Modulation by peripheral opioids of basal and distension-stimulated gastric acid secretion in the rat

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1 The influence of opioids in modulating gastric acid secretory responses has been investigated in the continuously perfused stomach of the anaesthetized rat.

2 Intravenous administration of morphine (0.75–3 mg kg⁻¹) or the peripherally acting enkephalin analogue, BW443C (0.75–3 mg kg⁻¹), substantially augmented acid secretion in basal conditions. These effects were significantly inhibited by the opioid antagonists naloxone (1 mg kg⁻¹) and the peripherally acting N-methylnalorphine (2 mg kg⁻¹). When administered alone, neither opioid antagonist influenced basal acid output.

3 Acid secretory responses to different levels of gastric distension (5–20 cmH₂O) were significantly and dose-dependently reduced in rats pretreated with morphine (3 mg kg⁻¹) or BW443C (1.5 mg kg⁻¹). Previous administration of either naloxone or N-methyl nalorphine reversed the inhibitory effects of opioids on gastric acid secretion stimulated by distension. Likewise, blockade of opioid receptors with naloxone or N-methylnalorphine significantly increased acid output induced by distension.

4 Levels of serum gastrin in control animals were not increased after intragastric distension (20 cmH₂O). Pretreatment with BW443C (1.5 mg kg⁻¹) did not modify the levels of gastrin present during basal or distension stimulated conditions.

5 Pretreatment with morphine or BW443C did not influence the acid responses to i.v. injection of pentagastrin (100 µg kg⁻¹), histamine (5 mg kg⁻¹) or carbachol (4 µg kg⁻¹). Acid secretion induced by i.v. administration of 2-deoxy-D-glucose (150 mg kg⁻¹) was reduced in rats pretreated with morphine but not with BW443C. Gastric secretory responses to insulin (0.3 i.u. kg⁻¹) were not modified by i.v. morphine.

6 These observations support a role for peripherally acting opioids in the regulation of gastric acid secretion during basal and distension-stimulated conditions.

Keywords: Gastric acid; gastric distension; pentagastrin; histamine; carbachol; insulin; 2-deoxy-D-glucose; morphine; peripheral opioids; capsaicin; sensory neurones.

Introduction

Distension of the stomach wall is one of the main stimulants of H⁺ production during the gastric phase of acid secretion (Debas, 1987). Although the processes involved in this secretory response are not fully clarified, two types of mechanisms have been proposed. Gastric distension is generally coupled with changes in the release of peptides, such as gastrin and somatostatin (Walsh, 1988) with profound influences on acid production. Furthermore, recent studies (Esplugues *et al.*, 1990; Raybould & Taché, 1989) have confirmed earlier evidence (Debas, 1987) that distension of the gastric wall activates a nervous reflex of acid secretion, in which both efferent and afferent fibres take part.

Opioids have been shown to modulate a great number of gastrointestinal functions in both physiological and pathophysiological circumstances. In the rat stomach, endogenous opioids play an important role in the control of motility (Kromer, 1988), blood flow (Piqué *et al.*, 1990) and the ability of the mucosa to withstand challenge (Esplugues *et al.*, 1989; Esplugues & Whittle, 1990). However, their role in the control of gastric acid secretion is still controversial (Kromer, 1988). Opioids have been shown to influence nervous functions affecting the gastric mucosa and the release of peptides (Walsh, 1988), including gastrin (Nishi *et al.*, 1987), and it is therefore feasible that they could modulate acid responses to distension. To evaluate this possibility the effects of low doses of morphine, and the peripherally acting enke-

phalin analogue, BW443C (Adcock *et al.*, 1988; Follenfant *et al.*, 1988) have been investigated and characterized by use of opioid antagonists in a model of distension-stimulated acid secretion in the anaesthetized rat. To confirm the specificity and the central or peripheral location of such effects, the actions of opioids have also been analyzed on the production of acid induced by direct stimuli of the oxyntic cell (pentagastrin, histamine and carbachol) or through stimulation of the CNS (insulin or 2-deoxy-D-glucose).

Methods

General

Wistar rats of either sex, weighing 200–250 g, were fasted for 24 h before the experiments but received drinking water *ad libitum*. The procedure used for the measurement of gastric acid secretion was that described by Ghosh & Schild (1958). In brief, animals were anaesthetized with urethane (1.5 g kg⁻¹, i.p.) and the trachea intubated. A soft catheter was inserted into the stomach through an incision in the cervical oesophagus and held in place by a ligature. After a laparotomy, a second polyethylene cannula was inserted into the stomach via an incision in the duodenum, held in place by two ligatures, and led outside the abdominal wall. The jugular vein was cannulated for administration of saline or drugs. At the beginning of the experiment, the stomach was flushed with 50–100 ml of saline to remove any solid content. Once the surgical preparation had been completed, a period of 1 h was allowed for stabilization. Thereafter, the

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stomach lumen was perfused continuously (0.9 ml min^{-1}) via the oesophageal catheter with saline at room temperature. The gastric effluent was collected every 30 min and H^+ output determined by automatic titration (Radiometer Copenhagen, Denmark) of aliquots (4 ml) of the perfusate to pH 7 with 0.01 N NaOH . In some experiments mean systemic arterial blood pressure (BP) was measured from a cannula in a carotid artery connected to a pressure transducer (Hewlett Packard HP-1280).

Once the gastric acid output had remained constant for 60 min it was considered as basal acid secretion. Thereafter, morphine ($0.75\text{--}3 \text{ mg kg}^{-1}$), the peripheral opioid agonist BW443C ($0.75\text{--}3 \text{ mg kg}^{-1}$) or saline were administered i.v. and acid output recorded for a further period of 30 min before stimulating acid secretion. To investigate the effects of opioid antagonists, rats were pretreated (i.v.) 10 min before morphine or BW443C with naloxone (1 mg kg^{-1}) or N-methylnalorphine (2 mg kg^{-1}). Various types of experiments were performed according to the stimulus of gastric acid secretion. In the first series of studies, gastric distension was used to promote acid output. Distension of the stomach was obtained by placing the tip of the antroduodenal cannula 5, 10 or 20 cm above the perfused stomach, where it was maintained for the remainder of the experimental period. To evaluate the possible influence of opioids on gastrin levels, in some animals blood samples were obtained from the carotid artery during the basal period and 120 min after starting the intragastric distension ($20 \text{ cmH}_2\text{O}$), an interval of time at which maximal levels of acid secretion were registered. Gastrin concentrations in serum were measured by radioimmunoassay (CIS biointernational, detection limit 10 pg ml^{-1}) and results expressed as fmol ml^{-1} .

In a second series of experiments gastric acid secretion was stimulated, 30 min after administration of opioids, by a bolus injection (i.v.) of histamine (5 mg kg^{-1}), pentagastrin ($100 \mu\text{g kg}^{-1}$), carbachol ($4 \mu\text{g kg}^{-1}$), insulin (0.3 iu kg^{-1}) or 2-deoxy-D-glucose (2DG, 150 mg kg^{-1}). To analyze the possibility that some differential effects attributed to opioids could be consequence of discrepancies in the time elapsed from the time of their administration till the maximal secretory response had been elicited by the various stimulants of acid production, in one experiment morphine (3 mg kg^{-1} , i.v.) was injected 120 min before pentagastrin ($100 \mu\text{g kg}^{-1}$).

In all cases each preparation was used for a single response only, with treatment being allocated randomly between preparations. Values of acid production during stimulation were obtained in each animal as the difference between the absolute production of acid after stimulation of H^+ and the basal levels of acid secretion in an equivalent period of time and expressed as $\mu\text{Eq H}^+ 100 \text{ g}^{-1} 30/60/180 \text{ min}^{-1}$.

Drugs

Histamine, carbachol, 2-deoxy-D-glucose and naloxone were purchased from Sigma Chemical Co. Morphine hydrochloride (Palex), pentagastrin (Peptavlon, ICI), and insulin (Humulina NPH, Lilly) were obtained as clinically available preparations. BW443C (H-Tyr-D-Arg-Gly-Phe[4- NO_2]-Pro- NH_2) and N-methylnalorphine were a gift from Dr S. Moncada and Dr B.J.R. Whittle (Wellcome Research Laboratories). All drugs were dissolved in saline immediately before use and administered in a volume of 2 ml kg^{-1} .

Statistical analysis

All data are expressed as mean $\pm$ s.e.mean. Comparisons between groups were made by Student's *t* test for unpaired data, and *P* values of 0.05 or less were taken as significant.

Results

Effects of opioids on basal acid secretion

As shown in Table 1, the i.v. administration of saline (2 ml kg^{-1}) did not modify the level of acid production in nonstimulated conditions. However, the basal level of gastric secretion was dose-dependently augmented by 38%, 50% ($P < 0.001$) and 95% ($P < 0.01$) following i.v. administration of 0.75, 1.5 and 3 mg kg^{-1} of morphine, respectively. Administration of the peripherally acting opioid agonist, BW443C likewise dose-dependently enhanced the output of acid in basal conditions by 147% ($P < 0.01$), 255% ($P < 0.001$) and 203% ($P < 0.001$) after 0.75, 1.5 and 3 mg kg^{-1} , i.v., respectively. Pretreatment (i.v.) with either the opioid antagonist naloxone (1 mg kg^{-1}), which acts on both central and peripheral opioid receptors, or N-methylnalorphine (2 mg kg^{-1}), a peripherally acting quaternary opioid receptor antagonist (Smith *et al.*, 1982), prevented the increased production of acid induced by both morphine (3 mg kg^{-1}) and BW443C (3 mg kg^{-1}). However if administered alone neither naloxone nor N-methylnalorphine produced any significant change in the rate of basal acid production.

Inhibition by opioids of acid responses to gastric distension

Distension of the rat stomach *in vivo* produced a progressive increase in acid secretion, which peaked 120–150 min after application of an intragastric pressure of $20 \text{ cmH}_2\text{O}$ with a H^+ production of $8.8 \pm 1.5 \mu\text{Eq } 100 \text{ g}^{-1} 30 \text{ min}^{-1}$. The total

Table 1 Effects of the i.v. administration of opioid agonists (morphine and BW443C) and antagonists (naloxone and N-methylnalorphine) on resting levels of acid secretion ($\mu\text{Eq H}^+ 100 \text{ g}^{-1} 30 \text{ min}^{-1}$) in the perfused stomach of the anaesthetized rat

Treatment (mg kg^{-1})	n	Resting	Treated	Δ
Saline	74	3.0 ± 0.8	2.5 ± 0.3	0.1 ± 0.2
Morphine				
(0.75)	5	2.4 ± 0.8	3.3 ± 1.0	0.9 ± 0.5
(1.5)	7	4.6 ± 0.9	6.9 ± 1.1	$2.6 \pm 1.0^{***}$
(3)	45	1.9 ± 0.4	3.7 ± 0.6	$2.0 \pm 0.6^{**}$
(3) + Naloxone (1)	5	1.6 ± 0.7	1.3 ± 0.5	0.3 ± 0.8
(3) + N-Me Nalorph (2)	5	0.1 ± 0.1	0.1 ± 0.1	0.0 ± 0.0
BW443C				
(0.75)	4	1.7 ± 0.2	4.2 ± 0.9	$2.5 \pm 0.8^{**}$
(1.5)	32	1.1 ± 0.4	3.9 ± 0.8	$2.8 \pm 0.7^{***}$
(3)	3	3.3 ± 1.6	10 ± 1.7	$6.8 \pm 3.3^{***}$
(3) + Naloxone (1)	6	3.0 ± 1.5	3.3 ± 1.4	0.3 ± 0.3
(3) + N-Me Nalorph (2)	3	0.1 ± 0.1	0.8 ± 0.5	0.8 ± 0.5
Naloxone (1)	3	2.7 ± 0.5	2.8 ± 0.3	0.1 ± 0.1
N-Me Nalorph (2)	3	3.0 ± 0.5	3.3 ± 0.6	0.3 ± 0.5

Values are means $\pm$ s.e.; n, number of experiments. Abbreviations: N-Me Nalorph = N-methylnalorphine. Statistical difference from the saline control group is shown by $^{**}P < 0.01$ and $^{***}P < 0.001$.

Figure 1 Inhibition by morphine and the peripheral opioid agonist BW443C (0.75–3 mg kg⁻¹, i.v.) of acid secretion induced by gastric distension with 20 cmH₂O. Results, expressed as the difference between basal and stimulated H⁺ output, are means (columns) ± s.e. mean (vertical bar), and the level of statistical difference from the control group is shown by **P*<0.05, ***P*<0.01 and ****P*<0.001. Numbers inside the columns represent the animals used per experimental group.

acid output during these experiments was $50.3 \pm 8.3 \mu\text{Eq H}^+ 100 \text{ g}^{-1} 180 \text{ min}^{-1}$ ($n = 17$). Intravenous pretreatment (30 min) with 0.75, 1.5 and 3 mg kg⁻¹ of morphine (Figure 1) dose-dependently decreases the acid response to 20 cmH₂O distension by $52 \pm 21\%$ ($n = 5$), $65 \pm 10\%$ ($P < 0.05$, $n = 7$) and $78 \pm 8\%$ ($P < 0.01$, $n = 9$) respectively. Likewise, H⁺ output caused by gastric distension (20 cmH₂O) was reduced by $18 \pm 33\%$ ($n = 4$), $87 \pm 3\%$ ($P < 0.001$, $n = 12$) and $96 \pm 4\%$ ($P < 0.05$, $n = 3$) following the i.v. injection of BW443C at the doses of 0.75, 1.5 and 3 mg kg⁻¹ respectively. As shown in Figure 2, pretreatment with morphine (3 mg kg⁻¹) or BW443C (1.5 mg kg⁻¹) significantly ($P < 0.05$) decreased gastric acid responses induced by intragastric distension with 5 cmH₂O by $84 \pm 15\%$ ($n = 6$) and $85 \pm 10\%$ ($n = 7$) and those produced by an intragastric pressure of 10 cmH₂O by $65 \pm 13\%$ ($n = 7$) and $56 \pm 13\%$ ($n = 9$) respectively. In control animals, basal plasma levels of gastrin ($22.7 \pm 2.4 \text{ fmol ml}^{-1}$, $n = 16$) were not significantly modified after 120 min of intragastric distension with 20 cmH₂O

Figure 2 Inhibition by morphine (3 mg kg⁻¹, i.v., hatched column) and the peripheral opioid agonist BW443C (1.5 mg kg⁻¹, i.v., stippled column) of acid secretion induced by various levels of gastric distension (5, 10 and 20 cmH₂O). Results, expressed as the difference between basal and stimulated H⁺ output, are means (columns) ± s.e. mean (vertical bars), and the level of statistical difference from the corresponding control group is shown by **P*<0.05, ***P*<0.01 and ****P*<0.001. Numbers inside the columns represent the animals used per experimental group.

($24 \pm 3.4 \text{ fmol ml}^{-1}$). Likewise, they were not significantly different from those of rats undergoing similar experimental conditions and pretreated with 1.5 mg kg⁻¹ of BW443C, respectively 20.1 ± 0.9 and $19.8 \pm 0.7 \text{ fmol ml}^{-1}$ ($n = 8$). Administration of morphine (3 mg kg⁻¹) or BW443C (1.5 mg kg⁻¹ each) did not significantly modify BP ($n = 4$ in both) which remained between 100–120 mmHg during the duration of the experiments.

In further experiments shown in Figure 3, the inhibitory effects of morphine (3 mg kg⁻¹) and BW443C (1.5 mg kg⁻¹) on the acid response to 20 cmH₂O distension were prevented by 5 min i.v. pretreatment with the opioid receptor antagonist naloxone (1 mg kg⁻¹) or the peripherally acting opioid antagonist N-methylnalorphine (2 mg kg⁻¹). Furthermore, administration of naloxone (1 mg kg⁻¹, $n = 7$) or N-methylnalorphine (2 mg kg⁻¹, $n = 6$) alone significantly increased the acid output stimulated by 20 cmH₂O gastric distension by $73 \pm 18\%$ and $64 \pm 15\%$ respectively.

Effects of opioids on acid secretion stimulated by other secretagogues

The i.v. injection of histamine (5 mg kg⁻¹), pentagastrin (100 μg kg⁻¹) or carbachol (4 μg kg⁻¹) induced rapid increases in acid output by the stomach which peaked 40 min later. Pretreatment with morphine (3 mg kg⁻¹) 30 min before did not modify the secretory responses elicited by these three agents (Figure 4). The values of total acid output in control and morphine-treated rats were, respectively, 48.7 ± 7.1 ($n = 7$) and 46.8 ± 5.5 ($n = 3$) μEq H⁺ 100 g⁻¹ 60 min⁻¹ for histamine, 22.8 ± 2.7 ($n = 7$) and 18.3 ± 3.2 ($n = 3$) μEq H⁺ 100 g⁻¹ 60 min⁻¹ for pentagastrin, or 72.9 ± 6.7 ($n = 11$) and 64.1 ± 10.1 ($n = 4$) μEq H⁺ 100 g⁻¹ 60 min⁻¹ for carbachol. The administration of morphine (3 mg kg⁻¹) 120 min before pentagastrin (100 μg kg⁻¹, i.v.) induced a rapid and sustained increase in basal acid output, with values comparable to those of Table 1, without modifying the secretory response elicited by pentagastrin ($20.7 \pm 2.8 \mu\text{Eq H}^+ 100 \text{ g}^{-1} 60 \text{ min}^{-1}$, $n = 4$) which was similar to that of control animals ($17 \pm 3.5 \mu\text{Eq H}^+ 100 \text{ g}^{-1} 60 \text{ min}^{-1}$, $n = 4$).

Administration (i.v.) of 2-deoxy-D-glucose ($n = 8$) or insulin ($n = 8$) induced a progressive increase in acid secretion, which peaked 140 min later with a H⁺ production of

Figure 3 Effects of pretreatment with the opioid antagonists naloxone (1 mg kg⁻¹, i.v.) and the peripherally acting antagonist N-methylnalorphine (NMN, 2 mg kg⁻¹, i.v.) on the inhibition by morphine (3 mg kg⁻¹, i.v.) and BW443C (1.5 mg kg⁻¹, i.v.) of acid secretion induced by gastric distension (20 cmH₂O). Results, expressed as the difference between basal and stimulated H⁺ output, are means (columns) ± s.e. mean (vertical bars), and the level of statistical difference from the group treated with morphine or BW443C is shown by **P*<0.05, ***P*<0.01, ****P*<0.001. The dotted line represents the level of acid output in control rats. Numbers inside the columns represent the animals used per experimental group.

Figure 4 Acid production induced by a i.v. bolus injection of histamine (5 mg kg^{-1}), pentagastrin ($100 \mu\text{g kg}^{-1}$) or carbachol ($4 \mu\text{g kg}^{-1}$) in the continuously perfused stomach of rats control (open columns) and pretreated with morphine (3 mg kg^{-1} , i.v., hatched columns). Results, expressed as the difference between basal and stimulated H^+ output, are means (columns) $\pm$ s.e. (vertical bars). Numbers inside the columns represent animals used per experimental group.

23 ± 8 and $36 \pm 9 \mu\text{Eq } 100 \text{ g}^{-1} 30 \text{ min}^{-1}$ and a total acid output 110 ± 35 and $137 \pm 31 \mu\text{Eq } 100 \text{ g}^{-1} 180 \text{ min}^{-1}$, respectively ($n = 8$ in both) (Figure 5). Acid responses to 2-deoxy-D-glucose were significantly ($P < 0.05$) reduced by $85.6 \pm 8.2\%$ in animals pretreated with morphine (3 mg kg^{-1} , $n = 6$) but not after administration of BW443C (1.5 mg kg^{-1}). Pretreatment with morphine (3 mg kg^{-1}) did not modify acid responses to insulin (0.3 iu kg^{-1}).

Discussion

Our results have shown that opioids can modulate the acid secretory responses stimulated by gastric distension in the rat. Thus, i.v. administration of morphine induced a significant and dose-dependent reduction in acid production following different levels of gastric distension. This effect appears to be exerted at peripherally-located opioid receptors because BW443C, a polar enkephalin analogue which does not cross the blood brain barrier (Adcock *et al.*, 1988; Follenfant *et al.*, 1988) likewise substantially inhibited acid responses to distension of the stomach. An inhibitory, non-specific action by opioids on acid secretion has been ruled out, since response to stimulation of the oxyntic cell with pentagastrin, histamine or the synthetic muscarinic agonist, carbachol, were not influenced by either morphine or BW443C.

Intravenous administration of the opiate antagonist, naloxone, abolished the actions of morphine and BW443C on gastric secretory responses to distension, thus implying an interaction with classical opiate receptors. The peripherally acting quaternary antagonist, N-methylnalorphine (Smith *et al.*, 1982) likewise reversed the inhibitory effects of both opioid agonists on gastric acid secretion induced by distension, giving further support to a peripheral site of action of opioids in this model. The finding that naloxone and N-methylnalorphine by themselves significantly increased acid responses to distension points to a physiological regulatory role for peripherally-acting endogenous opioids in responses to this stimulant of acid secretion. Although the opioid receptors involved have not been fully characterized, the low doses employed in the present study and the specificity of morphine, BW443C, naloxone and N-methyl nalorphine implicate μ receptors in this mechanism.

Insulin administration decreases the level of glucose in

blood which, once identified by the brain, leads to a vagally-mediated increase in acid output. The actions of 2DG on gastric acid production have been classically compared with those of insulin, since this analogue of glucose cannot be metabolized and causes the release of endogenous insulin by the pancreas (Debas, 1987). However, the effects of 2DG are more complex and a direct action on various hypothalamic, diencephalic and medullary sites in the CNS, as well as hepatic sites in the periphery have also been described (Debas, 1987). In the rat, Watanabe *et al.* (1987) and Ho *et al.* (1987) have previously shown that intravenous infusion of morphine decreased acid production stimulated by 2DG, but not that evoked by electrical stimulation of the vagus. Our results with a bolus injection of morphine confirm its inhibitory effect on secretory responses induced by this glucose analogue. However, acid responses by insulin were not influenced suggesting that effects of 2DG on gastric acid output are the consequence of actions other than insulin release. Furthermore, the fact that BW443C did not influence responses to 2DG, at doses that abolished responses to gastric distension, implies that both activation of acid output by 2DG and the inhibitory effects of morphine on this model are CNS-mediated events.

When other procedures have been used to stimulate gastric secretion in the rat, administration of morphine and related compounds have reproduced the actions shown here, i.e. either lacked any effect or decreased acid responses. Thus, in the rat isolated stomach, submaximal acid stimulation with pentagastrin, histamine, bethanechol or isoprenaline was not modified by high concentrations of morphine (Canfield & Spencer, 1981). Furthermore, i.v. or i.c.v. pretreatment with morphine *in vivo* reduced responses to pyloric occlusion (Glavin *et al.*, 1986; Ho *et al.*, 1986; Fox & Burks, 1988), TRH administration (Morley *et al.*, 1981) or electrical vagal stimulation (Rozé *et al.*, 1982). In contrast, in the present study administration of morphine in basal, non-stimulated conditions brought about a significant increase in acid secretion which was reversed by concomitant administration of naloxone. Such stimulatory effect has been previously described in the dog (Kromer, 1988), and in our experiments it seems the result of activation of opioid receptors located in

Figure 5 Acid production induced by a i.v. bolus injection of 2-deoxy-D-glucose (2-DG 150 mg kg^{-1}) and insulin (0.3 iu kg^{-1}) in the continuously perfused stomach of rats control and pretreated with morphine (3 mg kg^{-1} , i.v.) or the peripheral opioid agonist BW443C (1.5 mg kg^{-1} , i.v.). Results, expressed as the difference between basal and stimulated H^+ output, are means (columns) $\pm$ s.e. mean (vertical bars), and the level of statistical difference from the respective control group is shown by $*P < 0.05$. Numbers inside the columns represent the animals used per experimental group.

the periphery since administration of BW443C enhanced basal acid secretion, whereas N-methylnalorphine reversed the effects of both morphine and BW443C. The failure of opioid antagonist naloxone by itself to affect the level of the basal acid secretion suggests that endogenous opioids do not modulate this process. However, the present observations also imply that the release of high levels of enkephalins, possibly during different stress situations, may lead to increased levels of resting acid secretion in the fasting stomach, a circumstance that could partially account for changes in the susceptibility of the gastric mucosa to damage appearing in such conditions.

The mechanisms responsible for the changes in the rate of acid production brought about by the administration of opioids have not been fully evaluated in the present study and only an hypothesis can be suggested. In the anaesthetized rat, systemic ablation of sensory nerves after pretreatment with the neurotoxin capsaicin (Holzer, 1988) induces effects similar to those of morphine on stimulated acid secretion. Thus responses to gastric distension (Raybould & Taché, 1989; Esplagues *et al.*, 1990), 2DG (Evangelista *et al.*, 1989) and TRH (Raybould *et al.*, 1990) were reduced, whereas those to insulin, pentagastrin, histamine, carbachol (Esplagues *et al.*, 1990) or vagal electrical stimulation (Evangelista *et al.*, 1990) were not influenced by this treatment. The comparability of the effects of morphine to those of capsaicin pretreatment suggest a common mechanism of action. Opioid receptors have been located on sensory fibres, both in the periphery and the CNS, where they modulate the release of various neuropeptides including substance P and calcitonin gene-related peptide (Russell *et al.*, 1987; Holzer, 1988). In the stomach the inhibitory effects of opioids on this population of neurones has been suggested as one of the factors implicated in the regulation of blood flow and mucosal defense (Esplagues & Whittle, 1990; Pique

et al., 1990; Holzer *et al.*, 1991). Thus there is good circumstantial evidence to suggest that opioids may inhibit distension- or 2DG-stimulated acid secretion by actions on sensory neurones. This explanation would not cover their stimulatory effect on basal output, since this is not affected by pretreatment with capsaicin (Esplagues *et al.*, 1990), and implies the existence of other mechanisms. Opioids influence the release in the gastric tissue of neurohormonal mediators of acid secretion such as gastrin (Nishi *et al.*, 1987). However, the finding that BW443C did not modify gastrin levels rules out the possibility that this action could be responsible for the changes induced by opioids on basal acid secretion. Furthermore, gastrin levels were not modified after 120 min of gastric distension confirming the previous suggestion (Debas, 1987) that this peptide plays a limited role in the secretory response induced by this stimulant of acid production. The effect of opioids on the release of other modulators of acid secretion like somatostatin (Chiba *et al.*, 1980), acetylcholine (Kromer, 1988) or histamine (Garrison, 1990) has also been shown and new studies will be necessary for analyzing the possible involvement of such actions in this model of acid secretion. In conclusion, administration of opioids seems to induce a complex picture of superimposed stimulatory and inhibitory actions, affecting both the CNS and the periphery, the overall outcome of which would be manifested as increases or decreases in acid production depending on the stimuli of acid secretion and, possibly, the different mediators involved.

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