Extracellular Calcium and Cholinergic Stimulation of Isolated Canine Parietal Cells

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ABSTRACT The role of calcium gating in cholinergic stimulation of the function of parietal cells was studied using cells isolated from canine fundic mucosa by treatment with collagenase and EDTA and enriched by velocity separation in an elutriator rotor. Monitoring the accumulation of [14C]aminopyrine as an index of parietal cell response, stimulation by carbachol, but not by histamine, was highly dependent upon the concentration of extracellular calcium. Incubation of parietal cells in 0.1 mM calcium, rather than the usual 1.8-mM concentration, reduced the response to 100 μM carbachol by 92±2%, whereas histamine stimulation was impaired by 28±5%. A similar reduction in extracellular calcium suppressed the response to gastrin (100 nM) by 67±7%. The impairment of cholinergic stimulation found at low extracellular calcium concentrations was rapidly reversed with the readdition of calcium. Lanthanum, which blocks calcium movement across membranes, caused a similar pattern of effects on secretagogue stimulation of aminopyrine accumulation, with 100 μM lanthanum suppressing carbachol stimulation by 83±2%. This concentration of lanthanum suppressed gastrin stimulation by 40±7% and histamine stimulation by only 12±9%.

Carbachol, but not histamine nor gastrin, stimulated 45Ca++ uptake. The magnitude of carbachol-stimulated calcium uptake correlated with the parietal cell content of the fractions examined (r = 0.88), and was dose responsive over carbachol concentrations from 1 μM to 1 mM. Atropine (100 nM) caused surmountable inhibition, and these effects of carbachol and atropine on calcium uptake correlated with their effects on oxygen consumption (r = 0.93) and [14C]-aminopyrine accumulation (r = 0.90). Cells preloaded with 45Ca++ lost cellular calcium in a time-dependent fashion; however, this rate of egress was not accelerated by treatment with histamine, gastrin, or carbachol, thus failing to implicate mobilization of intracellular calcium as primary mechanism for activation of parietal cell function. These data indicate a close link between stimulation of parietal cell function and enhancement of calcium influx by cholinergic agents.

INTRODUCTION

Increases in cytosol calcium couple cell activation to cell response in a variety of cell types, with chemical transmitters enhancing either the influx of extracellular calcium or the release of calcium from intracellular binding sites to produce the rises in cytosol calcium concentration (2–6). Heart and skeletal muscle exemplify these diverse sources of calcium, with activation in heart muscle involving enhanced influx of extracellular calcium and activation in skeletal muscle triggering calcium release from sarcoplasmic reticulum. With removal of extracellular calcium, contractions immediately cease in heart muscle, but continue for hours in skeletal muscle (5).

In tissues where cell activation is linked to enhanced influx of calcium, the magnitude of cell response will be dependent upon the extracellular calcium concentration (5, 7–9). Lanthanum provides another tool for studying the role of calcium, since low concentrations of this trivalent cation impair both calcium influx and efflux across the plasma membrane and displace surface-bound calcium (10). Lastly, stimulant effects on calcium influx can be directly tested using 45Ca++ (2–4, 9, 11). Study of the role of mobilization of intracellular calcium in cell activation requires other approaches, such as monitoring the egress of 45Ca++ from preloaded cells or use of dye probes which will shift fluorescence with alteration of calcium concentrations (2–4, 6, 12).

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In previous studies with isolated canine parietal cells, histamine, cholinergic agents, and gastrin caused cell activation as evidenced by changes such as increased oxygen consumption (13) and the accumulation of \(^{14}\)C]aminopyrine (14). Activation produced by histamine, but not by cholinergic agents or gastrin, was linked to increased production of cyclic AMP (15). The present work examines the role of the calcium in the parietal cell response to stimulation. The dependence of cell activation upon the concentration of extracellular calcium was assessed by monitoring the accumulation of \(^{14}\)C]aminopyrine (AP) as an index of parietal cell response, a technique developed by Berglindh and co-workers in their studies with isolated rabbit gastric glands (16). AP concentrates within the tubulovesicles and secretory canaliculi of the parietal cell by pH partition, with the amount accumulating reflecting the quantity of acid sequestered within the parietal cell rather than the actual quantity of acid secreted (14). Additionally, the effects of lanthanum on parietal cell response to stimulation were assessed. Finally, alterations in the rate of \(^{45}\)Ca\(^{++}\) influx and egress with cell activation by histamine, carbachol, and gastrin, alone and in combination, were measured.

**METHODS**

Cells were dispersed from canine fundic mucosa by sequential treatment with crude collagenase and EDTA with the parietal cells enriched to a mean content of 50±3% using a Beckman elutriator rotor (Beckman Instruments, Fullerton, Calif.) (13, 14, 17). AP accumulation was determined on cell suspensions incubated for 20 min in the presence of 0.05 μCi/ml (3 μM) of \(^{14}\)C]aminopyrine, after which triplicate samples of each suspension were sedimented and the radioactivity in the pellet determined [11]. The quantity of accumulated AP was expressed as the AP accumulation ratio, the ratio of the AP concentration in the parietal cells to that in the medium (14). With the exception of the prolonged \(^{45}\)Ca\(^{++}\) uptake studies and the studies with lanthanum, the AP experiments were done using Earles’ balanced salt solution (purchased from Gibco Laboratories, Grand Island, N. Y., without Ca\(^{++}\) or Mg\(^{++}\)). Hepes (10 mM) and 0.1% bovine serum albumin (BSA) were added (pH 7.4); Ca\(^{++}\) was present in the concentrations indicated in the figure legends, and Mg\(^{++}\) was present at 0.8 mM, unless otherwise noted. For studies in which the calcium concentration was varied, cells were washed twice in the medium to be used. The AP incubation was started within 20 min of this final resuspension. The studies with lanthanum were done in a buffer formulated without PO\(_4\), SO\(_4\), or HCO\(_3\) (10), so as to avoid precipitation of the lanthanum (in mM, NaCl, 133; KCl, 3.6; CaCl\(_2\), 1.8; MgCl\(_2\), 0.3; glucose 16.0), and Hepes, 10). These methods and the materials used have been reported in detail in the indicated references. As in the previous studies (14), occasional preparations of canine parietal cells showed no AP accumulation in response to stimulation (less than two- to threefold increase over basal); 7 of 41 preparations were dropped using this criteria.

\(^{45}\)Ca\(^{++}\) uptake was studied on cells suspended in Earles’ buffer with 1.8 mM Ca\(^{++}\) and 0.8 mM Mg\(^{++}\). After an initial 10 min incubation at 37°C, 0.5 μCi/ml of \(^{45}\)Ca\(^{++}\) (0.5 μM) and the indicated stimulants were added. Triplicate 0.5 ml samples of each cell suspension were layered over 0.75 ml of 12% BSA in 80% Hanks’ salt solution in 1.5-ml microfuge tubes and centrifuged for 1 min at 8,700 × g. The supernate was aspirated, 1 ml of Hanks’ solution (0.1% BSA) was added without resuspension of the pellet, and the tubes were centrifuged again for 1 min. After aspirating, the tips were excised and submerged overnight under 0.5 ml of either tissue solubilizer (NCS, Amersham Corp., Evanston, Ill.) or water. ACS (8 ml) was then added and the radioactivity determined in a LKB scintillation counter (LKB Instruments, Inc., Rockville, Md.). The quantity of \(^{45}\)Ca\(^{++}\) present in the trapped extracellular volume in the cell pellet was estimated from the proportion of \(^{14}\)C]mannotitol retained by similar cell pellets or by adding 5 mM EDTA to cells suspensions followed by addition of \(^{45}\)Ca\(^{++}\). The counts trapped in the presence of EDTA were ~150 cpm for a cell pellet with 1.5 × 10\(^6\) cells, and these counts were subtracted. These latter counts represented <10% of \(^{45}\)Ca\(^{++}\) accumulated in the presence of carbachol (100 μM) at 10 min in most experiments. Data were expressed in nanomoles of calcium taken up per 10\(^6\) cells. \(^{45}\)Ca\(^{++}\) (24.1 μCi/μg) was purchased from New England Nuclear, Boston, Mass. Total cellular calcium determined on sonicated cell pellets using a Perkin-Elmer flame photometer (Perkin-Elmer Corp., Norwalk, Conn.) was 18±3 nmol/10\(^6\) cells (n = 3), with correction for trapped medium made on the basis of the \(^{14}\)H]mannotitol content of the pellets.

The mean of the triplicate samples from one or two cell suspensions was calculated and used for Student’s t test analyses, with n equal to the number of cell preparations. Standard errors are depicted in the figures and given following the ± signs in the text, table, and figure legends. For the cell separation experiments, correlation coefficients were calculated using simple linear regression analyses and combined using the Fisher “z” transformation (18).

**RESULTS**

The effects of the extracellular calcium concentration on AP accumulation. Cholinergic-stimulated AP accumulation was markedly dependent upon the extracellular calcium concentration. The response to 100 μM carbachol in 0.1 mM calcium was 7.9±1.6% (n = 15, P < 0.005) of that found in 1.8 mM calcium (Fig. 1B). The response to carbachol showed a high degree of dependence on the calcium concentration in the medium, as evidenced by the steep slope (50±2.8) and correlation coefficient of 0.90 (P < 0.005) found in the linear regression analysis.\(^\dagger\) The impairment of  

\(\dagger\) Correlations between the effects of stimulants on AP accumulation and extracellular calcium concentration were done on the data from the 10 cell preparations graphed in Fig. 1. AP accumulation was normalized as the percentage of response found for that treatment group in 1.8 mM calcium. The data were then fit by simple linear regression analysis to the expression y = a + bx. The correlation coefficient for the relationship was derived from the data for the separate cell preparations using the Fisher “z” transformation (18).
carbachol stimulation by a lowered extracellular calcium concentrations was not reversed with carbachol concentrations up to 1 mM (Fig. 2). In contrast, the response to histamine was minimally suppressed by removal of extracellular calcium; the response to 10 μM histamine in 0.1 mM calcium was 72.3±4.6% (n = 15, P < 0.05) of that found in 1.8 mM calcium (Fig. 1A). Reflecting this minimal dependency upon extracellular calcium, the slope for the linear regression line relating histamine-stimulated AP accumulation and the calcium concentration was shallow (18.6±5.0) and of borderline statistical significance (r = 0.70, P = 0.05). Only a small change was found in the dose response relation for histamine at different calcium concentrations (Fig. 2). Corresponding to the marked effect of calcium removal on cholinergic stimulation, the potentiated response to the combination of histamine and carbachol was markedly impaired at low calcium concentrations, with the response to the combination in 0.1 mM calcium equivalent to that found with histamine alone (Fig. 1A).

The small response to gastrin was also impaired at low calcium concentrations, with gastrin stimulation in 0.1 mM calcium 32.8±7.3% (n = 12, P < 0.01) of that found in 1.8 mM calcium (Fig. 1B). The slope for the line relating gastrin-stimulated AP accumulation and extracellular calcium concentration was intermediate between that found for carbachol and for histamine (34.3±7.3, r = 0.88, P < 0.05). Reflecting this moderate dependency of gastrin responsiveness upon extracellular calcium, the potentiated response to histamine and gastrin was also impaired at low calcium concentrations (Fig. 1A)

Basal uptake of AP was not altered by concentrations of calcium from 0.1 to 5.0 mM, as long as the magnesium concentration was held constant (Fig. 1, Table I). When the calcium concentration was 1.8 or 5.0 mM, the removal of magnesium produced an increase in basal AP accumulation (Table I). In contrast, basal AP accumulation was suppressed when the magnesium concentration was increased to 5.0 mM (Table I).

The impairment of the carbachol-stimulated AP accumulation at low calcium concentrations was rapidly reversible with restoration of extra-cellular calcium concentration. For these studies, cells were incubated for an initial 20-min period in a calcium concentration of either 0.1 or 1.8 mM. After this initial period, carbachol and AP were simultaneously added and the calcium restored to a concentration of 1.8 mM in one of two groups initially in 0.1 mM calcium. The accumulation of AP was measured over the next 20 min. Cells that remained in low calcium had the expected impaired response to carbachol (Fig. 3). When the calcium was restored to normal following an initial incubation in low calcium, the time course for carbachol-stimulated AP accumulation was similar to that
found for the cells incubated only in normal calcium (Fig. 3).

The effects of lanthanum on stimulated AP accumulation. In the presence of 100 μM lanthanum, the response to 10 μM carbachol was impaired by 83.4±1.5% (n = 8, P < 0.005), whereas the response to 10 μM histamine was reduced by only 12.0±8.8% (n = 8, 0.05 < P < 0.1) (Fig. 4). Lanthanum inhibition of carbachol was not surmounted at concentrations of carbachol up to 1 mM (Fig. 4). Concentrations of lanthanum between 0.1 μM and 1 mM inhibited the response to 100 μM carbachol, with 50% inhibition found with a lanthanum concentration of about 1 μM (Fig. 5). Lanthanum (100 μM) caused a 40.6±6.5% (n = 8, P < 0.05) impairment of the response to 100 nM gastrin and a 47.7±6.0% (n = 8, P = 0.01) impairment of the response to 10 nM gastrin (Fig. 4).

\[ ^{45}\text{Ca}^{++} \text{uptake}. \] Carbachol significantly increased \[ ^{45}\text{Ca}^{++} \text{uptake} \] by parietal cell enriched fractions (Fig. 6A). An enhanced accumulation of calcium was also evident after pelleting the cells through an albumin solution with 5 mM EDTA added to strip off the rapidly exchangeable calcium (Fig. 7). Cholinergic

### Table I

Effects of Calcium and Magnesium on Basal AP Accumulation

<table>
<thead>
<tr>
<th>Concentrations of calcium and magnesium during incubation</th>
<th>AP accumulation ratios</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Ca(^{++})], mM</td>
<td>1.8</td>
</tr>
<tr>
<td>[Mg(^{++})], mM</td>
<td>1.2</td>
</tr>
<tr>
<td>Treatment</td>
<td>Basal*</td>
</tr>
<tr>
<td></td>
<td>2.2±0.5</td>
</tr>
<tr>
<td></td>
<td>1.8±0.5</td>
</tr>
<tr>
<td></td>
<td>6.0±2.0</td>
</tr>
<tr>
<td></td>
<td>8.9±3.5</td>
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</table>

* Cells were incubated in Earle’s solution at the Ca\(^{++}\) and Mg\(^{++}\) concentrations indicated in the first two rows for a 20-min period, during which AP accumulation was determined as described in Methods. The AP ratios, from six separate preparations, for untreated cells and for cells treated with carbachol and histamine are indicated in the columns under the concentrations of Mg\(^{++}\) and Ca\(^{++}\) present during the incubations. The counts trapped in the presence of 0.1 mM dinatriphenol were subtracted.

1 Statistical significance of the difference by paired t test (P < 0.05) from cells incubated in 1.8 mM Ca\(^{++}\) and 1.2 mM Mg\(^{++}\).
enhancement of the rate of 45Ca++ uptake was evident over the first 30 min of incubation, with the rate of increase of the cell content of 45Ca++ during more prolonged incubation not different from that found with untreated cells (Fig. 7). During this 3-h period, 10–20% of the cellular calcium was exchanged (based upon an estimate of 18 nmol of total calcium/10⁶ cells); however, the cells did not reach a steady-state level of 45Ca++ accumulation during this period (Fig. 7). Carbachol stimulation of calcium uptake was dose dependent over a concentration range of carbachol from 1 μM to 1 mM (Fig. 8). Atropine (100 nM) produced a right-ward shift of the dose-response relationship for carbachol (Fig. 8). Carbachol stimulation of calcium uptake correlated with its effects on oxygen consumption (r = 0.93, Fig. 8), and on AP accumulation (r = 0.90, data not illustrated). In contrast to these effects of carbachol, neither histamine nor gastrin increased calcium uptake (Fig. 6B). The addition of histamine to carbachol did not significantly increase 45Ca++ uptake above that found with carbachol alone (Fig. 9). The combination of histamine and gastrin did not alter 45Ca++ uptake above that found with untreated cells (Fig. 9). Furthermore, the combination of the phosphodiesterase inhibitor isobutylmethylxanthine and 10 μM histamine did not alter the rate of 45Ca++ uptake found with untreated cells (P > 0.2, n = 3 for 3, 5, and 10 min of incubation).

The above studies were done with fractions enriched to a parietal cell content of ~50%. To establish that parietal cells accounted for the enhanced 45Ca++ uptake found with stimulation by carbachol, fractions of variable parietal cell content obtained with the elutriator rotor were examined. Carbachol failed to stimulate 45Ca++ uptake in the parietal cell-depleted fractions, and in the remaining fractions the magnitude of the carbachol-stimulated uptake correlated with the parietal cell content (r = 0.88, Fig. 10).

**The effects of stimulants on mobilization of intracellular calcium.** Evidence that gastric secretagogues activate parietal cell function by mobilizing intracellular calcium was sought by studying calcium egress from cells previously incubated in 45Ca++ containing medium. Several experimental protocols were used. When cells were incubated in a 45Ca++-containing medium for 1 h and then treated with gastrin (100 nM), histamine (10 μM), or carbachol (100 μM), no statistically
significant alterations in the cellular content of radioactivity were detected, although there was a trend suggesting an increased cellular content of \( ^{45}\text{Ca}^{++} \) during carbachol treatment \((n = 4, P > 0.1, \text{data not illustrated})\). Centrifuging the cells through EDTA to remove rapidly exchangeable \( ^{45}\text{Ca}^{++} \) did not alter these latter findings. After preloading cells with \( ^{45}\text{Ca}^{++} \) in a similar fashion, the addition of 5 mM EDTA to the incubation medium produced a rapid fall in cellular calcium, the rate of which was not altered by treatment with the same stimulants \((n = 5, P > 0.1, \text{data not illustrated})\). Cells preloaded with \( ^{45}\text{Ca}^{++} \) and then rapidly centrifuged twice to remove extracellular \( ^{45}\text{Ca}^{++} \) lost their cellular radioactivity in a time-dependent fashion, but this rate of calcium egress was not accelerated by treatment with stimulants (Fig. 11).

**DISCUSSION**

The effect of histamine, carbachol, and gastrin on parietal cell function were each dependent to some degree upon the concentration of extracellular calcium.
However, carbachol-stimulated AP accumulation was markedly impaired with reduction of the calcium concentration from 1.8 to 0.1 mM, while only modest impairment of histamine-stimulated parietal cell function occurred with this reduction. This degree of calcium removal produced an intermediate impairment of the small response to gastrin. The decrease in parietal cell responsiveness to cholinergic stimulation found under these conditions was reversed completely by restoration of the calcium concentration to normal. This recovery of cholinergic responsiveness was rapid; the time-course for carbachol stimulation of AP accumulation in the period immediately following restoration of the calcium concentration was not different from that found for cells that had remained in normal calcium.

Studies with lanthanum provided further evidence for the above pattern of dependency of secretagogue action upon extracellular calcium. Treatment of parietal cells with lanthanum caused marked suppression of the response to carbachol, intermediate impairment of the response to gastrin, and no alteration of histamine-stimulated parietal cell function. Lanthanum does not permeate plasma membranes of intact cells, and therefore probably acts at surface sites to block calcium movement across the plasma membrane (10). The present data therefore indicate that cholinergic stimulation requires the presence of a rapidly exchangeable calcium pool at a lanthanum-accessible site, presumably on the membrane of the parietal cell.

In several cell types, including heart muscle (5), chromaffin cells from the adrenal medulla (7), mast cells (9), and beta cells from the pancreatic islets (8), cell activation by certain chemical transmitters requires the presence of extracellular calcium and is associated with an enhanced influx of calcium upon activation (2–4, 11, 19). The possibility that activation of parietal cell function involved enhanced calcium influx, or calcium gating, was evaluated using \(^{45}\text{Ca}^{++}\). Carbachol, but not gastrin or histamine, enhanced calcium uptake during the 30 min following treatment. This cholinergic effect on calcium uptake occurred over a similar time period in which stimulation of AP accumulation was found. Furthermore, the dose response for cholinergic stimulation of calcium uptake correlated with effects on oxygen consumption and AP accumulation. Atropine in low concentrations produced surmountable, rightward displacement of the carbachol dose-response relationship, consistent with specific action at a muscarinic receptor. In cell separation experiments, the magnitude of the carbachol-stimulated calcium uptake was proportional to the parietal cell content, but not the pepsinogen content, of the various fractions, thus indicating that parietal cells accounted for the observed changes in calcium uptake with stimulation. These data do not exclude changes in calcium uptake occurring with cholinergic stimulation in other cell types; the present techniques simply do not detect such changes. The findings of an accelerated rate of calcium uptake 1 min following treatment with carbachol, at a time when the cellular content of \(^{45}\text{Ca}^{++}\) was low, and the failure to find an alteration in calcium egress from cells preloaded with \(^{45}\text{Ca}^{++}\) (vide infra) support the view that cholinergic agents, but not histamine or gastrin, enhance calcium influx into parietal cells. This conclusion does not account for the finding that histamine stimulation of AP accumulation was impaired with removal of extracellular calcium. However, this impairment was only minimal, and histamine stimulation was neither blocked by lanthanum nor associated with enhanced uptake or egress of calcium across the plasma membrane. The minimal dependency of histamine action upon extracellular calcium evident in the present studies may reflect diminution of intracellular

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**Diagram Description:**

The diagram (Figure 11) illustrates the effect of various treatments on the initial calcium content in preloaded cells. The graph shows the percentage initial \(^{45}\text{Ca}^{++}\) content over time for different conditions: control, carbachol (C), gastrin (G), histamine (H), IMX, and the combination of carbachol and IMX (G+H+IMX). The data are presented with error bars indicating the variability across different samples. The x-axis represents time in minutes ranging from 0 to 20, while the y-axis shows the percentage of initial calcium content from 0 to 100. The treatments show varying degrees of calcium content reduction over time, suggesting different degrees of calcium uptake or release.
calcium pools with calcium removal, with subsequent impairment of a calcium-dependent, rate-limiting step(s) in the parietal cell response to histamine.

Histamine and cholinergic agents trigger cell activation by distinct effector mechanisms, with histamine action linked to enhanced production of cyclic AMP (15) and cholinergic stimulation associated with enhanced calcium uptake. In contrast, gastrin action is clearly linked neither to enhanced cyclic AMP production (15) nor enhanced calcium uptake, although the moderate dependency of gastrin action upon extracellular calcium and impairment by lanthanum suggest a role for calcium in gastrin activation of cell function. It is possible that the failure to find gastrin effects on calcium uptake or cyclic AMP production may reflect a somewhat impaired response of canine parietal cells isolated by the present techniques to gastrin stimulation (13, 14). Alternatively, gastrin may act by yet another mechanism, such as mobilization of calcium from intracellular stores. In cell types, such as those from skeletal muscle (5), pancreatic acinae (12, 20), renal tubules (6), and insect salivary glands (21), activation by stimulants has been linked to release of calcium from intracellular binding sites. In these instances, cell activation does not show the same degree of immediate dependency upon changes in extracellular calcium concentration, although depletion of cellular calcium can impair responsiveness (12, 22). In the present study no evidence was found to link histamine, carbachol, or gastrin activation of cell function to enhanced egress of intracellular calcium. Even though these cell preparations responded to stimulation as evidenced by enhanced aminopyrine accumulation, negative data with isolated cells require cautious interpretation; the role of intracellular calcium in the activation of parietal cell function requires further study. Furthermore, with this preparation of cells, enhanced calcium uptake was detected when 45Ca++ and carbachol were added simultaneously, but only a trend suggesting increased uptake was found when carbachol was added 1 h after the 45Ca++. Whether this apparent discrepancy and the failure of cellular 45Ca++ accumulation to reach a steady state in a 3-h period reflect impaired cell function and viability after more prolonged incubation or reflect some other factor remains to be determined.

The role of calcium in the regulation of acid secretion in vivo has not been fully clarified. Calcium by intravenous infusion stimulates acid secretion (23, 24), an effect antagonized by magnesium (23, 25). This in vivo effect of calcium may be directly on oxyntic tissue in that antrectomy fails to abolish it (24), although this point is in controversy (26). These observations are consistent with the present findings with isolated parietal cells that calcium enhanced basal AP accumulation and that this effect was antagonized by magnesium. The role of calcium in secretagogue action in vivo is difficult to study, since one cannot selectively remove the calcium pool available to the parietal cell. Infusion of EDTA reduces the response to all stimulants, an effect which is difficult to interpret (27). Intravenous infusions of calcium enhances the response to pentagastrin and to cholinergic stimulation (25, 27), but these observations may be explained by mechanisms other than calcium involvement in parietal cell activation by secretagogues.

Potentiating interactions have been found between histamine and both gastrin and cholinomimetic agents, but not directly between gastrin and carbachol in their actions on the function of isolated canine parietal cells (28, 29). The existence of these potentiating interactions may explain the interdependency between secretagogues in their action on acid secretion in vivo (28). With isolated canine parietal cells, potentiating interactions occur with the combination of a cyclic AMP-dependent effector mechanism (histamine) and a calcium-dependent effector mechanism (carbachol and possibly gastrin), as was noted for pancreatic acinar cells (30). The mechanisms underlying these potentiating interactions are not known, and the data available at present only serve to exclude a few possibilities. Adding gastrin or carbachol to histamine did not alter the magnitude of histamine-stimulated cyclic AMP production (15), and adding histamine to carbachol failed to amplify cholinergic-stimulated calcium influx (present data), with these findings indicating that amplification occurs at a step after initial cell activation. New approaches will be necessary to elucidate the mechanisms underlying the potentiating interactions between secretagogues that appear to be a major regulating factor in parietal cell function in vivo.

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Calcium Dependence of Cholinergic-stimulated Parietal Cell Function


