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"GASTRIN" AND "CCK" RECEPTORS ON HISTAMINE- AND SOMATOSTATIN-CONTAINING CELLS FROM RABBIT FUNDIC MUCOSA—II

CHARACTERIZATION BY MEANS OF SELECTIVE ANTAGONISTS (L-364,718 AND L-365,260)

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Abstract—In the preceding paper, by means of selective agonists to gastrin (HG-17) and cholecystokinin (CCK-39), we evidenced the existence of "gastrin-type" receptors that could regulate histamine release and "CCK-type" receptors that could stimulate somatostatin release in isolated rabbit fundic non-parietal cells (F1 cells). Furthermore, these receptors could induce phosphoinositide breakdown. To confirm the involvement of these receptor types in these biological and biochemical processes, we used selective antagonists, L-364,718 (3-(benzoylamino)-benzodiazepine) specific to "CCK-A-type" receptor and L-365,260 (3-(acylamino)-benzodiazepine) specific to "gastrin/CCK-B-type" receptor. Neither L-364,718 nor L-365,260 alone caused any significant stimulation of [^{3}H]inositol phosphate ([^{3}H]InsP) production and release of histamine or somatostatin-like immunoreactivity (SLI). Each analogue inhibited in a dose-dependent manner [^{125}I]HG-17 or [^{125}I]CCK-39 binding to F1 cells, [^{3}H]InsP accumulation and histamine and SLI release stimulated by HG-17 or CCK-39. L-365,260 appeared to be 30–70 times more potent than L-364,718 in inhibiting [^{125}I]HG-17 binding to F1 cells, as well as HG-17-induced [^{3}H]InsP accumulation and HG-17- or CCK-39-enhanced histamine release (IC_{50} values: ≈5–20 nM for L-365,260 and ≈200–1500 nM for L-364,718). In contrast, L-364,718 was 200 to 400 times more potent than L-365,260 in inhibiting [^{125}I]CCK-39 binding to F1 cells, CCK-39-induced [^{3}H]-InsP accumulation and SLI release stimulated by CCK-39 or HG-17 (IC_{50} values: ≈0.3–1 nM for L-364,718 and 100–200 nM for L-365,260). These results led to conclude: (i) the existence of a "gastrin-type" receptor related to histamine release; (ii) the existence of a "CCK-A-type" receptor related to somatostatin release; (iii) the existence of "gastrin type" and "CCK-A-type" receptors linked to the phosphoinositide breakdown pathway.

As described in the preceding paper, gastrin (HG-17) and cholecystokinin (CCK-8 and CCK-39) could interact on a population of non-parietal cells (named "F1 cells") obtained following elutriation of isolated gastric fundic mucosal cells; this mucosal cell population was enriched in mucus and endocrine cells. These studies led us to suggest the existence on these cells of two types of receptors coupled to inositol phosphate (InsP) production: a "gastrin-type" receptor mediating histamine release and a "CCK-type" receptor mediating somatostatin release [1].

The use of selective antagonists could confirm the involvement of these receptor types in these biological and biochemical processes. Some compounds such as proglumide, dibutyryl cGMP or benzotript have been described as gastrin or cholecystokinin (CCK) antagonists, but they exhibit a low *in vitro* potency [2] and a lack of selectivity for CCK or gastrin receptors [3]. Recently, a new class of non-peptidic CCK/gastrin antagonists have been developed and one of these compounds, L-364,718 (3-(benzoylamino)-benzodiazepine) has been reported to exhibit high selectivity for CCK peripheral receptors compared with brain receptors [4, 5]. This agent allowed us to define two subtypes of CCK receptors: a CCK-A receptor with a high affinity for L-364,718 present in pancreatic acini and CCK-B receptors with a low affinity (1000-fold lower) present in some areas of the brain [4, 5]. Another compound, L-365,260 (3-(acylamino)-benzodiazepine), seems to be a potent and selective CCK-B and gastrin receptor ligand: it interacts competitively with these receptors [6, 7] and behaves as an antagonist of gastrin-stimulated acid secretion in various animal models [7]. In a recent report, the combined use of these compounds led us to demonstrate the existence of a "gastrin-type" receptor on rabbit gastric parietal cells which mediates gastrin-induced acid secretion from these cells [8].

Therefore, in order to further characterize what types of receptor (CCK-A, CCK-B or gastrin) mediate the effects of gastrin and cholecystokinin on "F1 cells", we investigated the ability of the benzodiazepine derivatives L-364,718 and L-365,260 to antagonize [^{125}I]HG-17 or [^{125}I]CCK-39 binding and to inhibit HG-17- or CCK-39-induced [^{3}H]InsP production as well as the release of histamine and somatostatin stimulated by these peptides.

MATERIALS AND METHODS

Unsulphated gastrin analogues, [Ahx11]-HG-17

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were gifts from Professors E. Wunsch and L. Moroder (Max Planck-Institut für Biochemie, Munich, F.R.G.), somatostatin (14–28) was from the Sigma Chemical Co. (St Louis, MO, U.S.A.). Highly purified pig CCK-39 was from Professor V. Mutt (Stockholm, Sweden). [^{125}I]CCK-39 was obtained following labeling of CCK-39 with the Bolton–Hunter reagent with a specific radioactivity of 2100 Ci/mmol and purified using reverse phase HPLC method described by Fourmy *et al.* [9]. [^{125}I]Tyr somatostatin was from N.E.N., *myo*-[2-^{3}H]inositol (17 Ci/mmol) was from C.E.A. (Saclay, France). AG1-X2 resin 200–400 mesh was from Biorad (Paris, France). Histamine radioimmunoassay was from Immunotech (Luminy, France). Somatostatin polyclonal antibody was kindly given by Dr D. Dussossoy (Sanofi, Montpellier, France). L364,718 and L-365,260 were obtained from Dr Paul Anderson (Merck, Sharp & Dohme, Rahway, NJ, U.S.A.); they were then dissolved at 500 μM in ethanol and then diluted in 50% (v/v) ethanol/water.

Standard medium comprised Earle's balanced salt solution without bicarbonate containing 10 mM Hepes and 0.2% bovine serum albumin (BSA) (pH 7.4). Earle's balanced salt solution was from Biomerieux (Lyon, France).

Preparation of isolated rabbit gastric non-parietal cells. Cell isolation was carried out following the collagenase/EDTA procedure as already described [10]. Cell separation was performed by counterflow centrifugation with a Beckman elutriator rotor JE6-B. Three fractions were collected at a rotor speed of 2100 rpm by increasing the flow rate from 24 to 44 and 68 mL/min. The first fraction (F1 cells) mainly contained small cells (8–12 μM) and was devoid of parietal cells and chief cells.

Binding experiments. Binding experiments were performed as previously described [10]; cells (5×10^6 cells per mL) were incubated in standard medium with [^{125}I]HG-17 or [^{125}I]CCK-39 (20 pM) under stirring for 25 min at 37° in the absence (control) or in the presence of various concentrations of antagonists. At the end of the incubation period, duplicate 0.2 mL samples of cell suspension were removed, rapidly diluted with 0.6 mL cold standard medium and centrifuged in an Eppendorf microfuge for 1 min to separate bound from free ligand. Non specific binding was assessed by incubating cells in the presence of an excess (1 μM) of unlabelled peptides (HG-17 or CCK-39).

Measurement of [^{3}H]inositol phosphate accumulation. [^{3}H]InsP accumulation was determined as previously described [11]. F1 cells (2×10^7 per mL) were incubated for 2 hr at 37° under continuous gassing(95% O_2/5% CO_2) in standard medium containing 40 μCi/mL of *myo*-[2-^{3}H]inositol. After two washings with standard medium, cells (3×10^6 per tube) were equilibrated for 15 min at 37° in the presence of 10 mM LiCl and further incubated for 5 min at 37° in the presence or the absence of various concentrations of antagonists. Cells were finally incubated for an additional period of 10 min with or without (control) HG-17 or CCK-39 (100 nM). The extraction and the quantification of the [^{3}H]InsP accumulation was performed as described previously [11].

Histamine release studies. Cells were washed three times in standard medium without bovine (BSA) and then incubated (200,000 per mL) with or without (control) stimulants in the presence or in the absence of various concentrations of antagonists at 37° for 30 min. Samples were centrifuged (30 sec; 12,000 *g*) and aliquots (0.1 mL) of supernatant were used for the measurement of histamine content by radioimmunoassay as previously described [1]. All samples were assayed in duplicate.

Somatostatin release studies. Cells were washed three times in standard medium without BSA and then incubated (10^6 cells/mL) with or without stimulant at 37° for 30 min in the presence or in the absence of various concentrations of antagonist. Samples were centrifuged (30 sec; 12,000 *g*) and aliquots (0.2 mL) of supernatant were used for assay of somatostatin-like immunoreactivity (SLI). SLI was measured by radioimmunoassay as previously described [1]. All samples were assayed in duplicate.

RESULTS

Effects of L-364,718 and L-365,260 on [^{125}I]HG-17 and [^{125}I]CCK-39 binding

L-364,718 and L-365,260 dose-dependently inhibited HG-17 and CCK-39 binding to F1 cells (Fig. 1). L-365,260 caused a detectable inhibition of [^{125}I] HG-17 binding at 0.3 nM, half maximal inhibition at 4.25 ± 0.65 nM and complete inhibition at 1 μM. L-364,718 is about 30 times less potent, causing half maximal inhibition at 147 ± 32 nM and complete inhibition at 10 μM. In contrast, L364,718 was the most potent inhibitor of [^{125}I]CCK-39 binding to F1 cells: this antagonist caused a detectable inhibition at 0.1 nM, half maximal inhibition at 0.80 ± 0.32 nM and total inhibition at 100 nM. L-365,260 was about 200 times less potent than L-364,718 in inhibiting [^{125}I]CCK-39 binding, causing half maximal inhibition at 185 ± 52 nM and complete inhibition at 10 μM.

Effects of L-364,718 and L-365,260 on HG-17- and CCK-39-stimulated [^{3}H]InsP accumulation

HG-17 and CCK-39 were shown to stimulate [^{3}H]-InsP accumulation in F1 cells. L-364,718 and L-365,260 inhibited HG-17- and CCK-39-induced [^{3}H]-InsP accumulation in a dose-dependent manner (Fig. 2). These compounds did not significantly affect the basal [^{3}H]InsP accumulation over the range of concentrations used (10 pM–10 μM) (not shown). Concerning [^{3}H]InsP accumulation induced by 10 nM HG-17, L-365,260 caused a detectable inhibition at 0.1 nM, half-maximal inhibition at 5.62 ± 1.08 nM, and total inhibition at 1 μM. In contrast, L-364,718 was about 40 times less potent, causing half-maximal inhibition at 215 ± 62 nM and total inhibition at 10 μ. Concerning [^{3}H]InsP accumulation induced by 100 nM CCK-39, L-364,718 was the most potent inhibitor: this compound caused a detectable inhibition at 0.03 nM, half-maximal inhibition at 0.39 ± 0.16 nM at complete inhibition at 100 nM. In that case, L-365,260 was about 250 times less potent, giving half-maximal inhibition at 112 ± 35 nM and total inhibition at 10 μM.

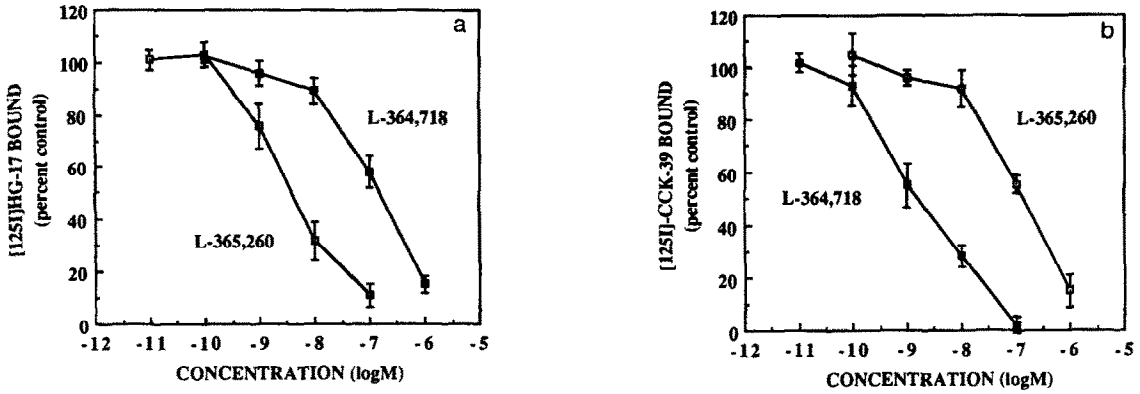

Fig. 1. Abilities of L-364,718 and L-365,260 to inhibit [^{125}I]HG-17 and [^{125}I]CCK-39 binding to F1 cells. Cells (5×10^6 cells per mL) were incubated at 37° for 25 min with 20 pM [^{125}I]HG-17 (a) and [^{125}I]CCK-39 (b) with or without the indicated concentrations of L-364,718 or L-365,260. Results are the per cent of saturable binding without added L-364,718 or L-365,260 (per cent control). Data are means ± SE from four separate experiments assayed in duplicate.

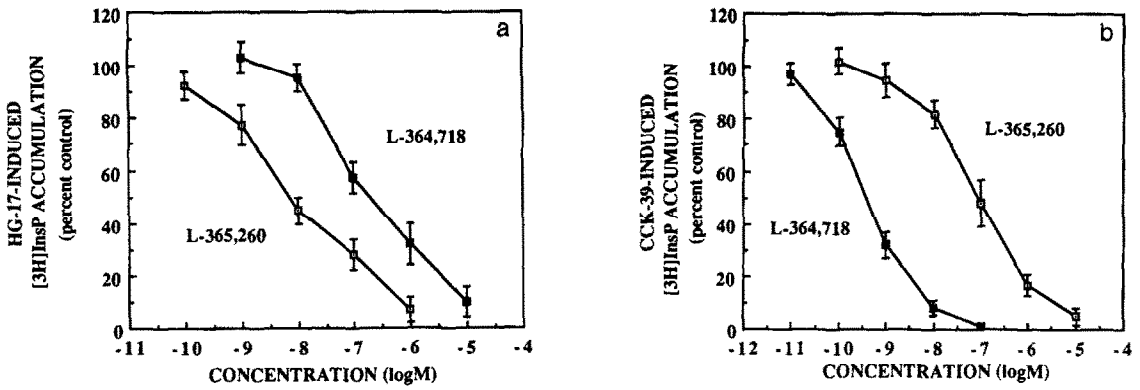

Fig. 2. Abilities of L-364,718 and L-365,260 to inhibit HG-17- and CCK-39-induced [^{3}H]inositol phosphates accumulation into "F1" cells. [^{3}H]Inositol prelabelled parietal cells were incubated at 37° for 15 min with 10 mM LiCl and then incubated for 5 min at 37° with or without the indicated concentrations of L-364,718 or L-365,260. Cells were finally incubated for an additional period of 10 min without (control) or with 10 nM HG-17 (a) or 10 nM CCK-39 (b). Results are the per cent of [^{3}H]InsP accumulation caused by HG-17 alone (5210 ± 132 dpm) or CCK-39 alone (5332 ± 124 dpm) without added L-364,718 or L-365,260 (per cent control); [^{3}H]InsP basal accumulation value was 3107 ± 130 dpm. Data are means ± SE from four separate experiments.

Effects of L-364,718 and L-365,260 on HG-17- and CCK-39-induced histamine release

The effects of L-364,718 and L-365,260 have been investigated on HG-17- and CCK-39-induced histamine release from F1 cells. Both antagonists did not significantly affect basal histamine release (not shown). As shown in Fig. 3, these compounds inhibited in a dose-dependent manner histamine release stimulated by HG-17 (10 nM) or CCK-39 (100 nM). L-365,260 caused a detectable inhibition at 1 nM, half-maximal inhibition at 12.2 ± 3.8 nM (HG-17) and 18 ± 6.5 nM (CCK-39) and complete inhibition at 1 μM. L-364,718 was about 30 to 70 times less potent than L-365,260: half-maximal inhibition occurred at 312 ± 97 nM (HG-17) and 1540 ± 550 nM (CCK-39) and complete inhibition at ≥10 μM. Furthermore, each antagonist displayed the same profile of action to inhibit either HG-17- or CCK-39-induced histamine release. To evaluate the competitive nature of the inhibition of HG-17-stimulated histamine release caused by L-365,260, we examined the effect of a fixed concentration of L-365,260 (10 nM) on the dose–response curve to HG-17. As illustrated in Fig. 4, L-365,260 induced a parallel rightward shift of the dose–response curve suggesting that this compound behaves as a competitive antagonist of the action of HG-17 on histamine release.

Effects of L-364,718 and L-365,260 on HG-17- and CCK-39-stimulated SLI release

The effects of L-364,718 and L-365,260 were then investigated on HG-17- and CCK-39-induced SLI release from the F1 cells. Both antagonists did not significantly affect basal SLI release (not shown).

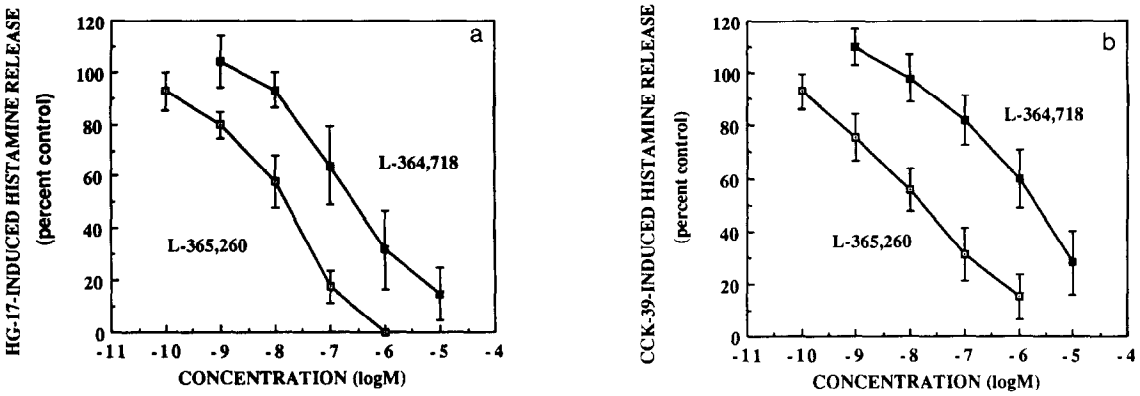

Fig. 3. Abilities of L-364,718 and L-365,260 to inhibit HG-17- and CCK-39-induced histamine release from "F1 cells". Cells (0.2×10^6 per mL) were incubated at 37° for 30 min with HG-17 (10 nM) (a) or CCK-39 (100 nM) (b) and with the indicated concentrations of L-364,718 and L-365,260. Results are the per cent of histamine release induced by HG-17 alone (9.26 ± 0.49% of cell content) or CCK-39 alone (6.44 ± 0.69%) (per cent control). Basal histamine release was 2.68 ± 0.37% of cell content. Data are means ± SE from five separate experiments assayed in duplicate.

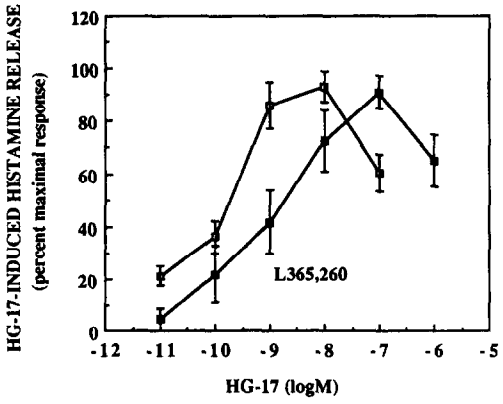

Fig. 4. Effect of L-365,260 on the dose–response curve for HG-17-stimulated histamine release from "F1 cells". Cells (0.2×10^6 per mL) were incubated at 37° for 30 min with the indicated concentrations of HG-17 without or with 10 nM L-365,260. Results are the per cent of histamine release induced by 10 nM HG-17 alone and are means ± SE from five separate experiments assayed in duplicate.

As shown in Fig. 5, these compounds inhibited in a dose-dependent manner SLI release stimulated by CCK-39 (1 nM) or HG-17 (100 nM). L-364,718 caused a detectable inhibition at 0.01 nM, half-maximal inhibition at 0.12 ± 0.03 nM (CCK-39) and 0.35 ± 0.11 nM (HG-17) and complete inhibition at 100 nM. L-365,260 was ≥300 times less potent than L-364,718; half-maximal inhibition occurred at 123 ± 43 nM (CCK-39) and 112 ± 42 nM (HG-17) and complete inhibition at 10 μM. Furthermore, each antagonist displayed the same profile of action to inhibit either CCK-39- or HG-17-induced SLI release. To evaluate the competitive nature of the inhibition of CCK-39-stimulated SLI release caused by L-364,718, we examined the effect of a fixed concentration (0.3 nM) of L-364,718 on the dose–response curve to CCK-39. As illustrated in Fig. 6, L-364,718 induced a parallel rightward shift of the dose–response curve suggesting that this compound behaves as a competitive antagonist of the action of CCK-39 on SLI release.

DISCUSSION

In this report, we investigated the effects of selective antagonists L-364,718 (specific to "CCK-A type" receptor) and L365,260 (specific to "gastrin/CCK-B" receptor) on [^{125}I]HG-17 and [^{125}I]CCK-39 binding to F1 cells, on [^{3}H]InsP accumulation and on histamine and SLI release stimulated by HG-17 or CCK-39.

Existence of a "gastrin type" receptor mediating histamine release

We demonstrated that L-365,260 and L-364,718 inhibited in a dose-dependent manner the binding of [^{125}I]HG-17 to F1 cells, as well as HG-17-stimulated [^{3}H]InsP production and histamine release; when comparing the effects of both antagonists, it appeared that, on these three events, L-365,260 was 30 to 40 times more potent than L-364,718. Moreover, the IC_{50} value for the inhibition of [^{125}I]HG-17 binding to F1 cells by L-365,260 (4.25 ± 0.65 nM) is in good agreement with the IC_{50} values obtained from isolated rabbit parietal cells (3.85 ± 0.5 nM) [8] or guinea pig pancreatic acini (7.3 ± 0.8 nM) [12]. These results evidenced the existence of a "gastrin type" receptor on F1 cells that may regulate [^{3}H]InsP accumulation and histamine release induced by gastrin. The fact that both antagonists inhibited in a similar manner [^{125}I]-HG-17 binding to F1 cells, [^{3}H]InsP accumulation and histamine release stimulated by HG-17 led to suggest a relationship between these different events.

The fact that L-365,260 at a fixed concentration caused a parallel rightward shift of the dose–response curve for gastrin-induced histamine release,

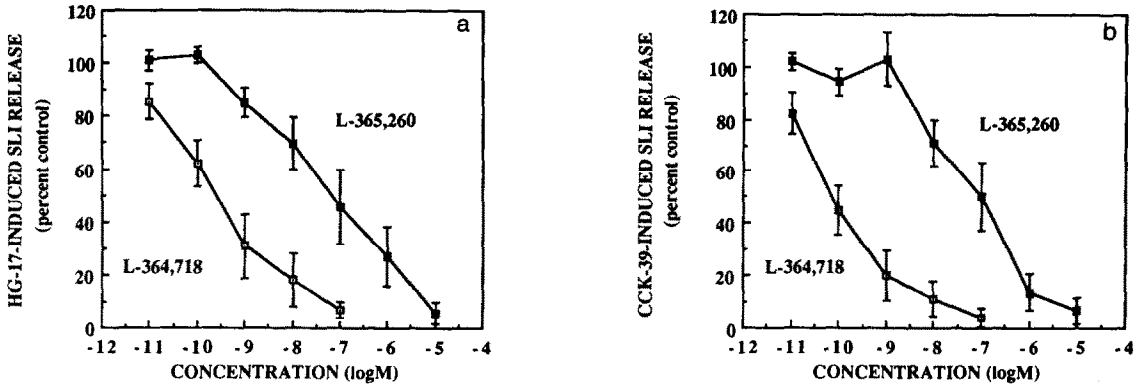

Fig. 5. Abilities of L-364,718 and L-365,260 to inhibit HG-17- and CCK-39-induced Somatostatin Like Immunoreactivity (SLI) from "F1 cells". Cells (1×10^6 per mL) were incubated at 37° with HG-17 (100 nM) (a) or CCK-39 (1 nM) (b) and with the indicated concentrations of L-364,718 and L-365,260. Results are the per cent of SLI release induced by HG-17 alone (1.11 ± 0.09% of cell content) or CCK-39 alone (1.32 ± 0.12%) (per cent control). Basal SLI release was 0.60 ± 0.08% of cell content. Data are means ± SE from five separate experiments assayed in duplicate.

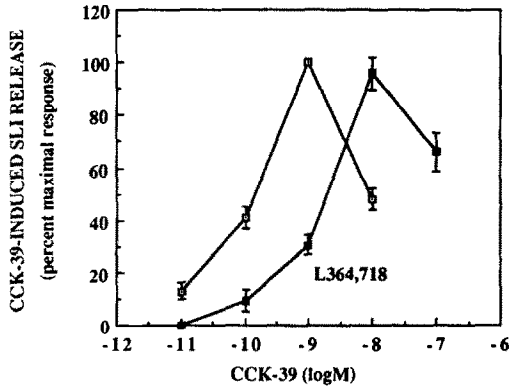

Fig. 6. Effect of L-364,718 on the dose–response curve for CCK-39-stimulated SLI release from "F1 cells". Cells (1×10^6 per mL) were incubated at 37° for 30 min with the indicated concentrations of CCK-39 without or with 0.3 nM of L-364,718. Results are the per cent of SLI release induced by 1 nM CCK-39 alone and are means ± SE from five separate experiments assayed in duplicate.

confirmed that this compound behaved as a competitive antagonist as previously observed on isolated rabbit parietal cells [8] or on guinea pig gastric glands [7].

CCK-39 was shown to induce histamine release from F1 cells; thus the presence of "CCK-type" receptors that could mediate histamine release can not be precluded. Nevertheless, CCK-39 displayed a 15-fold lower potency and a 2-fold lower efficacy than gastrin to enhance the release of histamine. Furthermore, no significant difference can be observed for the inhibitory effect of these antagonists on HG-17- or CCK-39-induced histamine release: L-365,260 was 30 to 70 times more potent than L-364,718. Taken together, these results strongly suggest that CCK-39 could induce histamine release from "F1 cells" via an interaction with the "gastrin-type" receptor as previously observed on isolated rabbit gastric parietal cells [8].

Existence of a "CCK-A-type" receptor mediating somatostatin release

L-364,718 and L-365,260 inhibited in a dose-dependent manner [^{125}I]CCK-39 binding to F1 cells as well as CCK-39-induced [^{3}H]InsP production and SLI release and, in all cases, L-364,718 was 200–1000 times more potent than L-365,260. The fact that both antagonists inhibited in a similar manner [^{125}I]CCK-39 binding to F1 cells, [^{3}H]InsP accumulation and SLI release induced by CCK-39 suggests a possible relationship between these three events. As L-364,718 at a fixed concentration caused a parallel rightward shift of the dose–response curve for CCK-39-stimulated SLI release, it is likely that this compound behaved as a competitive antagonist as previously observed on rat pancreatic acini [5].

It can be noticed that L-364,718 inhibited with a similar potency [^{125}I]CCK-39 binding to F1 cells (IC_{50}: 0.80 ± 0.32 nM) and [^{125}I]CCK-8 binding to "CCK-A-type" receptors present on guinea pig pancreatic acini (IC_{50}: 4 ± 1 nM) [12]. Furthermore, these results fit in well with the potency of both antagonists to inhibit CCK-8-stimulated amylase release from guinea pig pancreatic acini [12] where L-364,718 was found to be 200 fold more potent than L-365,260. These observations clearly evidenced, on F1 cells, the existence of a "CCK-A-type" receptor related to [^{3}H]InsP accumulation and SLI release. These present results are in agreement with a recent report showing that CCK-8-induced inhibition of pentagastrin-stimulated gastric acid secretion in urethane-anaesthetized rats was mediated via specific "CCK-A-type" receptors [13]. All these findings led us to postulate that CCK-8 exerted an inhibitory effect on gastric acid secretion via activation of "CCK-A-type" receptors which enhanced the release of somatostatin. Such an

hypothesis is further supported by a recent report showing that CCK-8 but not gastrin could stimulate somatostatin release and inhibit, in the meantime, histamine-induced aminopyrine uptake (an index of *in vitro* acid secretion) in isolated rabbit gastric glands [14].

HG-17 has been shown to induce SLI release from F1 cells; thus, the presence of a "gastrin-type" receptor on fundic D-cells can not be precluded. Nevertheless, the fact that gastrin could interact with a "CCK-A-type" receptor to enhance SLI release is supported by several observations: (i) HG-17 enhanced SLI release with a 50–100 times lower potency and a 2-fold lower efficacy than did CCK-39; (ii) pentagastrin and HG-17 enhanced SLI release with a similar potency and efficacy (not shown); (iii) no significant difference could be observed for the inhibitory effects of both antagonists on HG-17- or CCK-39-induced SLI release: L-364,718 was 300 to 1000 times more potent than L-365,260.

In conclusion, the use of L-364,718 and L-365,260 established that different receptor-types mediate the effects of gastrin and cholecystokinin on isolated non-parietal cells from rabbit gastric mucosa: a "gastrin-type" receptor that regulates histamine release and a "CCK-A-type" receptor that regulates somatostatin release. Furthermore, the use of these antagonists suggests that the phosphoinositide breakdown pathway is involved in the mediation of gastrin and cholecystokinin effects on these non-parietal cells. Finally, these results could explain, in part, the different effects of gastrin and cholecystokinin on *in vivo* acid secretion.

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