Bile Acid Accumulation in Gastric Mucosal Cells (43272)

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Abstract. **Bile acids are one of the components of the gastric contents capable of disrupting the mucosal barrier to diffusion. The mechanism by which bile acids can damage the gastric epithelium is not completely understood. Several studies have emphasized mucosal lipid solubilization by bile acids in the pathogenesis of mucosal injury. Bile acid entry into gastric mucosal cells may be a critical and early step in the genesis of mucosal injury, but this possibility has not yet been investigated. The present study was designed to explore the interaction of bile acids with dispersed gastric mucosal cells isolated from the rabbit and guinea pig stomach. Results showed that both glycocholic and deoxycholic acid rapidly associated with the gastric cells and reached a steady state concentration by 30 min. Glycocholic acid accumulated in the cells to a concentration approximately eight times greater than that in the surrounding medium. The amount of bile acid associated with the cells was greater at an acidic than at a neutral pH, and was a function of the concentration of both the cells and the bile acid. The process did not require cellular energy, was nonsaturable, and was not species specific. Experiments with ^{86}Rb, a cytoplasmic marker, revealed that approximately one half of the cellular glycocholic acid was associated with the cytoplasmic compartment and the rest with the membranes. These findings are consistent with a combination of intracellular entrapment of the bile acids due to intracellular ionization and bile acid binding to cellular membrane components being the mechanisms by which bile acids accumulate in cells. Acid-driven bile acid accumulation may explain how relatively low luminal concentrations of bile acid can be damaging to the gastrointestinal mucosa.** [P.S.E.B.M. 1991, Vol 197]

Bile acids have been implicated as a cause of gastritis, stress gastric ulceration, and chronic gastric ulcer (1–6). The mechanism by which bile acids interact with the mucosa to injure it is not well understood. One possibility is that bile acids damage mucosal cells by dissolving lipids out of mucosal cell membranes, thereby acting as detergents within the bowel lumen without necessarily entering the cells. Support for this mechanism comes from studies in dogs with Heidenhain pouches in which mucosal injury by bile salts was correlated with cholesterol release into the lumen (7). This theory was also corroborated by studies in which bile acids were shown to release cholesterol and phospholipids from the rat stomach (8) and from dispersed gastric mucosal cells (9).

In conjunction with the above, or as an alternative possibility, bile acids may first enter the mucosa and cause some intracellular disturbance that results in altered mucosal function. For example, in experimental esophagitis, bile acid entry and accumulation in the mucosa have been correlated with bile acid-mediated disruption of the mucosal barrier (10). In fact, the intramucosal concentration of bile acids in the esophagus can exceed the luminal concentration by as much as 7-fold (11). Moreover, bile acid entry into the esophageal mucosa has been shown to precede mucosal injury (12), and bile acids can cause barrier disruption without dissolving mucosal lipid (13). These observations indicate that, while lipid solubilization does occur under certain conditions during bile acid injury of the gastrointestinal mucosa, bile acid entry into the mucosa also appears to play an important role in the process.

The current experiments were designed to explore the possibility that mechanisms similar to those in the esophagus are operative in the gastric mucosa. The rate

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of association of bile acids with isolated gastric mucosal cells and the cellular bile acid concentrations were measured. When the bile acids were found to accumulate in the cells, experiments were performed to characterize the process and to localize the bile acid within the cells.

Materials and Methods

New Zealand White rabbits (1–2 kg) and male Hartley guinea pigs (200–250 g) were obtained from Camm Research Center, Wayne, NJ. Glycocholic acid was from Calbiochem, La Jolla, CA. [^{14}C]-Glycocholic acid (53 mCi/mmole), [^{3}H]-deoxycholic acid (4 Ci/mmole), and ^{86}RbCl (50 Ci/g) were from New England Nuclear Corp., Boston, MA. Buffer solutions were prepared in our laboratory with the following compositions: (i) *pH 7 buffer*—132.4 m*M* NaCl, 5.4 m*M* KCl, 5.0 m*M* Na_2HPO_4, 1.0 m*M* NaH_2PO_4, 1.2 m*M* $MgSO_4$, 1.0 m*M* $CaCl_2$, 11.0 m*M* glucose, 2 mg/ml of bovine albumin, and 0.001% (w/v) phenol red (pH 7.0); (ii) *pH 6 and pH 7.5 buffers*—same as pH 7 buffer, except that the pH was adjusted with HCl or NaOH; (iii) *pH 5 buffer*—same as pH 7 buffer, except that the phosphate was replaced with 15 m*M* acetate, and the pH was adjusted to 5.0; (iv) *pH 7 Hanks' buffer*—137 m*M* NaCl, 5.37 m*M* KCl, 1.26 m*M* $CaCl_2$, 0.47 m*M* $MgCl_2$, 0.41 m*M* $MgSO_4$, 0.34 m*M* Na_2HPO_4, 0.44 m*M* KH_2PO_4, 2.0 m*M* glutamine, 5.55 m*M* glucose, 15 m*M* $NaHCO_3$, 15 m*M* Hepes (pH 7.0), 0.001% (w/v) phenol red, and BME vitamin solution (Gibco, St. Lawrence, MA); (v) pH 5 Hanks' buffer—same as pH 7 Hanks' buffer, except that the bicarbonate was replaced with 15 m*M* acetate, and the pH was adjusted to 5.0.

Preparation of Gastric Cells. Dispersed rabbit gastric cells were prepared from rabbit gastric glands (14), as described in detail elsewhere (15, 16). In short, gastric glands were harvested from rabbit gastric mucosa, which was excised after high pressure aortic injection. After the glands were prepared, they were washed once with Ca^{2+}-free pH 7 buffer and incubated with 1 m*M* EGTA for 10 min at 37°C. They were washed twice with pH 7 buffer containing 0.1 m*M* Ca^{2+}, then resuspended in pH 7 buffer containing 0.1% collagenase with 0.2% bovine serum albumin. After a 20-min incubation at 37°C with gentle stirring, an equal volume of fresh pH 7 buffer was added and the suspension, containing mostly single cells, was passed through a nylon mesh to remove cell clumps. The cells were collected by centrifugation (100*g* for 5 min) and resuspended in the appropriate buffer containing 1 m*M* Ca^{2+}. The viability of the isolated cells under those conditions was 97 ± 3% (mean ± 1 SE), as measured by the trypan blue exclusion test.

Guinea pig gastric cells were prepared as described elsewhere (17), with the modifications that the passage of the mucosal fragments through the stainless steel mesh was omitted and the removal of the mucosa was carried out at 22°C. Briefly, the fundic mucosa was scraped, washed once, and incubated at 37°C in pH 7 Hank's buffer containing 0.1% w/v bovine serum albumin and 10 m*M* EDTA. After 10 min, the digestion solution was replaced with a fresh one containing no EDTA. Incubation for 20 min was continued with intermittent mechanical passage of the mucosal fragments through a pasteur pipette. At the end of this and two subsequent identical incubation periods, mucosal fragments were allowed to settle and the supernatant, containing the single cells, was collected. The supernatants from the second and third incubations were pooled and passed through a nylon mesh. The cells were collected by centrifugation at 100*g* for 10 min, washed twice, and rsuspended in pH 7 Hank's buffer. The viability of the isolated cells under those conditions was 97 ± 3% (mean ± SE) as measured by the trypan blue exclusion test.

Measurement of Bile Acid Association with Gastric Cells. The amount of glycocholic acid (GC) associated with the dispersed cells was measured by our centrifugation technique (18). Rabbit gastric cells were incubated in 0.5 ml of pH 7 or pH 5 buffer containing 0.1–0.2 μCi of [^{14}C]-GC with various concentrations of GC at 37°C. At the end of the incubation, the cells were washed twice by resuspension in 10 ml of the same incubation solution, but with no radioactivity. The cells were then centrifuged (250*g* for 1 min) and dissolved in 1 ml of 1% (v/v) Triton X-100. The radioactivity of the pellet was determined by scintillation counting. The amount of GC associated with the cells was calculated from the amount of radioactivity in the pellet and the specific radioactivity of GC in the cell suspension. This technique does not allow distinction between GC association with viable or nonviable cells. The result was expressed as a percentage of the total GC present in the incubation suspension for that particular experiment. The viability of the gastric cells at pH 7.0 or 7.5 in the presence of relatively low concentrations of bile acids was the same as without bile acids (see Fig. 5). Because at pH 7 there was no time-dependent association of GC with the cells, the net cell-associated GC at pH 5 was calculated by subtracting the cell-associated radioactivity at pH 7.

Compartmental Distribution of Cell-Associated GC. Rabbit gastric cells were suspended in pH 7 buffer, and the buffer was divided into two equal portions. Each portion was centrifuged (100*g* for 1 min) and resuspended in pH 7 or pH 5 buffer containing 0.1–0.2 μCi of [^{14}C]-GC and 0.1 m*M* GC. The cells were incubated for 20 min to allow the GC to interact with the cells. Incubations were stopped by adding 20 vol of the same iced isotope-free pH 7 buffer or iced distilled water. The suspension was then centrifuged at 10,000*g* for 10 min and the pellets were dissolved in 1% Triton

X-100. Centrifugation will sediment most cellular components such as membranes and major organelles. Radioactivity of the pellets was determined by scintillation counting. Values were corrected for nonspecific binding by subtracting the amount of [^{14}C]-GC associated with the cells after a 10-sec incubation (i.e., zero time).

The cellular distribution of GC was estimated by comparing the amount of ^{86}Rb with the amount of [^{14}C]-GC in the pellet following hypotonic lysis. It was assumed that the GC released into the supernatant upon lysis originated from the cytosol of viable cells. Similarly, the GC remaining in the pellet after lysis represented association of GC with the cytosol of unlysed, intact cells, and with the membranes and organelles of either lysed or unlysed cells.

Statistical Analysis. Each experiment was performed at least three times and each given incubation was carried out in triplicate. Significant differences at the 95% confidence level were computed using analysis of variance or the Student t test. Results are expressed as the mean ± 1 SE for the number of experiments performed.

Results

Bile Acid Association with Mucosal Cells. At pH 7, there was no significant GC association with the rabbit gastric mucosal cells during a 60-min incubation with 0.1 mM GC (Fig. 1). Under those conditions, at pH 7.0 the viability of the cells was not significantly changed and remained at 96 ± 3% (results not shown). Reducing the pH of the incubation solution from pH 7 to pH 5—a pH that is closer to the pKa value of GC, 4.4 (19), and in which a larger portion of GC is unionized—increased the cell-associated radioactivity by 5- to 7-fold. The amount of cell-associated GC at pH 5 was time dependent and reached steady state by 30–50 min, at which time 0.3 ± 0.04 nmole of GC was associated with 10^6 gastric cells.

The next experiment was designed to investigate whether bile acids other than GC, such as deoxycholic acid (DC), also associate with gastric mucosal cells. The association of [^{3}H]-DC with the gastric cells was measured at pH 7.5 and at pH 6, which are just above and below the pKa value for DC of 6.58 (19). At the higher pH, most of the DC is ionized, whereas at the lower pH of 6.0, most of it is unionized. At pH 6, the amount of DC associated with the cells was significantly higher than that at pH 7.5 (Fig. 2). At pH 6.0 in the presence of 25 μM DC, the cell-associated DC was 0.75 ± 0.23 nmole/10^6 cells, whereas at pH 7.5 this amount was lowered significantly ($P < 0.05$) to 0.25 ± 0.08 nmole/10^6 cells, which was not significantly different from the amount of DC association at time zero. The fraction of DC that was associated with the cells was higher than the fraction of GC in the prior experiment (i.e., 4–8% of the total for DC compared with 1–2% for GC). Finally, the cell-associated DC at time zero was significantly higher than that of GC. Because the results obtained with DC showed much more variability than those with GC, and because GC is generally the bile acid in highest concentration in the human gastric

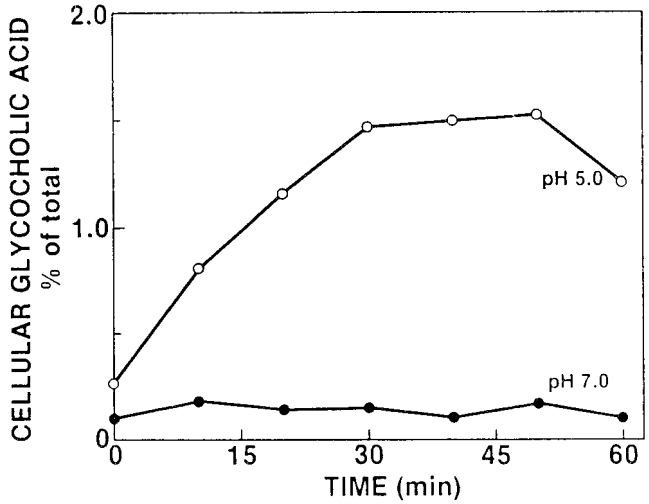

Figure 1. GC association with rabbit gastric cells. Cells (2 × 10^6 cells/ml) were suspended in pH 7 or pH 5 buffer and incubated with 0.1 mM [^{14}C]-GC for the indicated lengths of time at 37°C. The cellular GC is the amount found in the pellet after centrifugation. Results are expressed as the percentage of the total GC present in the incubation solution, and are normalized in each experiment to the value at time zero. At 30 min, the amount of cell-associated [^{14}C]-GC was 0.3 ± 0.035 nmole/10^6 cells. The amount of cellular GC was significantly higher at pH 5 than at pH 7. This experiment represents at least three other similar experiments.

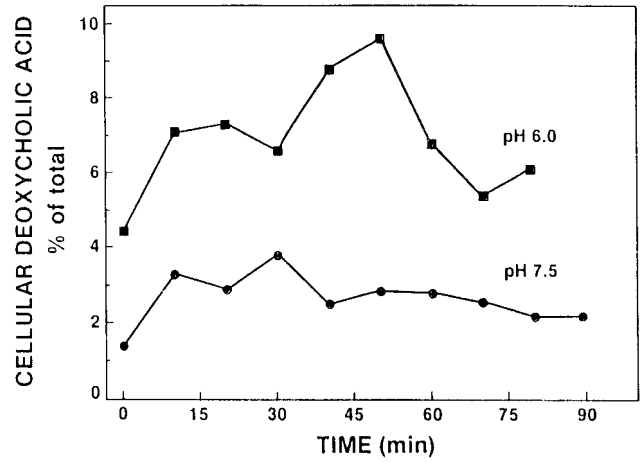

Figure 2. DC association with rabbit gastric cells. Cells (2 × 10^6 cells/ml) were suspended in pH 6 or pH 7.5 buffer and incubated with 25 μM [^{3}H]-DC for the indicated lengths of time at 37°C. The cellular DC is the amount found in the pellet after centrifugation. Results are expressed as the percentage of the total DC present in the incubation solution, and are normalized in each experiment to the value at time zero. The mean DC associated with the cells at the plateau was 6.7 ± 2.1% of total, which translates to 0.75 ± 0.23 nmole/10^6 cells. The mean association at pH 7.5 was 2.5 ± 0.7% of total, which translates to 0.3 ± 0.08 nmole/10^6 cells. The results at pH 6.0 were compared by analysis of variance to those at pH 7.5 and were found to be significantly different ($P < 0.05$). This experiment represents at least three other similar experiments.

contents, the majority of the investigation was focused on GC.

Dependence on Cell Concentration. In order to determine whether the bile acid found in the pellet was truly associated with the cells or whether it was actually an artifact of the experimental system, cell-associated GC was measured as a function of gastric cell concentration. Increasing the cell concentration from 1.0 to 10.0 × 10^6 cells/ml caused a linear increase in the cell-associated GC (Fig. 3). Regression analysis of these results revealed that at 0.1 m*M* GC, the amount of GC associated with the cells was 0.35 ± 0.04 nmole/10^6 cells (three experiments). These results indicate that the radioactivity measured in the cell pellet was indeed associated with the cells.

Dependence on Cellular Energy. Association of GC with the cells was not an active process requiring a cellular energy supply, in that dinitrophenol, an uncoupler of oxidative phosphorylation, did not inhibit the process. With 1 m*M* GC, the cell-associated [^{14}C]-GC after a 30-min incubation was practically the same (4.1 ± 0.5 nmole/10^6 cells) as that in the presence of 0.1 m*M* dinitrophenol (4.4 ± 1.1 nmole/10^6 cells). Similar results were obtained with lower concentration of GC, 0.1 m*M*. The cell-associated [^{14}C]-GC after a 30-min incubation was 0.32 ± 0.03 and 0.35 ± 0.05 nmole/10^6 cells with and without 0.1 m*M* dinitrophenol, respectively.

Saturability of the Accumulation Process. The amount of GC associated with the cells at pH 5 depended on the extracellular concentration of GC. Increasing the concentration of GC in the incubation solution caused a progressive increase in the amount of cell-associated GC (Fig. 4). There was a linear relationship between the extracellular GC concentration and the amount of GC taken up by the cells (Fig. 4A). Accordingly, the fraction of GC taken up from the medium (i.e., the percentage of the total) was the same regardless of the extracellular concentration (Fig. 4B). For example, at a GC concentration of 20 μM, the cell-associated GC was approximately 1% of the total, and at 1 m*M* GC (50-fold higher concentration) the amount of GC associated with the cells was also about 1% of the total. These results suggested that the accumulation process is not saturable, because as the extracellular concentration increased, the cell-associated GC increased in a similar proportion. From this experiment we cannot distinguish between association of GC to the cytosol of intact cells or to the membranes. Regression analysis of the results depicted in Figure 4 and of those from three similar experiments indicated a mean of 3.0

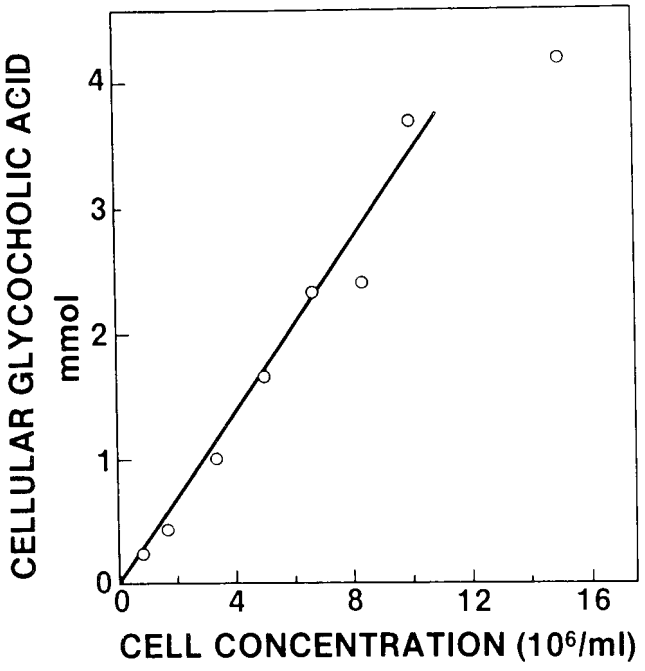

Figure 3. Amount of cellular GC associated with guinea pig gastric cells as a function of the cell concentration. Cells at the indicated concentrations were suspended at pH 5 Hank's buffer with 0.1 m*M* [^{14}C]-GC and incubated at 37°C. Cellular GC was a linear function of the cell concentration, with a mean cell-associated GC of 0.35 ± 0.04 nmole/10^6 cells (three experiments). Results confirm that the [^{14}C]-GC measured in the pellet was indeed associated with the cells, and was not an artifact of the system.

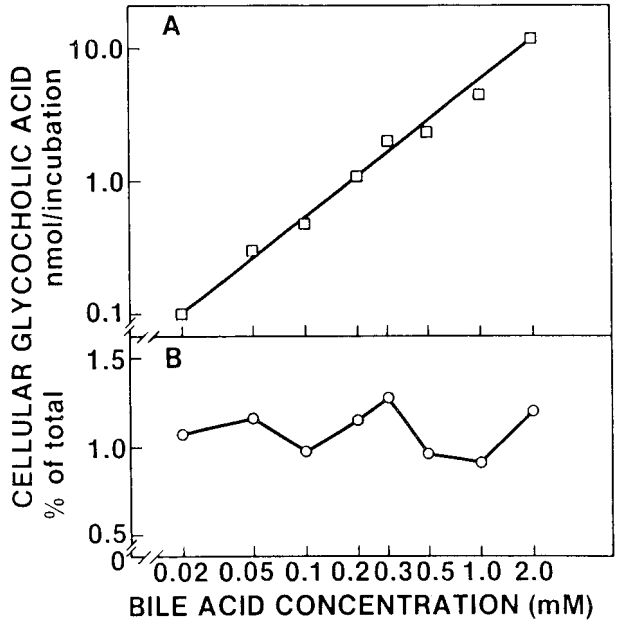

Figure 4. GC association with rabbit cells as a function of the GC concentration. Cells (2 × 10^6 cells/ml) were suspended in pH 5 buffer and incubated with the indicated concentrations of GC for 30 min at 37°C. (A) The amount of (cellular) GC associated with 2 × 10^6 cells in the incubation buffer was a linear function of the extracellular GC concentration. The slope of the line revealed a mean GC association of 3.0 ± 0.4 nmoles/mg dry weight/m*M* extracellular GC. (B) Same results expressed as the percentage of the total GC present in the incubation medium. A constant fraction of the amount of GC present in the medium was associated with the cells with a mean of 0.99 ± 0.12%. This experiment represents three other similar experiments.

± 0.4 nmole of cell-associated GC/mg dry weight of cells/m*M* extracellular GC.

Lytic Effect of Bile Acids. Experiments were designed to test the lytic effects of bile acids at a neutral pH. Lysis was measured by the ability of the cells to retain ^{86}Rb, which distributes in the cell the same as potassium ion. Cells were incubated with ^{86}Rb for 30 min to reach isotopic equilibrium. Then, varying concentrations of GC or DC were added and incubation was continued for an additional 10 min. Cells were then washed and analyzed for their cellular ^{86}Rb. Results showed that GC had less of a lytic effect on the gastric cells than did DC (Fig. 5). One half maximal loss of cell-associated ^{86}Rb occurred with 0.5–0.6 m*M* DC, whereas GC was approximately 10-fold less potent. The concentrations of GC and DC used in our association experiments are below the concentrations that caused 50% lysis, and are well below the reported critical micellar concentration for GC (10 m*M*) and DC (3 m*M*) (19). At a neutral pH, significant cell lysis did not occur until the extracellular GC concentration was at least 5 m*M*, at which point only a 25% reduction in cellular ^{86}Rb was observed. It should be noted that these experiments with GC reflect the distribution of ^{86}Rb in the viable cells under conditions in which no accumulation of GC occurs (i.e., pH 7).

Distribution of GC in Gastric Cells. In the next series of experiments, we explored the distribution of GC in gastric cells using [^{14}C]-GC. The rationale behind these experiments was that hypotonic lysis will release into the supernatant all cellular GC that is not bound to membrane components. Gastric cells were incubated with [^{14}C]-GC, lysed by water, and then centrifuged to separate the membranes (pellet) from the cytoplasmic fraction (supernatant). Hypotonic lysis of cells incubated at pH 5 resulted in a loss of only 51% of the cell-associated [^{14}C]-GC (Table I). These findings demonstrate that approximately one half of the cell-associated [^{14}C]-GC is associated with membrane components.

Species Specificity of GC Accumulation. In order to determine whether the bile acid accumulation process was species specific, several of the experiments were repeated with gastric cells from the guinea pig. Results similar to those obtained with the rabbit were observed (Fig. 6). That is, the association of GC within the guinea pig cells was time and pH dependent in that it occurred at pH 5 and reached steady state by 30 min. As with rabbit cells, with a GC concentration of 0.1 m*m* in the medium, between 0.3 and 0.5 nmole of GC/mg dry

Table I. Effect of Hypotonic Lysis on Cellular GC[a]

Incubation solution	Cell-associated radioactivity		
	Before lysis	After lysis	Percentage of loss on
^{14}C-GC	1.00	0.49	51%

[a] Cells were incubated at pH 5 for 20 min with 0.1 m*M* ^{14}C-GC. Results are normalized such that the "Before lysis" value is 1.00. Results indicate that the amount of ^{14}C-GC lost from the pellet on hypotonic lysis was significantly higher than background. Therefore, approximately one half of the ^{14}C-GC is bound to membrane components and the other one half is in the cytosolic compartment.

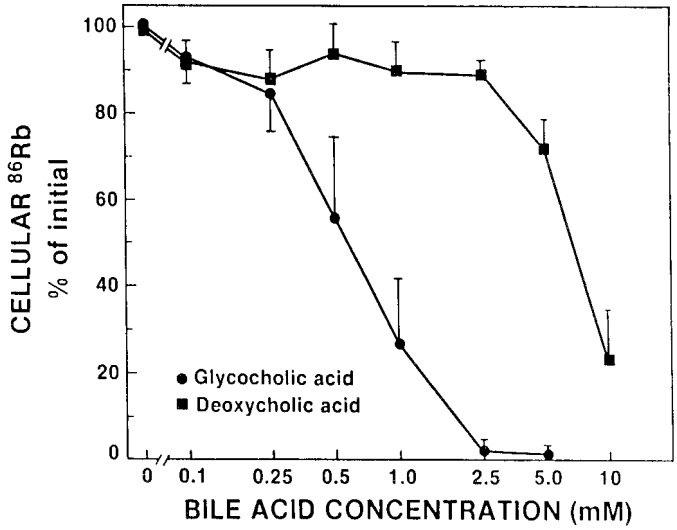

Figure 5. Cell lysis by glycocholic acid and deoxycholic acid. Rabbit gastric cells (2×10^6 cells/ml) were suspended in pH 7.5 buffer and incubated for 30 min with ^{86}Rb. After a 30-min incubation, the indicated concentrations of bile acid were added and incubation was continued for an additional 10 min. Cells were then washed, and their cellular ^{86}Rb was determined. Values are the mean ± 1 SD (vertical bars) of four experiments. Cellular ^{86}Rb is inversely related to the degree of cell lysis. Under these conditions, GC was less potent than DC in causing cell lysis.

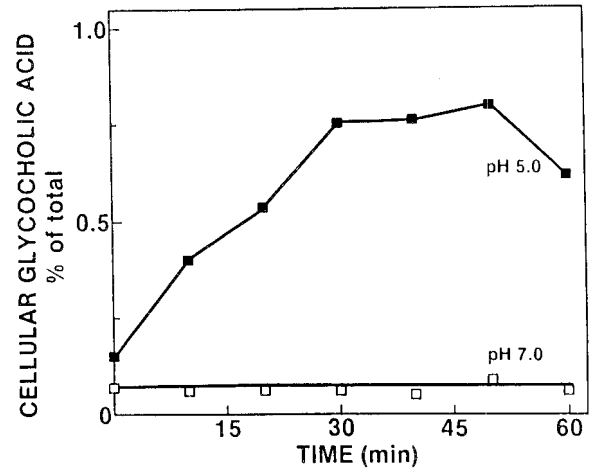

Figure 6. GC association with guinea pig gastric cells. Cells (2×10^6 cells/ml) were suspended in pH 7 or pH 5 Hank's buffer and incubated with 0.1 m*M* [^{14}C]-GC for the indicated lengths of time at 37°C. The cellular GC is the amount found in the pellet after centrifugation. Results are expressed as the percentage of the total GC present in the incubation solution, and are normalized in each experiment to the value at time zero. The amount of cellular GC was significantly higher at pH 5 than at pH 7. After 30 min of incubation, the cell-associated GC at pH 5.0 was 0.37 nmole/10^6 cells, whereas at pH 7.0, this amount was 0.05 nmole/10^6 cells, not significantly different from zero. The similarity of the results to those in Figure 1 indicates a lack of species specificity.

weight of cells (or 0.27 ± 0.06 nmole/10^6 cells) was associated with the guinea pig cells. Cellular GC at the steady state exceeded the extracellular concentration of GC by severalfold, and the accumulation process also appeared to be nonsaturable in the guinea pig cells. Incubating the guinea pig cells with increasing concentrations of GC resulted in a progressive and linear increase in the cell-associated GC. As with rabbit cells, regression analysis revealed a mean of 2.2 ± 0.4 nmoles of cell-associated GC/mg dry weight/m*M* extracellular GC (not shown).

Discussion

These studies demonstrate for the first time that bile acids rapidly associate with gastric mucosal cells, and that the bile acids accumulate in the cells. One mechanism that could explain bile acid accumulation in the cytosol of gastric cells is entrapment due to intracellular bile acid ionization. This mechanism is supported by the pH dependence of the process. Bile acid accumulation occurred with glycocholic acid at pH 5 but not at pH 7, and with deoxycholic acid at pH 6 but not at pH 7.5. This implies that the physiochemical form of the bile acid, which changes with the hydrogen ion concentration, is an important component of the process. For example, the pKa for GC is 4.4, and at that pH about 50% is in the unionized form. In this form, glycocholic acid could pass through the lipophylic lipid membrane and enter the cell. Once inside the cell (pH 7), the molecule would convert to the ionized form, becoming relatively impermeable to the membrane and thus trapped.

Some of the bile acid was also found to be associated with the cellular membranes. This was evident from the fact that only 51% of the [^{14}C]-labeled glycocholic acid was released when the cells were lysed by water. Association of bile acid with membrane components might occur through the interaction of the bile acid molecule with membrane lipid, or through binding to membrane protein. Bile acid binding to the membrane lipid would explain why deoxycholic acid accumulated to a greater degree than did glycocholic acid, since the former bile acid is more lipophilic. Either of these models are supported by the experimental observations that the process did not depend on cellular energy and that it was nonsaturable.

Examination of the differences in the experimental results between glycocholic acid and deoxycholic acid is informative. Glycocholic acid accumulated in the cells to a lesser degree than did deoxycholic acid. It was also less potent than deoxycholic acid in causing cell lysis. The differences in potency of bile acids in causing cell damage in other studies have been explained on the basis of their critical micellar concentrations (CMC). The CMC concentration in 0.15 *M* NaCl of DC and GC is 3 m*M* and 10 m*M*, respectively (19). It has been suggested that the bile acids with a low CMC are more toxic to cells because they can more readily dissolve membrane lipid. The results of the present study are concordant with this hypothesis, since the CMC of deoxycholic acid is lower than that of glycocholic acid. However, the present study suggests that the physical properties of a bile acid that confer its particular CMC, e.g., the molecular polarity, may also contribute to its tendency to accumulate in the cells. Bile acid accumulation in the cells and lipid solubilization may both be stages of the process by which bile acids cause cell lysis.

Bile acid accumulation in mucosal cells is not species specific, as demonstrated in the present study, nor is it organ specific, since it also occurs in the esophageal mucosa (11). If the process also occurs in the human stomach, then it may have clinical relevance to conditions in which bile acids are thought to contribute to gastric mucosal damage. For example, bile acid injury of the gastric mucosa is currently attributed to solubilization of mucosal lipids into the lumen. This mechanism of injury is incongruous with the clinical observation that bile acid concentrations in the gastric contents are relatively low, in the range of 1–3 m*M* (5, 6). Until now, it has not been clear how these relatively low concentrations of bile acids in the lumen could injure the mucosa, if injury is indeed due to lipid solubilization. The data from the present study suggest that acidity such as that found in the gastric lumen drives accumulation of bile acids in the mucosa by ionic trapping. The bile acid in its unionized form can enter the cell. In the face of higher intracellular pH, the molecules undergo ionization and are thus trapped. This may lead to acidification of the cells and/or accumulation that exceeds the threshold for lipid solubilization. This accumulation of bile acids by mucosal cells could result in intracellular bile acid concentrations that exceed the threshold for lipid solubilization, despite low luminal concentrations. These high intracellular bile acid concentrations would then be expected to cause cellular injury by dissolution of cellular membranes.

The present studies have demonstrated and characterized a process by which bile acids accumulate in gastric mucosal cells. This process may be an important aspect of the mechanism by which bile acids can cause gastric mucosal injury.

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