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Exogenous and endogenous cholecystokinin protects gastric mucosa against the damage caused by ethanol in rats

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Abstract

Cholecystokinin (CCK) shows a potent influence on gastric secretion and motility but its role in gastric mucosal integrity has been little examined. In this study we found that exogenous CCK octapeptide protected gastric mucosa against ethanol-induced gastric injury but was ineffective against aspirin-induced damage. The protective effects of CCK were dose-dependent and almost completely reversed by pretreatment with the specific CCK_A receptor antagonist, loxiglumide, while the CCK_B receptor antagonist, L-365,260, was not effective. The CCK-induced protection against ethanol injury was accompanied by a significant increase in gastric blood flow. The inhibition of nitric oxide (NO) synthase by N^G-nitro-L-arginine methyl ester attenuated the gastroprotection and gastric hyperemia induced by CCK while the concurrent treatment with L-arginine, but not D-arginine restored the protective activity of CCK and the accompanying increase in gastric blood flow. Endogenous CCK released by intraduodenal instillation of oleate prevented the formation of acute gastric lesions induced by both ethanol and aspirin and the protective effects were abolished by pretreatment with loxiglumide. We conclude that CCK exerts protective activity against ethanol-induced damage and that this effect is mediated through specific CCK_A receptors and hyperemia involving NO.

Keywords: CCK (cholecystokinin); CCK receptor; Cytoprotection; Stomach; Gastric hyperemia

1. Introduction

Cholecystokinin (CCK) has been reported recently to inhibit gastrin-stimulated gastric acid secretion in rats (Lloyd et al., 1992), dogs (Konturek et al., 1992a) and humans (Konturek et al., 1993) and to protect the rat gastric mucosa against the damage caused by topical application of 25% ethanol (Evangelista and Maggi, 1991). These inhibitory and protective effects were reversed by pretreatment with CCK_A but not CCK_B receptor antagonists. The protective effects afforded by CCK were not observed in rats after vagotomy and after capsaicin-deactivation of afferent nerves, suggesting that CCK_A receptors are present in vagal capsaicin-sensitive fibers.

This study was designed to assess the protective effects of CCK against ethanol- and aspirin-induced damage and to determine whether CCK released endogenously is also involved in the maintenance of gastric mucosal protection against the damage caused by topical irritants.

2. Materials and methods

Male Wistar rats, weighing 200–250 g and fasted (except for water) for 24 h, were used in these studies.

Acute gastric lesions were induced by an intragastric (i.g.) application of 100% ethanol or acidified aspirin as described previously (Konturek et al., 1983). Briefly, 100% ethanol (1.5 ml) or acidified aspirin (100 mg/kg in 1.5 ml of 200 mM HCl) was administered i.g. to 24-h fasted rats by means of a metal orogastric tube. After 60 min, the animals with intact stomachs (receiving only saline, 1.5 ml i.g.) and those treated with ethanol or aspirin were anesthetized with ether, the abdomen was opened and the stomach was exposed to measure gastric blood flow using laser Doppler flowmetry (Laserflo, BPM 403D, Vasamedics Inc., St. Paul, MN, USA) as described before (Konturek et al., 1992b). Then the stomach was washed with 1 ml of saline and

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finally it was opened to measure the area of necrotic lesions in oxyntic mucosa by using computerized planimetry (Morphomat, Carl Zeiss, FRG) under blinded conditions.

Three series (A, B and C) of experiments were carried out. Series A determined the effects of subcutaneous (s.c.) injection of various doses of CCK (Peninsula Laboratories, Belmont, CA) or intraduodenal (i.d.) instillation of oleate (to release endogenous CCK) without or with the CCK receptor antagonist. Loxiglumide (DL-4-benzamido-*N*,*N*-dipropyl-glutaramic acid) (gift of Dr L. Rovati, Rotta Laboratories, Milano, Italy) was used as CCK_A receptor antagonist and L-365,260 (*N*-2,3-dihydro-1-methyl-2-oxo-5-phenyl-1*H*-1,4-benzodiazepin-3-yl)-*N'*-(3-methylphenyl)urea) (Merck, Sharp and Dohme, West Point, PA) was used as CCK_A receptor antagonist, and their effects on the area of gastric mucosal lesions induced by absolute ethanol or acidified aspirin and on gastric blood flow were determined.

Series B investigated the involvement of endogenous nitric oxide (NO) in the protective effects of CCK using N^G-nitro-L-arginine methyl ester (Clinalfa, Laufelfingen, Germany) as a specific inhibitor of NO synthase, L-arginine as a substrate for this enzyme (to reverse the enzyme inhibition caused by *N*-nitro-L-arginine methyl ester) or, for comparison, D-arginine (which is not a substrate for NO synthase). Series C determined studies the effect of exogenous CCK or CCK released by intraduodenal fat without or with its receptor antagonists on basal gastric acid secretion.

The following groups of rats in series A were used: (I) vehicle (1 ml of saline s.c.) given 30 min before 100% ethanol or aspirin; (II) CCK (0.06–10 nmol/kg s.c.) followed 30 min later by 100% ethanol or aspirin; (III) CCK (10 nmol/kg i.g.) followed 30 min later by 100% ethanol or aspirin; (IV) loxiglumide or L-365,260 (25 μmol/kg i.p.) followed 60 min later by 100% ethanol or aspirin; (V) loxiglumide or L-365,260 followed 30 min later by CCK (5 nmol/kg s.c.) and then 30 min later by 100% ethanol or aspirin; (VI) duodenal vehicle (saline adjusted to pH 7.0) followed 30 min later by 100% ethanol or aspirin; (VII) duodenal oleate followed 30 min later by duodenal vehicle and then 30 min later by 100% ethanol or aspirin; (VIII) loxiglumide or L-365,260 (25 μmol/kg i.p.) followed 30 min later by vehicle and then 30 min later by 100% ethanol or aspirin and, finally, (IX) loxiglumide or L-365,260 (25 μmol/kg i.p.) followed 30 min later by duodenal oleate and then 30 min later by 100% ethanol or aspirin.

In experiments to determine the effect of endogenous CCK released by i.d. fat, the rats were lightly anesthetized with ether and the abdomen was opened by a midline incision. The proximal duodenum was exposed and the pylorus was temporarily occluded by clamping to prevent any reflux of duodenal content to the stomach. Then 1 ml of 100 mM sodium oleate (pH 7.0 and osmolarity adjusted to about 300 mOsm/1) or vehicle (saline adjusted to pH 7.0) was instilled i.d. through the needle followed 30 min later by 100% ethanol or aspirin. Another group of rats was treated similarly except that loxiglumide (25 μmol/kg) or L-365,260 (25 μmol/kg) was injected intraperitoneally (i.p.) 30 min prior to i.d. administration of oleate or vehicle. This particular dose (25 μmol/kg) of loxiglumide or L-365,260 was used because in our earlier experiments this dose caused a maximal reduction in CCK- or pentagastrin-induced gastroprotection against ethanol damage.

In series B, the role of endogenous NO in the gastroprotection induced by CCK was assessed in rats by using pretreatment with N^G-nitro-L-arginine methyl ester, a specific inhibitor of NO synthase, injected intravenously (i.v.) without or with D-arginine or L-arginine (Sigma Chemical Co., St. Louis, MO, USA), the substrate of NO synthase, as described before (Konturek et al., 1992b). The following groups were used: (I) CCK (5 nmol/kg s.c.) followed 30 min later by 100% ethanol; (II) N^G-nitro-L-arginine methyl ester (5 mg/kg i.v.) followed 15 min later by CCK (5 nmol/kg s.c.) and then 30 min later by 100% ethanol; (III) L-arginine or D-arginine (300 mg/kg i.v.) followed 15 min later by N^G-nitro-L-arginine methyl ester (5 mg/kg i.v.), then 15 min later by CCK (5 nmol/kg s.c.) and finally 30 min later by 100% ethanol; (IV) L-arginine or D-arginine (300 mg/kg i.v.) followed 15 min later by CCK (5 nmol/kg s.c.) and finally 30 min later by 100% ethanol. N^G-nitro-L-arginine methyl ester, L-arginine or D-arginine was injected into the tail vein.

In series C, 12 rats were equipped with gastric fistulas about 1 month earlier, as described previously (Konturek et al., 1983). Six of these animals had a polyethylene cannula (PE_{50}) inserted into the proximal part of the duodenum and brought outside in the neck area. The cannula was fixed to the skin by a snap fastener and was used for the i.d. instillation of oleate during collection of gastric juice. The animals had free access to water 24 h before the experiment and they were placed in individual Bollman-type cages to maintain the minimum restraint necessary. The gastric fistula was opened and the stomach was rinsed gently with about 5 ml of tap water at 37 C. The basal gastric acid secretion was collected for 60 min and then CCK was injected s.c. in various doses (0.06–20 nmol/kg) either alone or in combination with loxiglumide or L-365,260 injected intraperitoneally (i.p.) in a standard dose similar to that in protection studies (25 μmol/kg i.p.). In tests with loxiglumide or L-365,260, CCK (5 nmol/kg) was injected s.c. 60 min after the i.p. administration of these CCK receptor antagonists. In tests with fat, 1 ml of 100 mM oleate was instilled i.d. 60 min

after the assessment of basal gastric secretion. In tests with CCK receptor antagonists, loxiglumide or L-365,260 was administered i.p. in a standard dose 60 min before duodenal oleate. The collection of gastric juice was continued after the administration of s.c. CCK or i.d. oleate for the final 60 min. The results are expressed in terms of μmoles of acid per 30 min.

Results are presented as means ± S.E.M. Statistical evaluation was made by standard ANOVA and, when appropriate, by the unpaired Student's *t*-test. Repeated measured ANOVA was used to analyze the results related to basal gastric acid outputs. A value of $P < 0.05$ was considered significant.

3. Results

3.1. Effects of CCK and duodenal oleate on ethanol- and aspirin-induced mucosal damage and blood flow

CCK injected s.c. in various doses reduced dose dependently the formation of acute gastric lesions induced by 100% ethanol (Fig. 1). The threshold reduction occurred at a dose of 1.2 nmol/kg s.c. of CCK and the dose reducing the area of gastric lesions by about 50% (ID_{50}) averaged 3.0 nmol/kg of CCK. CCK at 10 nmol/kg s.c. caused about 90% reduction of the ethanol-induced area of gastric lesions but the same dose applied i.g. did not affect significantly the ethanol-induced damage.

Gastric blood flow in rats treated with vehicle averaged 62 ± 10 ml/min · 100 g and after the administration of 100% ethanol it was reduced by about 65%. With gradually increasing doses of CCK administered before 100% ethanol, the gastric blood flow showed a dose-dependent rise, starting with a dose of 1.2 nmol/kg of CCK and reaching about 50% at a dose of about 2.0 nmol/kg of CCK (Fig. 1).

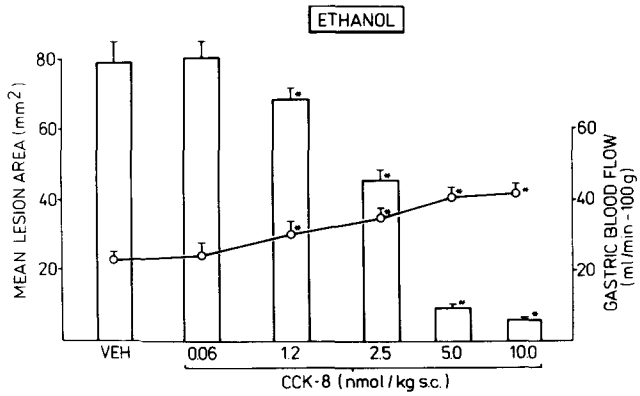

Fig. 1. The area of ethanol-induced gastric lesions and gastric blood flow in rats treated with vehicle (saline) or with various doses of CCK-8 (0.06–10 nmol/kg s.c.). Means ± S.E.M. of eight tests on eight rats. Columns represent the mean area of gastric lesions and plots show the values of gastric blood flow. An asterisk indicates a significant ($P < 0.05$) change as compared to the vehicle control values.

Pretreatment with loxiglumide (25 μmol/kg i.p.) did not influence the area of gastric mucosa caused by 100% ethanol but almost completely reversed the CCK-induced gastric protection and accompanying increase in gastric blood flow in rats given 100% ethanol. Pretreatment with L-365,260 at a dose of 25 μmol/kg did not affect significantly the area of gastric lesions induced by 100% ethanol without or with CCK. These results have been omitted for the sake of clarity.

Sodium oleate instilled into the duodenum caused a marked reduction in the area of gastric lesions compared to that attained with CCK at a standard dose of 5 nmol/kg s.c. Pretreatment with loxiglumide (25 μmol/kg) completely abolished the protective effect of duodenal oleate and attenuated significantly the gastric blood flow (Fig. 2). Pretreatment with L-365,260 failed to affect the area of gastric lesions and the changes in

Table 1
Area of acute gastric lesions (mm) and gastric blood flow (ml/min · 100 g) induced by acidified aspirin in rats without or with pretreatment with CCK (5 nmol/kg s.c.) or duodenal oleate (1 ml of 100 mM oleate) without or with loxiglumide (25 μmol/kg i.p.) or L-365,260 (25 μmol/kg i.p.)

	Lesion area (mm^2)	Gastric blood flow (ml/min · 100 g)
Vehicle (saline)	0	62 ± 10
Vehicle + aspirin	41 ± 7	27 ± 2 [a]
CCK + aspirin	51 ± 9	31 ± 3 [a]
Loxiglumide + aspirin	50 ± 10	30 ± 4 [a]
Loxiglumide + CCK + aspirin	54 ± 12	32 ± 5 [a]
Duodenal oleate + aspirin	18 ± 4 [a]	39 ± 5 [a,b]
Lox + Duo oleate + aspirin	42 ± 5	24 ± 4 [a]
L-365,260 + Duo oleate + Asp.	30 ± 4 [a]	38 ± 4 [a,b]

Means ± S.E.M. of eight to ten tests on eight to ten rats.
[a] Values of lesion area; significant change as compared to the value obtained with vehicle (saline) + acidified aspirin. [a] Values of gastric blood flow: significant decrease below the values in rats treated with vehicle (saline) (without aspirin). [b] Significant increase above the value obtained in rats treated with vehicle (saline) + acidified aspirin.

blood flow induced by ethanol in rats without or with pretreatment with CCK. These results have not been included.

Unlike ethanol injury, aspirin-induced mucosal damage is acid-dependent, and i.g. administration of acidified aspirin produced gastric lesions of a mean area smaller (41 ± 7 mm^2) than that of lesions induced by ethanol. The gastric blood flow in aspirin-damaged stomach was reduced to a similar extent as in ethanol injury (Table 1). Pretreatment with CCK tended to increase the area of gastric lesions but this was not significant and was not altered by the administration of loxiglumide given i.p. prior to CCK. In contrast, duodenal instillation of oleate resulted in a marked reduction in the area of aspirin-induced damage and in a significant increase in gastric blood flow. Pretreatment with loxiglumide almost completely reversed the decrease in the lesion area and the rise in gastric blood flow caused by duodenal oleate. Pretreatment with L-365,260 reduced significantly the aspirin-induced gastric damage and enhanced gastric blood flow over that observed in aspirin-treated rats. When combined with duodenal oleate, L-365,260 significantly attenuated the reduction produced by duodenal oleate and the area of lesions caused by aspirin without causing a significant change in gastric blood flow as compared to that recorded after duodenal oleate in aspirin-treated rats (Table 1).

3.2. Effects of CCK and duodenal oleate on gastric acid secretion

The effects of various doses of s.c. CCK on gastric acid secretion from the gastric fistula of conscious rats

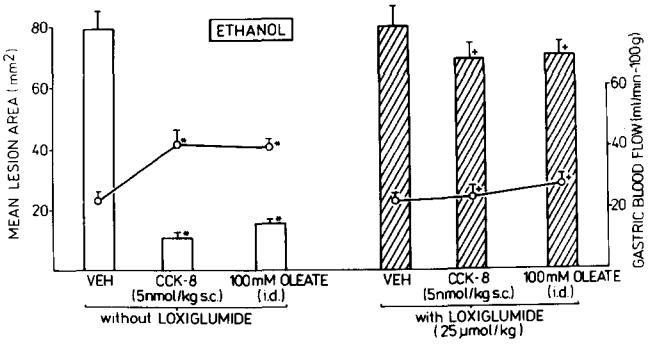

Fig. 2. The area (means ± S.E.M. of eight rats) of acute gastric lesions induced by 100% ethanol and gastric blood flow in rats pretreated with vehicle (saline), CCK (5 nmol/kg s.c.) or oleate (1 ml of 100 mM oleate i.d.) in tests without and with pretreatment with loxiglumide (25 μmol/kg i.p.). Columns represent the mean area of gastric lesions and plots show the values of gastric blood flow. An asterisk indicates a significant change as compared to the value obtained in the test with vehicle. A cross indicates a significant change as compared to the values obtained in rats without administration of loxiglumide.

Table 2
Gastric acid secretion in conscious rats injected s.c. with various doses of CCK or with i.d. oleate alone or combined with loxiglumide or L-365,260 administered 60 min earlier

	Acid output (μmol/30 min)
Vehicle (control)	112 ± 5
CCK (nmol/kg s.c.)	
0.06	115 ± 9
1.2	124 ± 5
2.5	139 ± 4 [a]
5.0	143 ± 7 [a]
10.0	196 ± 5 [a]
20.0	180 ± 6 [a]
Loxiglumide (25 μmol/kg i.p.)	115 ± 8
L-365,260 (25 μmol/kg i.p.)	43 ± 2 [b]
Loxiglumide + CCK (5 nmol/kg s.c.)	167 ± 6 [b]
L-365,260 + CCK (5 nmol/kg s.c.)	94 ± 11
Duodenal oleate (1 ml of 100 mM)	52 ± 7 [a]
L-365,260 + duodenal oleate	57 ± 8 [a]
Loxiglumide + duodenal oleate	98 ± 9 [b]

Means ± S.E.M. of 6 tests on 6 rats.
[a] Significant change as compared to the vehicle control values.
[b] Significant change as compared to the value obtained in tests without pretreatment with loxiglumide or L-365,260.

are shown on Table 2. CCK without pretreatment with loxiglumide or L-365,260 caused a small but significant increase in basal gastric acid output, reaching a peak (about 75% above basal value) at a dose of 10 nmol/kg. Administration of loxiglumide alone failed to affect gastric secretion but when combined with CCK at a dose of 5 nmol/kg s.c. it resulted in a further increase in acid output. Duodenal instillation of oleate resulted in a significant decrease in acid secretion and this decrease was almost completely abolished by the pretreatment with i.p. loxiglumide. L-365,260 given i.p. reduced significantly basal gastric acid secretion by about 60% but failed to affect the acid secretion induced by CCK or the fall in this secretion caused by i.d. administration of oleate.

3.3. The role of endogenous NO in CCK protection

N^G-Nitro-L-arginine methyl ester (5 mg/kg i.v.) administered 15 min before 100% ethanol caused a small (by about 16%) but significant increase in the area of ethanol-induced gastric damage but failed to cause any significant change in the gastric blood flow reduced by ethanol (Fig. 3). When N^G-nitro-L-arginine was combined with CCK given s.c. in a standard dose (5 nmol/kg), a several fold increase in the area of ethanol-induced gastric injury and a marked fall in the gastric blood flow were observed as compared to those found in rats given CCK alone. Pretreatment with L-arginine, but not D-arginine (300 mg/kg i.v.), almost completely restored the protective and hyperemic effects of CCK. Neither L-arginine nor D-arginine injected i.v. affected ethanol-induced gastric damage or

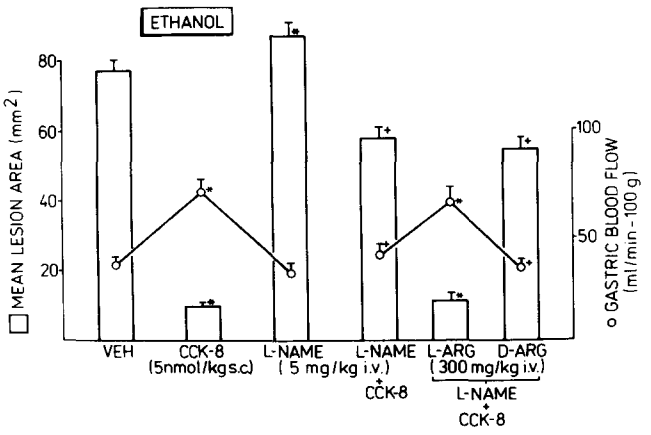

Fig. 3. The area (means ± S.E.M. of eight rats) of acute gastric lesions induced by 100% ethanol in rats pretreated with vehicle (saline) or CCK without or with administration of N^G-nitro-L-arginine methyl ester (L-NAME), a specific inhibitor of NO synthase, alone or combined with L-arginine (L-Arg) or D-arginine (D-Arg). Columns indicate mean area of gastric lesions and plots show the values of gastric blood flow. An asterisk indicates a significant change as compared to the value obtained in vehicle-treated rats. A cross indicates a significant change as compared to the value recorded in rats not treated with N^G-nitro-L-arginine methyl ester.

gastric blood flow. These results have been omitted for the sake of clarity.

4. Discussion

Peptides of the gastrin/CCK family are released from the stomach and proximal portion of the gut upon the ingestion of certain nutrients, such as fat and proteins, and affect gastric secretory and motor functions (Lloyd et al., 1992; Walsh, 1987) through peripheral CCK_A or CCK_B receptors (Corwin and Smith, 1993) involving, in part, sensory nerves (Raybould and Tache, 1988).

Pentagastrin was reported to prevent, in part, acute gastric mucosal damage induced by absolute ethanol but not by acidified aspirin (Konturek et al., 1983). Recently, CCK, which possesses a *C*-terminal amino acid sequence similar to gastrin, was found to prevent the formation of acute ethanol-induced gastric lesions (Evangelista and Maggi, 1991) through the activation of specific CCK_A receptors and vagal capsaicin-sensitive fibers, which have been implicated previously in a local mucosal defense mechanism (Holzer et al., 1990). Our present results confirm that parenteral administration of CCK prevents ethanol-induced gastric injury in a dose-dependent manner and enhances mucosal blood flow. The threshold dose of CCK (1.2 nmol/kg s.c.) that significantly reduced ethanol-induced gastric damage also resulted in a small but significant increase in gastric blood flow. With increasing doses of CCK a gradual reduction in the gastric lesion area was accompanied by a stepwise increase in gastric blood flow, with similar dose of CCK producing a 50% change in gastric damage and hyperemia.

Since NO generated in the mucosa through the action of NO synthase on L-arginine (Palmer et al., 1988; Peskar et al., 1991) has been implicated in the maintenance of mucosal circulation during gastroprotection, we studied whether the blockade of NO synthase by *N*-nitro-L-arginine methyl ester affects the mucosal protection and mucosal blood flow induced by CCK. Indeed, pretreatment with this nitro-L-arginine analog reduced significantly the gastric blood flow and prevented, in part, the protective activity of CCK, effects that were reversed by the addition of L-arginine to this analog. These results indicate that NO plays a crucial role in both the mucosal hyperemia and the gastroprotection afforded by CCK.

The major finding of this study is that CCK released endogenously by intraduodenal oleate was highly effective in gastroprotection and gastric hyperemia, and that both these effects were mediated by CCK_A but not CCK_B receptors.

The question remains what could be the mechanism of the protection afforded by duodenal fat as compared to that induced by exogenous CCK. The observation that gastric damage and the fall in gastric blood flow induced by aspirin (which is known to abolish the mucosal generation of prostaglandins) were not prevented by exogenous CCK suggests that endogenous prostaglandins may be required for the induction of gastric protection and gastric hyperemia by this hormone. Previous studies suggested a close interaction between cyclooxygenase products and nitric oxide on gastric mucosal integrity and gastric blood flow (Whittle et al., 1990).

An alternative explanation could be that CCK released endogenously (Shiratori et al., 1992) by intraduodenal instillation of fat increases the release of somatostatin (Lloyd et al., 1992), which in turn contributes to the gastroprotective activity of CCK (Konturek et al., 1983). It should be mentioned, however, that exogenous CCK was also reported recently to release somatostatin (Lloyd et al., 1994). Thus, the difference observed between exogenous CCK and intraduodenal fat is probably more related to the recruitment by duodenal oleate of additional protective mechanisms than to the release of endogenous CCK, though the latter substance seems to play an important role because the antagonism of CCK_A receptors by loxiglumide almost completely eliminated the protective effects of duodenal oleate.

Our studies on basal gastric acid secretion in conscious rats demonstrate that exogenous CCK had a stimulatory effect on gastric acid secretion, whereas duodenal fat caused a marked inhibition of this secretion, again indicating the major difference between exogenous CCK and duodenal oleate. It is likely, there-

fore, that the failure of exogenous CCK to prevent aspirin-induced gastric damage could be due to the additive effect of gastric acid (stimulated by CCK) on aspirin-induced injury. This notion is supported by our observation that pretreatment with L-365,260, which inhibits basal gastric acid secretion, reduced significantly the aspirin-induced gastric injury. These results could be interpreted as showing that exogenous CCK is capable of protecting the gastric mucosa only from a necrotizing agent such as 100% ethanol, whose damaging effect is acid-independent, but fails to affect aspirin-induced injury, which is acid-dependent. Alternatively, the results suggest that CCK plays only a limited role in the protection of gastric mucosa against aspirin, and that the changes observed after duodenal oleate could be due to the activation of additional protective mechanisms that are independent of CCK release.

Although the duodenal the fat-induced inhibition of basal gastric acid secretion seems to be mediated by CCK_A receptors because it could be reduced by the pretreatment with loxiglumide or another potent CCK_A receptor antagonist (Lloyd et al., 1992), it is possible that other gut peptides are involved such as secretin, neurotensin, PYY or GIP, which are released by fat (Shiratori et al., 1992; Walsh, 1987). These enterohormones could be responsible for the stronger gastroprotective action of duodenal fat as compared to that of exogenous CCK. It is also likely that duodenal fat triggers vago-vagal reflexes that could mediate the protection and hyperemia and which could contribute to the stronger protective effects of duodenal oleate as compared to exogenous CCK, but this requires further studies.

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