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

CHARACTERIZATION BY MEANS OF AGONISTS

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Abstract—A previous study has suggested the presence of two distinct binding sites for gasrin and cholecystokinin (CCK) in isolated non-parietal cells from rabbit gastric mucosa: a receptor which binds CCK-8 and CCK-39 with a high affinity and a receptor which binds gastrin and CCK-8 with the same high affinity and CCK-39 with a lower affinity. To characterize these receptors, their ability to induce phosphoinositide breakdown was investigated. Gastrin (HG-17), CCK-39 and CCK-8 induced [^{3}H]-inositol phosphate ([^{3}H]InsP) accumulation from [^{3}H]inositol prelabelled cells with a high potency (EC_{50}: 0.3–2.7 nM) but CCK-8 exhibited a higher efficacy than HG-17 or CCK-39. HG-17, CCK-8 and CCK-39 induced a rapid accumulation of [^{3}H]inositol monophosphate ([^{3}H]$InsP_1$), [^{3}H]inositol bisphosphate ([^{3}H]$InsP_2$) and [^{3}H]inositol trisphosphate ([^{3}H]$InsP_3$) but CCK-8 caused a two times higher accumulation than HG-17 or CCK-39. Histamine- and somatostatin-containing cells appeared to be located in this non-parietal cells population. HG-17, CCK-8 and CCK-39 dose-dependently induced histamine release with the following order of potency: HG-17 = CCK-8 ($EC_{50} \approx 0.2$ nM) > CCK-39 ($EC_{50} \approx 4$ nM). In addition, HG-17 exhibited the highest efficacy. HG-17, CCK-8 and CCK-39 enhanced somatostatin-like immunoreactivity (SLI) release with the following order of potency: CCK-8 ($EC_{50} \approx 0.1$ nM) = CCK-39 > HG-17 ($EC_{50} \approx 10$ nM); CCK-8 and CCK-39 exhibited the highest efficacy. These results led us to the following conclusions: (i) existence of a "gastrin-type" and of a "CCK-type" receptor mediating phosphoinositide breakdown in these gastric non-parietal cells. CCK-8 interacts with both receptor-types with the same affinity; (ii) the release of histamine from histamine-containing cells could be induced following "gastrin-type" receptors activation; (iii) somatostatin release from D-cells present in this non-parietal cells population could be induced following "CCK-type" receptors activation.

Gastrin and cholecystokinin (CCK) are two related peptides that share homology at their biologically active pentapeptidic C-terminal sequence. Despite their structural similarities, these peptides display different effects on acid secretion. Gastrin is a potent *in vivo* stimulant of H^+ secretion [1]; in contrast CCK-8, the C-terminal octapeptide of CCK, is a weak stimulant [1] and behaves as an inhibitor of pentagastrin-induced *in vivo* acid secretion [2, 3]. Conversely, *in vitro* studies revealed that gastrin and CCK-8 stimulate acid secretory activity of parietal cells with the same potency and efficacy [4, 5]. These findings suggest that, in addition to their direct effect on parietal cells, gastrin and CCK regulate *in vivo* acid secretion through activation of gastric non parietal cells.

In this way, somatostatin, a well known inhibitor of acid secretion [1], is stored in D-cells present in gastric mucosa. The release of somatostatin can be stimulated by CCK-8 or gastrin as shown in rabbit gastric glands [6] or in an enriched D-cells preparation from canine fundic mucosa [7]. On another hand, histamine, a potent stimulant of acid secretion [8] appeared, in gastric mucosa, to be stored in mast cells or in enterochromaffin-like cells (ECL) (for review, see Ref. 8). The release of histamine can be stimulated by pentagastrin as shown in rabbit gastric glands [9] or in amphibian gastric mucosa [10]. Thus, it seems likely that somatostatin and histamine may play an important role in the regulation of *in vivo* gastrin- and CCK-induced acid secretion.

Specific binding sites for gastrin have been found in a population of isolated non-parietal cells from canine fundic mucosa [11]. This cell population contained several cell types including ones storing somatostatin, glucagon, histamine and the enterochromaffin-like cell markers serotonin and DOPA-decarboxylase [12]. More recently, specific binding sites for gastrin and CCK-8 were evidenced in an enriched preparation of D-cells from canine gastric mucosa placed in short-term culture [13]. Using iodinated gastrin, CCK-8 or CCK-39, we previously reported the existence of specific binding sites for these ligands on a non-parietal cells population (named F1 cells) isolated from rabbit fundic mucosa [14]; this cell population mainly contained mucus and endocrine cells and was devoid of parietal and chief cells. These results suggested the presence of two separate receptor sites on these non-parietal cells: a "gastrin-type" receptor which recognizes with a similar high affinity both gastrin and CCK-8 because of their structural homology at the

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pentapeptidic C-terminal sequence, and a "CCK-type" receptor which binds CCK-8 and the longer molecular forms of CCK (CCK-33 and CCK-39) with a high affinity and gastrin with a lower affinity.

Gastrin and CCK-8 are known to induce phosphoinositide breakdown [5, 15, 16] leading to inositol(1,4,5)trisphosphate ($Ins(1,4,5)P_3$) production (a promoter of Ca^{2+} release from intracellular stores) and 1,2*sn*-diacylglycerol production (a strong activator of protein kinase C) (for review see Ref. 17). Recently, Chiba *et al.* [13] demonstrated that the stimulatory effects of gastrin and CCK-8 on somatostatin-like immunoreactivity (SLI) release were closely related to their abilities to induce [^{3}H]-inositol trisphosphate ([^{3}H]$InsP_3$) accumulation from [^{3}H]inositol prelabelled canine D-cells.

Therefore to further characterize these two receptor types, we have studied, in this paper, the ability of gastrin (HG-17) and cholecystokinin (CCK-8 and CCK-39) to induce the phosphoinositide breakdown in a non-parietal cells population (F1 cells) isolated from rabbit gastric mucosa; furthermore, since histamine- and somatostatin-containing cells are present in this cell population, we investigated the effects of these peptides on histamine and somatostatin release. As CCK-8 can bind to both "gastrin-type" and "CCK-type" receptors [14], we also studied the effects of CCK-39, a longer molecular form of cholecystokinin, more specific for CCK receptors.

MATERIALS AND METHODS

Unsulphated gastrin analogues, [Ahx11]-HG-17 were gifts from Professors E. Wunsch and L. Moroder (Max Planck-Institut für Biochemie, Martinsried, F.R.G.), CCK-8, [14–28] somatostatin 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]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).

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 [18]. Cell separation was performed by the counterflow centrifugation with a Beckman elutriator rotor JE6-B [14]. 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 (diameter about 8–12 μM) and was devoid of parietal cells or chief cells (<1%).

Measurement of [^{3}H]*inositol phosphate accumulation.* [^{3}H]Inositol phosphate ([^{3}H]InsP) accumulation was determined as previously described [19]. Non-parietal 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 *myo*-[2-^{3}H]inositol. After washing with standard medium, cells (3×10^6 per mL) were equilibrated for 20 min at 37° in the presence of 10 mM LiCl and further incubated for the indicated time at 37° without (control) or with the various concentrations of peptides. The reaction was stopped by addition of 1 mL 10% perchloric acid and the pH of the supernatants was adjusted to 7 by addition of 3 M KOH. The neutralized extracts were diluted with 6 mL of formic acid 0.1 M and applied to freshly prepared AG1-X2 (200–400 mesh, formate form) Dowex column equilibrated with formic acid (0.1 M) and inositol (5 mM). [^{3}H]Inositol was washed from the resin by 10 mL of 0.1 M formic acid. Total water soluble [^{3}H]InsP were eluted with 9 mL of 2 M ammonium formate/0.1 M formic acid. For quantification of the different inositol phosphate, the neutralized extracts were applied to the Dowex column and [^{3}H]inositol was washed from resin as above, then inositol monophosphate ($InsP_1$), inositol bisphosphate ($InsP_2$) and inositol trisphosphate ($InsP_3$) were stepwise eluted with 6 mL each of 0.2, 0.4 and 0.8 M ammonium formate/0.1 M formic acid. Eluates were collected and assayed for radioactivity content.

Histamine release studies. Cells were washed three times in standard medium without bovine serum albumin (BSA) and then incubated (200,000 cells per mL) with or without stimulants at 37° for 30 min. Samples were centrifuged (30 sec, 12,000 *g*) and aliquots (0.1 mL) of supernatant were used for the assay of histamine. Total histamine content was determined after lysis of cells with perchloric acid (3% w/v). Histamine was measured by radioimmunoassay (Immunotech, Luminy, France). All samples were assayed in duplicate. Data are expressed as the percentage of total histamine content that was released in the medium during a 30 min incubation period.

Somatostatin release studies. Cells were washed three times in standard medium without BSA and then incubated (1×10^6 cells per mL) with or without stimulant at 37° for 30 min. Samples were centrifuged (30 sec 12,000 *g*) and aliquots (0.2 mL) of the supernatant were used for assay of somatostatin-like immunoreactivity (SLI). Total cellular SLI content was determined after lysis of cells with perchloric acid (3% w/v). SLI was measured by radioimmunoassay using sheep polyclonal anti-somatostatin antibody (1:30,000 final dilution) and [^{125}I]Tyr-somatostatin (5000 cpm per assay). After 48 hr incubation at 4°, 0.5 mL of 10% activated charcoal/1% Dextran T-70 mixture was added to separate bound from free [^{125}I]somatostatin. Samples were then centrifuged (15 min, 2000 *g*) and the pellet radioactivity was measured. All samples were assayed in duplicate. Data are expressed as the percentage of total SLI content that was released in the medium during a 30 min incubation period.

RESULTS

Effects of gastrin and CCK on [^{3}H]*InsP accumulation*

The effects of HG-17, CCK-8 and CCK-39 on

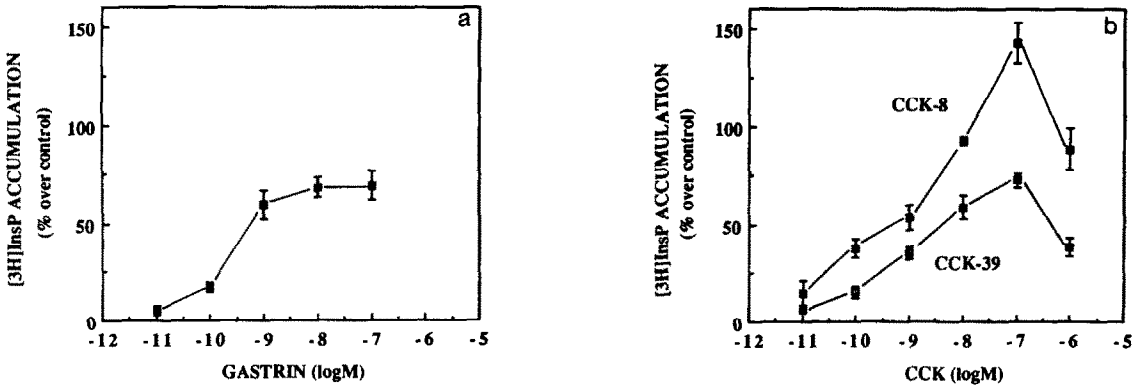

Fig. 1. Effects of HG-17, CCK-8 and CCK-39 on [^{3}H]inositol phosphates accumulation in "F1 cells". F1 cells were preincubated for 2 hr at 37° with *myo*-[2-^{3}H]inositol followed by a 20 min incubation in the presence of LiCl (10 mM). Cells (2×10^6 per mL) were then incubated with the various concentrations of (a) HG-17 (■); (b) CCK-8 (■) and CCK-39 (□), for 10 min at 37°. Data (mean ± SE from five to seven separate experiments) were expressed as the percentage of the control value (cells without stimulant) (1452 ± 62 dpm).

[^{3}H]InsP accumulation were studied in [^{3}H]inositol prelabelled F1 cells. HG-17, CCK-8 and CCK-39 stimulated [^{3}H]InsP production in a dose-dependent manner with a high apparent affinity: the deduced EC_{50} values were respectively: 0.30 ± 0.06 nM for HG-17, 1.34 ± 0.18 nM for CCK-39 and 2.70 ± 0.54 nM for CCK-8 (Fig. 1a and b). The maximal effects following HG-17 and CCK-39 stimulation were obtained for a 100 nM concentration and represented respectively 68.0 ± 7.2% and 72.3 ± 3.6% stimulation over the control. Concerning CCK-8, in the range of concentrations used (10 pM–1 μM), this peptide caused a more pronounced increase in [^{3}H]InsP accumulation than did CCK-39 or HG-17 (Fig. 1b). Furthermore, the maximal effect caused by CCK-8 (100 nM) appeared to be two times higher than the maximal effect caused by HG-17 or CCK-39: 142.8 ± 10.0% increase over control.

We then examined the time-course of the different [^{3}H]InsP accumulation induced by HG-17, CCK-39 and CCK-8 (100 nM). As shown in Fig. 2, these peptides stimulated a rapid accumulation of [^{3}H]-$InsP_1$, [^{3}H]$InsP_2$ and [^{3}H]$InsP_3$; HG-17 and CCK-39 displayed the same profile of action on the accumulation of the different [^{3}H]InsP. CCK-8 caused an about two times higher increase in [^{3}H]-$InsP_1$, [^{3}H]$InsP_2$ and [^{3}H]$InsP_3$ accumulation than did HG-17 or CCK-39.

Effects of gastrin and CCK on histamine release

The effects of gastrin and CCK were then examined on histamine release from F1 cells. The histamine content (determined after acidic lysis of cells) represented 381 ± 55 pmol per 10^6 cells. Basal histamine release (cells without stimulant) was 2.68 ± 0.32% of the total cell content. HG-17, CCK-8 and CCK-39 enhanced histamine release, maximal within 30 min stimulation (not shown). HG-17, CCK-8 and CCK-39 dose-dependently increased the release of histamine and the maximal effects were obtained for a 10 nM HG-17 and CCK-8 concentration, and for 100 nM CCK-39 (Fig. 3). HG-17 and CCK-8 enhanced histamine release with the same potency: EC_{50} values were respectively 0.211 ± 0.025 nM (HG-17) and 0.126 ± 0.030 nM (CCK-8); but HG-17 exhibited a significant higher efficacy than CCK-8: 9.26 ± 0.49% of cell content for HG-17-induced histamine release against 7.63 ± 0.35% for CCK-8. At the opposite, CCK-39 stimulated histamine release with a >15 fold lower potency than did HG-17 or CCK-8 (EC_{50}: 3.56 ± 1.50 nM) and exhibited a lower efficacy than CCK-8 (6.44 ± 0.69% of cell content).

Effects of gastrin and CCK on SLI release

The effects of gastrin and CCK were then examined on SLI release from F1 cells. SLI content represented 0.91 ± 0.046 pmol per 10^6 cells. Basal SLI release (cells without stimulant) was 0.60 ± 0.07% of the total cell content. Gastrin and cholecystokinin enhanced SLI release, maximal within 30 min incubation (not shown). HG-17, CCK-8 and CCK-39 dose-dependently increased SLI release (Fig. 4); CCK-8 and CCK-39 appeared to be the most potent stimulants (Fig. 4a). CCK-8 and CCK-39 exhibited similar potencies and efficacies: EC_{50} values were respectively: 0.058 ± 0.017 nM for CCK-8 and 0.188 ± 0.036 nM for CCK-39; maximal SLI release was 1.38 ± 0.10% of cell content for CCK-8 (10 nM) and 1.32 ± 0.12% of cell content for CCK-39 (1 nM). HG-17 appeared to enhance SLI release with a >50 fold lower potency (EC_{50}: 9.07 ± 3.42 nM) than did CCK (Fig. 4b). Maximal SLI release was observed for a 100 nM concentration and represented 1.11 ± 0.09% of cell content.

DISCUSSION

In this present report, we studied the ability of HG-17, CCK-8 and CCK-39 to induce phosphoinositide breakdown as well as to enhance histamine and somatostatin release from a non-parietal cells population (named "F1 cells"). This cell population,

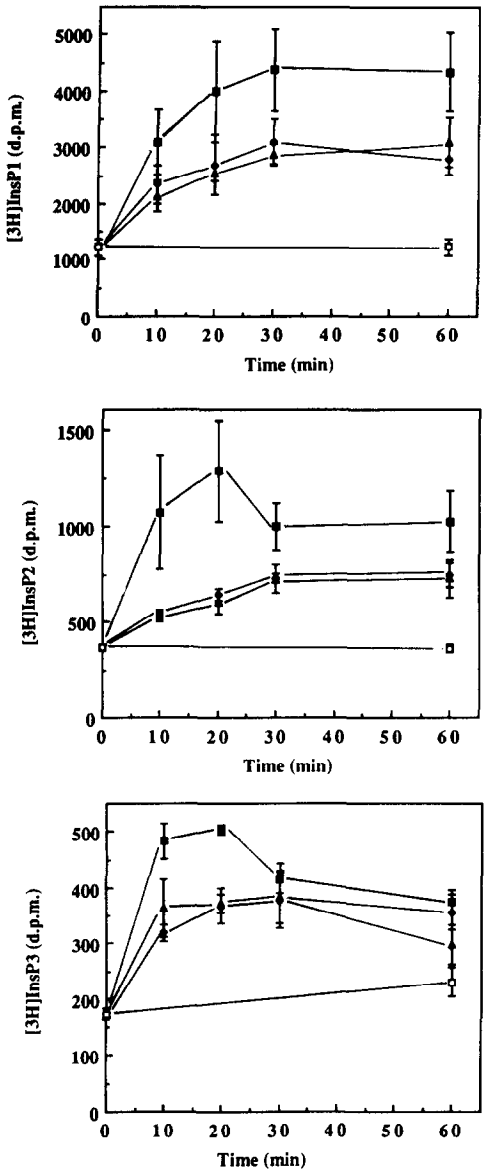

Fig. 2. Time-course of $[^3H]InsP_1$, $[^3H]InsP_2$ and $[^3H]InsP_3$ accumulation in "F1 cells" stimulated by HG-17, CCK-8 and CCK-39. F1 cells were preincubated for 2 hr at 37° with *myo*-[2-^{3}H]inositol followed by a 20 min incubation in the presence of LiCl (10 mM). Cells (2×10^6 per mL) were then incubated with HG-17 (100 nM) (▲), CCK-8 (100 nM) (■) and CCK-39 (100 nM) (◆) for various periods of time. $[^3H]InsP_1$, $[^3H]InsP_2$ and $[^3H]InsP_3$ produced were then quantified as described in Materials and Methods. Results (mean ± SE from four separate experiments) were expressed as the radioactivity (dpm) in the [^{3}H]InsP fraction.

obtained following elutriation of isolated rabbit fundic mucosal cells, mainly contained mucus cells [14] and endocrine cells and was devoid of parietal or chiefs cells. Gastric fundic D-cells and histamine-containing cells were present in this "F1 cells" population.

Effect of gastrin and CCK on InsP production

Gastrin and CCK were shown to stimulate [^{3}H]-InsP production in F1 cells as previously described in pancreatic acini [16] or in parietal cells [5, 15]. HG-17 and CCK-39 induced [^{3}H]InsP accumulation with a potency similar to the previously described [14] affinity for their respective binding sites. CCK-8 caused a more pronounced increase in [^{3}H]InsP accumulation than did CCK-39 or HG-17. In addition, the maximal effect caused by CCK-8 was two times higher than the maximal effects caused by HG-17 or CCK-39; these results were in agreement with the number of CCK-8 binding sites previously observed on these cells (two times higher than that of CCK-39 or HG-17) [14]. Taken together, these observations strongly suggest the existence of two separate receptors mediating the InsP production: a "gastrin-type" receptor which can be activated with a high apparent affinity by HG-17 and CCK-8 because of the structural homology of this peptide with gastrin and a "CCK-type" receptor which can be activated by CCK-8 and CCK-39 with a high apparent affinity. Thus, the two times higher degree of phosphoinositide hydrolysis caused by CCK-8 than by CCK-39 or by gastrin must be the result of the activation with the same potency of phospholipase *c* coupled to both receptor types.

$Ins(1,4,5)P_3$ may play an important role in the mediation of the effects of gastrin and CCK in this cell population, since these peptides induced a large accumulation of $[^3H]InsP_3$ content which is the sum of $[^3H]Ins(1,3,4)P_3$ and $[^3H]Ins(1,4,5)P_3$ accumulation.

Effects of gastrin and CCK on histamine release

The biological function of these "gastrin-type" and "CCK-type" receptors was then investigated. It seems unlikely that both receptors stimulated mucus cells present in F1 cell populations since pentagastrin did not enhance mucus secretion from fundic rabbit mucosal explants [20] and HG-17 unaffected mucus secretion from isolated rat gastric mucosal cells [21].

In agreement with a previous study performed on rabbit gastric glands [9], gastrin and CCK were shown to enhance histamine release from F1 cells. In addition, these present results support the fact that histamine release could be mediated by "gastrin-type" receptors since (i) HG-17 exhibited the highest efficacy and potency to induce histamine release; (ii) in contrast, CCK-39 exhibited a two times lower efficacy and a 15 times lower potency than HG-17; (iii) CCK-8, known to interact with a high affinity on "gastrin-type" receptors [5, 14, 22], was as potent as HG-17 to stimulate histamine release. The fact that HG-17 inhibited [^{125}I]HG-17 binding (IC_{50}: 0.2 ± 0.08 nM) [14], stimulated InsP production and histamine release with the same potency, could suggest a relationship between these three events.

It can be noticed that our results differ from a previous study which evidenced a lack of stimulatory effect of gastrin on histamine release from dog gastric mucosa [23]; but in that case, histamine was mainly found in mast-like cells [24] insensitive to gastrin; conversely, in rabbit or rat gastric mucosa, histamine is stored in enterochromaffin-like cells

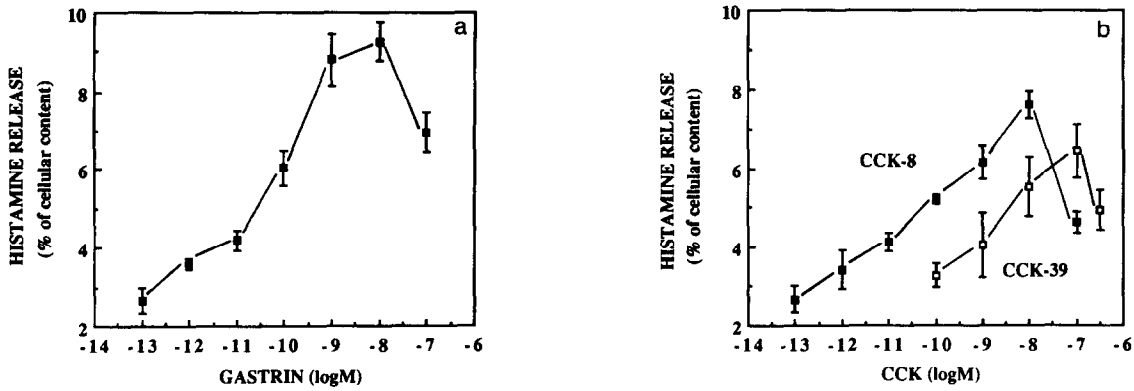

Fig. 3. Effects of HG-17, CCK-8 and CCK-39 on histamine release. Cells (0.2×10^6 per mL) were incubated with the indicated concentrations of (a) HG-17, (b) CCK-8 (■) or CCK-39 (□), at 37° for 30 min. Histamine released in the medium was quantified by radioimmunoassay. Data (mean ± SE from five separate experiments) were expressed as the percentage of histamine cell content (380 ± 55 pmol/10^6 cells).

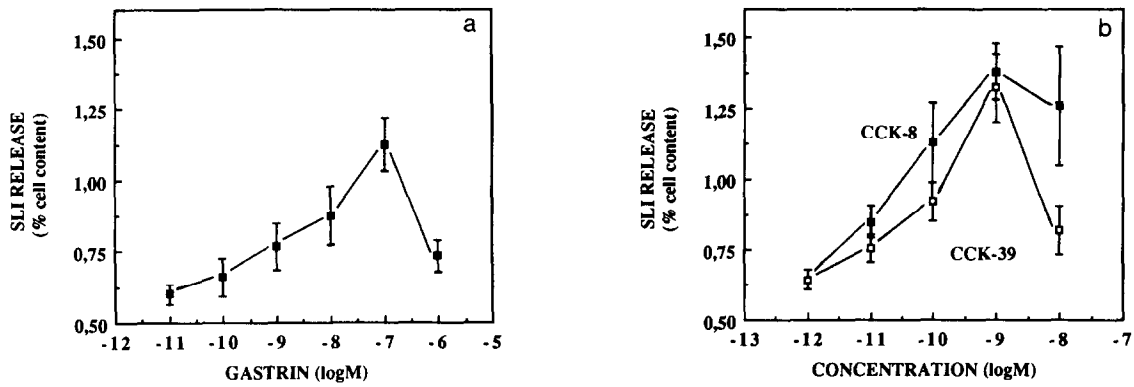

Fig. 4. Effects of HG-17, CCK-8 and CCK-39 on somatostatin-like immunoreactivity (SLI) release. Cells (1×10^6 per mL) were incubated with the indicated concentrations of (a) HG-17; (b) CCK-8 (■) or CCK-39 (□), at 37° for 30 min. SLI released in the medium was quantified by radioimmunoassay. Data (mean ± SE from five to six separate experiments) were expressed as the percentage of total SLI cell content (0.91 ± 0.046 pmol/10^6 cells).

(ECL) [8] sensitive to hormonal stimulation. In human gastric fundic mucosa, Lönroth *et al.* [25, 26] recently evidenced the existence of histamine-containing ECL cells sensitive to pentagastrin. Thus, it seems likely that gastrin-induced histamine release could play an important role in acid secretion stimulated by this hormone.

Effects of gastrin and CCK on SLI release

In agreement with the effects of gastrin and CCK on SLI release from rabbit gastric glands [6] or isolated dog fundic D-cells [7], these hormones were shown to regulate SLI release from F1 cells. In addition, these results suggest the existence of "CCK-type" receptors mediating SLI release: (i) CCK-8 and CCK-39 exhibited the highest potency and efficacy on SLI release; (ii) in contrast, HG-17 enhanced SLI release with a 50 times lower potency and a 2 times lower efficacy than did CCK. It can be noticed that these results are in agreement with those obtained from canine fundic D-cells in which CCK-8 enhanced SLI release with a 2 times higher efficacy than did HG-17 [7].

CCK-39 inhibited [^{125}I]CCK-39 binding (IC_{50}: 0.3 ± 0.1 nM) [14], stimulated [^{3}H]InsP production and SLI release in the same range of potency suggesting a possible relationship between these three events. In this way, Chiba *et al.* reported a strict correlation between the inhibition of [^{125}I]-CCK-8 binding, phosphoinositide breakdown and SLI release induced by CCK-8 in canine fundic D-cells [8].

It is of some note that an apparent inhibitory effect was observed either on [^{3}H]InsP production or on SLI release induced by high concentration of CCK-8 or CCK-39; this effect could be rather due to a desensitization phenomenon occurring at high agonist concentration than to the stimulation of low

affinity receptor sites as proposed for the reduction of CCK-8 evoked amylase release from pancreatic acini [27], since a single class of CCK-8 receptor sites was found on these non parietal cells in binding experiments [14]. However, the use of highly enriched fundic D-cell population could allow us to confirm such an hypothesis.

In conclusion, we demonstrated the existence of "gastrin-type" and "CCK-type" receptors related to phosphoinositide hydrolysis in non-parietal cells isolated from rabbit fundic mucosa. Furthermore, our results strongly suggest that "gastrin-type" receptors could mediate the release of histamine and "CCK-type" receptors could mediate the release of somatostatin. However, the use of selective antagonists which discriminate between "gastrin/CCK-B-type" or "CCK-A-type" receptors made it possible to establish the involvement of these receptor-types in these biochemical and biological processes.

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