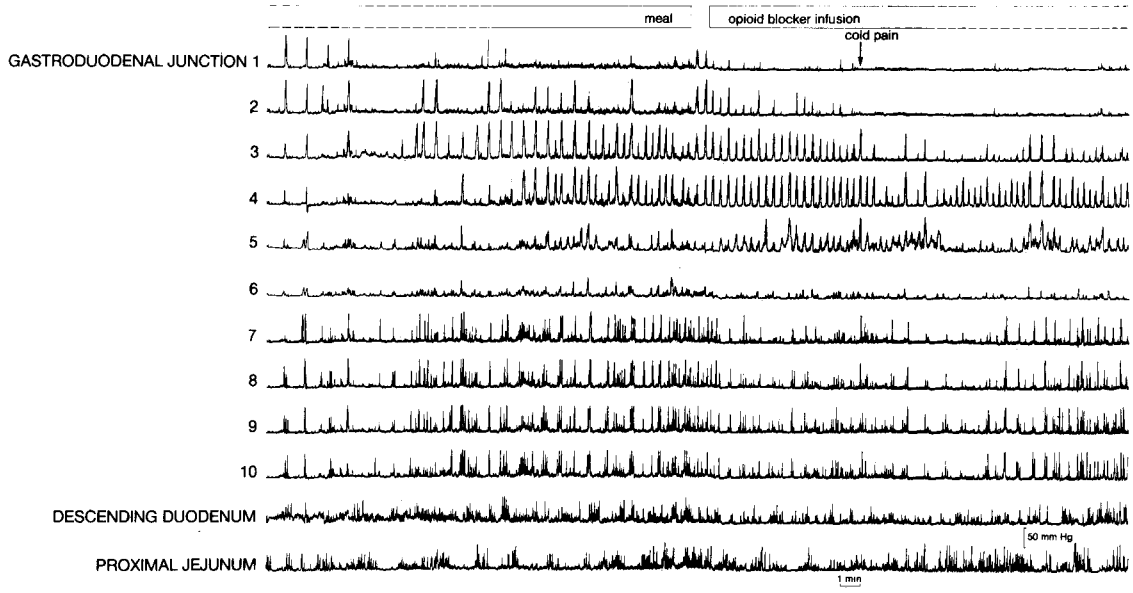

Figure 4. Effect of naloxone on gastrointestinal responses to cold pain. Cold pain does not affect gastroduodenal fed motor activity, when applied during an infusion of naloxone.

sary, though not sufficient criterion for demonstrating mediation of a response by an endogenous opiate (30). Naloxone has been shown to influence some pharmacologic responses to nonopiate drugs (30). Further, naloxone interacts with different affinity with several classes of opioid receptors (19,31,32) and some of them, including receptors to opioid peptides Leu- and Met-enkephalins, would not be expected to be blocked by naloxone at doses comparable to those used in the present study (33).

Adrenergic blockers antagonized the inhibitory action of cold pain on fed antral motor activity but appeared to be much less effective in preventing the effects of labyrinthine stimulation. The relative selectivity of the action of adrenergic blockers could be explained by cold pain eliciting a stronger sympa-

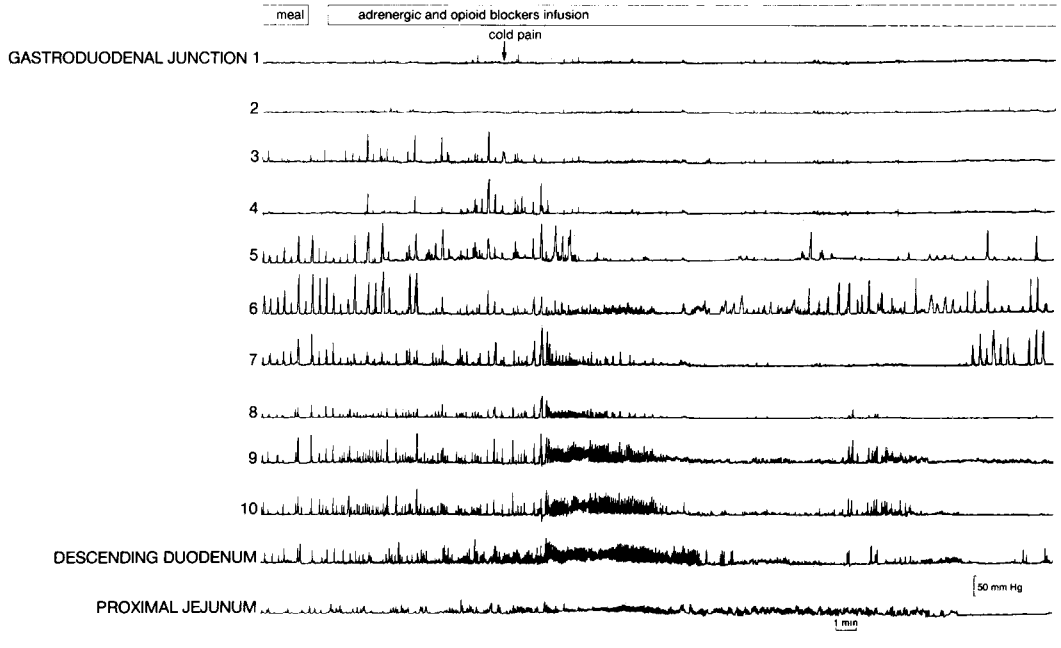

Figure 5. Effect of adrenergic and opioid blockers on gastrointestinal responses to cold pain. Cold pain induces a marked inhibition of fed antral contractions and the appearance of an intestinal burst of contractions during the infusion of a combination of naloxone and adrenergic blockers.

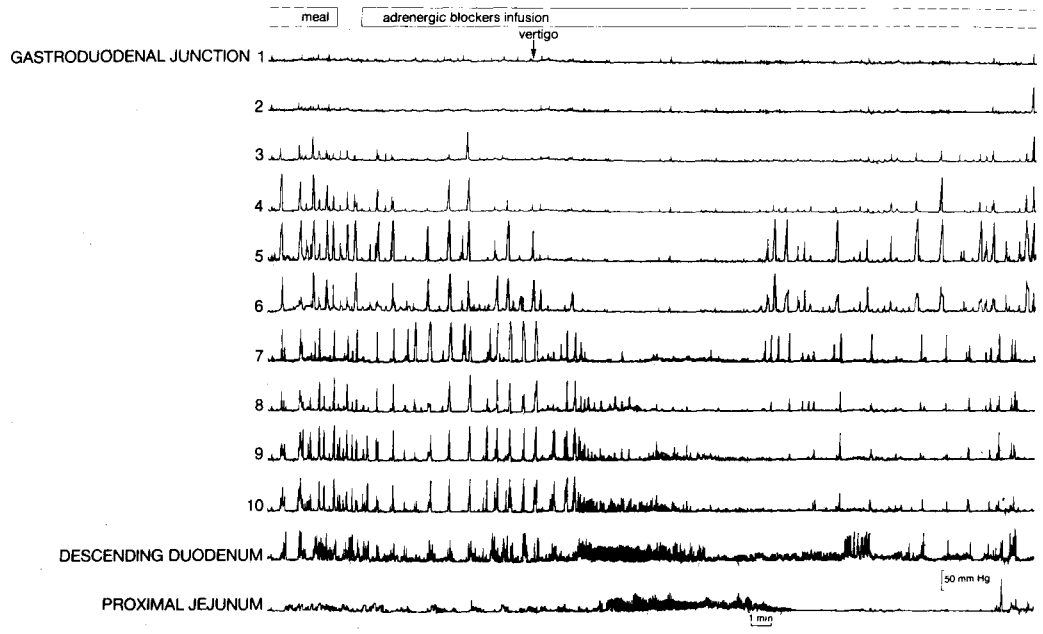

Figure 6. Effect of adrenergic blockers on gastrointestinal motility responses to vertigo. Vertigo markedly modifies gastroduodenal fed motor activity in spite of the infusion of adrenergic blockers. Note the inhibition of antral contractions and the appearance of the complexlike burst of contractions in the proximal small bowel.

thetic response (hence blocked by the adrenergic antagonists) than labyrinthine stimulation. Evidence for this interpretation may be found in the significantly greater elevations in blood pressure and skin conductance caused by cold pain than labyrinthine stimulation (4) and the blocking of these autonomic responses by the α- and β-antagonist infusion. Dopamine may act as a mediator in gastric inhibitory reflexes but as no specific dopaminergic blockers were used in this study, the potential role of dopamine as a mediator of gastric stress responses cannot be inferred by our results.

An intriguing aspect of our results is the apparent interaction between adrenergic blockers and naloxone. They are capable of blocking the inhibitory effects of external stimuli on fed antral activity when given separately. Together, they appear to be ineffective, although the sample size for this comparison is small. It is conceivable that the interaction between naloxone and adrenergic blockers could have been due to factors not measured in our study, such as corticosteroid release, as it is known that the potency of intravenous β-endorphin is profoundly enhanced in adrenalectomized mice, an effect that is reversed by dexamethasone (34).

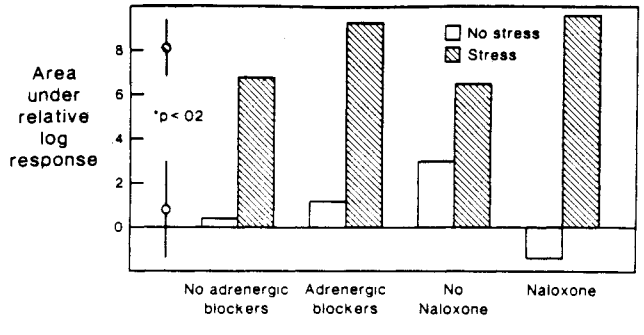

Figure 7. Effect of naloxone and adrenergic blockers on plasma β-endorphin response to stress. Cold pain and labyrinthine stimulation, alone or in combination, increased plasma β-endorphin levels regardless of infusion of blockers.

The upper intestine responded to adrenergic and opiate blockers in an altogether different manner than the stomach. Whereas naloxone effectively blocked stress-induced inhibition of antral activity, it did not prevent the interruption of the intestinal fed pattern, or the appearance of a migrating burst of phase III-like activity during labyrinthine stimulation. Conversely, the combination of α- and β-adrenergic blockers appeared to promote or contribute to the development of bursts of phase III-like activity in response to external stimuli in the intestine after feeding. Thus, in every individual receiving adrenergic blockers (with or without naloxone), subnauseant labyrinthine stimulation induced such complexlike bursts of activity, whereas in previous studies (3,4) only one-third of individuals similarly tested responded in this fashion. Earlier studies (12,13) in which nausea was purposely induced by strong labyrinthine stimulation also showed only a 30% response rate for bursts of duodenal contractile activity. In contrast, in the presence of adrenergic blockers, even cold pain elicited (in 1 subject) a complexlike burst of activity, a distinctly unusual

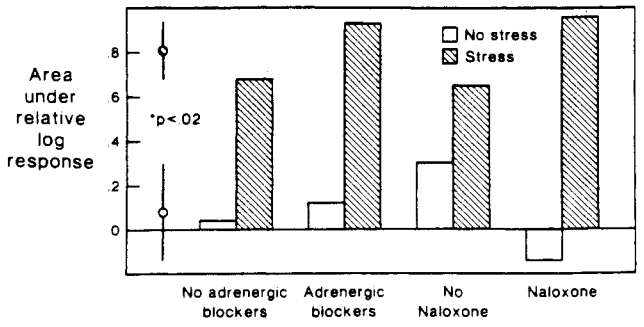

Figure 8. Effect of naloxone and adrenergic blockers on plasma norepinephrine response to stress. Cold pain and labyrinthine stimulation, alone or in combination, increased plasma norepinephrine levels regardless of infusion of blockers.

event that we had never observed with cold pain alone (2). It is possible that the adrenergic blockers as used in the present study interrupted an inhibitory pathway that might have otherwise acted to prevent or reduce the disruptive effects of external stress on the intestinal fed pattern.

Hence, the following comprehensive hypotheses might be put forward to explain our observations: (a) stressful stimuli trigger an inhibitory response upon antral feeding activity which is mediated through both humoral pathways (β-endorphin and norepinephrine release) and neural pathways (vagal noncholinergic, nonadrenergic, or sympathetic, or any combination thereof); (b) stress also causes in some individuals an acute inhibition of fed intestinal motor activity with appearance of a complexlike burst of activity. These intestinal effects are mediated through discharge of opiate peptides at enteric nerve terminals, which are relatively naloxone-resistant (24,31). These intestinal disruptive effects are counteracted by the activity of the sympathetic system through α- or β-receptors, or both.

Our observations may thus have potential pathophysiologic implications with regard to the general gut response to stress. It appears that the fed antral activity is quite sensitive to a variety of stressful stimuli; but, at the same time, the preservation of antral motor response by pretreatment with naloxone suggests that it can be protected by blockade of opiate receptors. Conversely, the intestine can be disrupted only by selective forms of stress, such as labyrinthine stimulation, but the degree of disruption may depend to a large extent on the sympathetic "tone" prevailing at the time. Thus, adrenergic α- and β-receptor blockade renders the small bowel more susceptible to the disruptive effects of stress.

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