ABSTRACT

Bile acids increase the proliferative activity of rat colonic epithelium. However, the mechanisms responsible are unknown. The present study examined the relationships between deoxycholate (DOC) induced surface cell sloughing, as measured by loss of DNA into the lumen and by light microscopy, and the subsequent increases in mucosal ornithine decarboxylase (ODC) activity and [3H]thymidine incorporation into mucosal DNA induced by deoxycholate. Intracolonic instillation of DOC (10 μmol; 5 mm) resulted in a progressive increase in luminal DNA content which was significant by 1 min and maximal by 4 h. No further increase in luminal DNA occurred between 1 and 4 h after DOC. Similarly, light microscopy demonstrated a progressive loss of surface epithelium between 10 min and 1 h after DOC instillation. By 4 h after DOC, the colonic mucosal surface was normal histologically. The rapid repair of the epithelial surface occurred without a detectable increase in [3H]dThd incorporation into DNA within 4 h. The latter finding thus suggested that upward migration of nondividing crypt epithelial cells rather than the rapid initiation of new DNA synthesis and new mitotic activity was responsible for surface repair. Enhanced proliferative activity of colonic mucosa, as measured by increased [3H]dThd incorporation into DNA, did occur subsequently (12 to 24 h) after instillation of DOC. The dose response of early surface cell loss and the subsequent proliferative response to DOC were identical, consistent with a link between these two DOC mediated events. However, two observations suggested that surface epithelial loss alone was not sufficient to trigger the proliferative response to DOC: (a) intracolonic instillation of DOC followed by removal of the DOC solution at 1 h, at which time surface epithelial loss was maximal, did not result in an increase in ornithine decarboxylase activity or [3H]dThd incorporation into DNA when these parameters were assessed at 4 h or 12 to 48 h, respectively; (b) phenidone, an antioxidant and radical scavenger, and bis(3,5-diisopropyl-salicylato) (O,O) copper(II), a lipophilic agent with Superoxide disimilase activity, abolished the DOC mediated proliferative response but did not prevent the early loss of surface cells. The results imply that events other than or in addition to surface cell loss are necessary for the expression of the action of DOC to stimulate the proliferative activity of colonic epithelium.

INTRODUCTION

Studies from our own (1, 2) and other laboratories (3–5) have shown that bile acids stimulate the proliferative activity of colonic mucosa. This action in turn is thought to be related to the activity of bile acids as cocarcinogens in colon (5–7). Under certain conditions, bile acids also cause rapid sloughing of the surface epithelium (5, 8, 9). However, the precise relationship between bile acid induced increases in colonic epithelial proliferative activity and early surface cell sloughing have not been delineated. Specifically, whether bile acids stimulate proliferation of colonic epithelium through mechanisms independent of or in addition to their action to increase loss of surface cells is not known. This possibility is raised, however, by the findings that chronic cholic acid ingestion increases the proliferative activity of colonic epithelium without evident surface cell damage (6). This question is also relevant to our earlier findings which have implicated bile acid induced increases in reactive oxygen species as a key initial event mediating the subsequent change in epithelial proliferation (2). Reactive oxygen can induce intestinal mucosal injury and loss (10–12), and this in turn might stimulate compensatory or reparative proliferative activity.

Accordingly, in the present study we examined in the rat the effects of DOC on colonic surface cell sloughing, as assessed by loss of DNA into the colonic lumen (8, 9) and by light microscopy. The effects of DOC on loss of surface epithelium were correlated with changes in mucosal proliferation, as reflected by mucosal ODC and [3H]dThd incorporation into mucosal DNA. Since our previous studies had implicated reactive oxygen species in the mediation of DOC induced increases in mucosal proliferative activity (2), we examined the potential role of these species in both the early loss of surface epithelial cells induced by DOC and the subsequent enhancement of proliferative activity.

The results indicate that under certain conditions the rapid loss of surface epithelium induced by DOC can occur without a proliferative response. These observations indicate that increases in colonic mucosal proliferative activity induced by bile acids involve mechanisms in addition to loss of the surface epithelium.

MATERIALS AND METHODS

Determination of [3H]dThd Incorporation into Colonic Mucosal DNA and Luminal DNA Content. Female Sprague-Dawley rats (Zivic-Miller Laboratories, Pittsburgh, PA) were fasted for 8 h before surgery and throughout the study period. Rats were anesthetized with pentobarbital (50 mg/kg i.p.), and the colon was exposed through a midline abdominal incision. In preliminary experiments, it was determined that the effects of intracolonic instillation of DOC on luminal DNA and ODC were similar in rats anesthetized with pentobarbital or ketamine (100 mg/kg i.p.). Test agents were administered intracolically as previously described in detail (1). Briefly, a 20-gauge needle was inserted into the lumen of the large intestine at the cecal junction. The large intestine was thoroughly flushed free of visible luminal contents with 0.15% NaCl (saline) that had been warmed at 37°C. A ligature was then placed externally at the anorectal junction to prevent escape of test solutions. Saline (2 ml) or a solution of test agents in 2 ml of saline (37°C) was instilled into the lumen of the distal colon. In some studies, as indicated in the text, 30 min after insertion, the first test solution was withdrawn and a second instillation of 2 ml of saline or test agents in 2 ml of saline (37°C) was made. The needle puncture site was then oversewn. The abdominal incision was closed with wound clips. In all studies using DOC, the sodium salt was used. The pH of solutions of the sodium salt of DOC in saline was 8.0. At timed intervals, control and experimental rats were again anesthetized with pentobarbital, 50 mg/kg i.p. For determination of [3H]dThd incorporation into DNA, [3H]dThd (100 μCi/kg) was injected i.p. at time intervals after the initial DOC or saline instillation had been made. Rats were sacrificed 15 min after the injection of [3H]dThd. Distal colons were excised and placed in saline at 4°C. The mucosa was scraped and DNA content was extracted, counted, and assayed as previously described (1, 13). Luminal DNA content was determined in separate rats prepared and treated as

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1 This work was supported by Grant CA31680 from the National Cancer Institute through the Large Bowel Cancer Project.

2 The abbreviations used are: ODC, ornithine decarboxylase activity; DOC, deoxycholate; [3H]dThd, tritiated thymidine; CuDIPS, bis(3,5-diisopropyl-salicylato) (O,O) copper(II).
Three groups of 3 rats each received an intracolonic instillation of 2 ml
of 5 mM DOC in 0.15 M NaCl, pH 8.0 exactly as described above except that 1 MCi
of [14C]DOC (58.2 mCi/mmol) was also included in the solution for instillation. At 1, 2 or 4 h after DOC exposure, rats were anesthetized with pentobarbital, the solution was removed, the volume was measured, and an aliquot was counted in the scintillation counter.

Determination of Rate of Absorption of DOC from the Colonic Lumen. Three groups of 3 rats each received an intracolonic instillation of 2 ml of 5 mM DOC in 0.15 M NaCl, pH 8.0 exactly as described above except that 1 MCi of [14C]DOC (58.2 mCi/mmol) was also included in the solution for instillation. At 1, 2 or 4 h after DOC exposure, rats were anesthetized with pentobarbital, the solution was removed, the volume was measured, and an aliquot was counted in the scintillation counter.

Determination of ODC. Rats were prepared and treated with test agents by intracolonic instillation exactly as described above for [3H]-
dThd incorporation into DNA except that injection of [3H]dThd was omitted. Animals were sacrificed 4 h after intraluminal instillation of bile salts or saline. The mucosal surface of the distal colon was scraped and 150 mg wet weight was homogenized in 1 ml of 50 mM sodium phosphate, pH 7.4 which contained 0.1 mM pyridoxal phosphate and 0.1 mM EDTA. Homogenates were centrifuged at 38,000 × g for 20 min and the supernatants were assayed immediately. Enzyme activity was determined from the release of [14C]CO₂ from D,L-ornithine as previously described (1, 4). Briefly, reaction mixtures contained 0.02 mM pyridoxal phosphate, 4 mM dithiothreitol, 1 mM EDTA, 0.4 mM L-ornithine, 40 mM sodium phosphate (pH 7.2), 100 µl of the colonic mucosal soluble fraction (approximately 100 µg of protein), and 0.5 µCi of D,L-[1-14C]ornithine in a final volume of 0.25 ml. Assays were done in duplicate. Blanks contained buffer alone or the heated (95°C for 10 min) soluble fraction. Results were corrected for the blank value obtained. ODC was linear with time for 60 min with 20–200 µg of protein under all conditions of study.

Light Microscopy. Distal colonic segments (1 x 1 mm) were fixed in 2% paraformaldehyde in 0.1 M sodium phosphate buffer, pH 7.4. The tissues were washed in 0.1 M sodium phosphate buffer, pH 7.4 and postfixed in 1% osmium tetroxide. The segments were dehydrated in graded alcohols and embedded in Marglas (Polysciences, Inc., Warrington, PA). Sections were poststained with hematoxylin and eosin and examined by light microscopy.

Preparation of CuDIPS. CuDIPS was prepared as previously described (2, 14). Briefly, 5 g of 3,5-diisopropyl salicylic acid was dissolved in 100 ml H₂O by addition of 50% NaOH, filtered, and adjusted to pH 8–9. The solution was added to CuCl₂ dihydrate solution (0.59 g/300 ml H₂O) slowly with continuous stirring. The brown precipitate which formed was collected on a Buchner funnel and redissolved in ether. The formed was collected on a Buchner funnel and redissolved in ether. The precipitate formed from ether were collected and dried at 125°C for 3 h at which time they appear brown and melt at 142–144°C

Materials. CuCl₂, cupric acetate, and 3,5 diisopropyl salicylic acid were obtained from Aldrich Chemical Co., Milwaukee, WI. [14C]Deoxycholate (58 mCi/mmol) was obtained from ICN Radiochemicals, Irvine, CA. Phenidone, esculetin, and DOC were obtained from Sigma Chemical Co., St. Louis, MO. The sources of all other reagents have been previously reported (1).

Statistics. Statistical significance of differences between mean values was determined by the t test for unpaired data. Studies were conducted on 6 rats of each experimental group. Between 8 and 12 rats could be studied on any given day. Experiments were thus repeated until the indicated number of rats in each group had been studied. For the purposes of statistical analysis, the average of replicate determinations for any parameter from a single rat colon was entered as a single value (degrees of freedom = 4 or 10 comparing any 2 values by independent t test).

RESULTS

Fig. 1 illustrates the effects of intracolonic instillation of saline or 10 µmol of DOC (5 mM) dissolved in saline on recovery of DNA into the colonic lumen as a function of time (1 min–4 h). As shown, intracolonic instillation of saline alone resulted in recovery of a small amount of DNA in the luminal contents. The amount of DNA recovered did not vary with time of exposure to saline between 1 and 60 min. By contrast, exposure of the colon to DOC resulted in a prompt 2-fold increase in the amount of DNA in the colon lumen compared to that observed in rats exposed to saline alone. The increase in luminal DNA occurred within 1 min of exposure to DOC, the earliest time point studied. DNA loss into the colon increased progressively between 1 and 60 min and did not change between 60 min and 4 h. In other experiments the rate of absorption of DNA from the colon lumen was assessed with labeled DOC as described in detail in the “Materials and Methods.” By 1, 2, and 4 h after DOC administration 79, 88, and 93%, respectively, of the labeled DOC had been absorbed. This corresponds to concentrations remaining in the lumen at 1, 2, and 4 h of 1, 0.6, and 0.35 mM, respectively.

Fig. 2 illustrates the time course of effects of saline or DOC on [3H]dThd incorporation into DNA. In these studies, 2 ml of saline or 10 µmol DOC dissolved in saline was instilled intracolonically. At the times indicated in Fig. 2, [3H]dThd was injected and incorporation of [3H]dThd into DNA was determined 15 min after injection. Exposure of the colon to saline produced no sequential changes in [3H]dThd incorporation into mucosal DNA with time (10 min–24 h). Moreover, values for [3H]dThd incorporation in these operated controls did not differ from values observed in colon from rats not treated surgically. Intracolonic instillation of DOC did not significantly influence [3H]dThd incorporation into DNA between 10 min and 8 h after instillation of DOC. Consistent with previous results (1,
Table 1 illustrates the concentration response relationship between DOC and loss of DNA into the colonic lumen at 1 h or alterations in [3H]dThd incorporation into DNA at 24 h. Intracolonic instillation of 0.5 mM DOC did not increase luminal DNA content or alter [3H]dThd incorporation into DNA. Increasing the concentration of DOC from 1-25 mM resulted in a progressive increase in luminal DNA. [3H]dThd incorporation into DNA also increased progressively as the concentration of DOC was raised from 1-25 mM. The concentration response relationships observed in the present study between DOC and alterations in [3H]dThd incorporation into DNA or luminal DNA content are entirely analogous to those previously reported between DOC and formation of reactive oxygen in colonic mucosa (2), or between DOC and increases in colonic mucosal ODC activity (1).

Table 1 illustrates the concentration response relationship between DOC and loss of DNA into the colonic lumen at 1 h or alterations in [3H]dThd incorporation into DNA at 24 h. Intracolonic instillation of 0.5 mM DOC did not increase luminal DNA content or alter [3H]dThd incorporation into DNA. Increasing the concentration of DOC from 1-25 mM resulted in a progressive increase in luminal DNA. [3H]dThd incorporation into DNA also increased progressively as the concentration of DOC was raised from 1-25 mM. The concentration response relationships observed in the present study between DOC and alterations in [3H]dThd incorporation into DNA or luminal DNA content are entirely analogous to those previously reported between DOC and formation of reactive oxygen in colonic mucosa (2), or between DOC and increases in colonic mucosal ODC activity (1).

Table 1. Concentration response relationship between DOC and DNA loss into the colonic lumen or alterations in [3H]dThd incorporation into mucosal DNA

<table>
<thead>
<tr>
<th>Intracolonic instillation</th>
<th>Luminal DNA (µg/µl) 1 h</th>
<th>[3H]dThd incorporation (cpm/µg DNA) 24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>54 ± 7</td>
<td>11 ± 1</td>
</tr>
<tr>
<td>DOC, 1 µmol; 0.5 mM</td>
<td>58 ± 6</td>
<td>12 ± 1</td>
</tr>
<tr>
<td>DOC, 2 µmol; 1 mM</td>
<td>123 ± 18*</td>
<td>23 ± 4*</td>
</tr>
<tr>
<td>DOC, 10 µmol; 5 mM</td>
<td>763 ± 71*</td>
<td>34 ± 4*</td>
</tr>
<tr>
<td>DOC, 50 µmol; 25 mM</td>
<td>987 ± 102*</td>
<td>48 ± 6*</td>
</tr>
</tbody>
</table>

*P < 0.05 compared to corresponding value in rats receiving saline.

DISCUSSION

The present study clearly demonstrates that a single intracolonic instillation of DOC induces a dose dependent increase in loss of DNA into the colonic lumen, a measure of cell sloughing (8, 9). Luminal DNA content increased significantly within 1 min after intracolonic instillation of 10 µmol of DOC and continued to increase progressively between 1 and 60 min. No further increase in luminal DNA content was observed between 1 and 4 h. The lack of further increase in luminal DNA between 1 and 4 h may be related to the rapid uptake of 80% of the instilled DOC which was observed during the first 60 min. Nevertheless, the concentration of DOC remaining in the lumen after 1 h was still 1 mM. In separate experiments 1 mm
DOC was sufficient to cause a 2-fold increase in luminal DNA (Table 1). Accordingly, other factors may also be involved. The increase in luminal DNA was closely correlated with the degree of surface epithelial loss, as assessed by light microscopy of segments of colon from rats which had been exposed to DOC for 10 min or 1 h. Nevertheless, consistent with our own previous observations (1), by 4 h after a single intracolonic instillation of 10 μmol of DOC, the colons were normal histo-

logically. No evidence of cell sloughing was observed by light microscopy at this time. Further, sequential studies of the influence of DOC on [³H]dThd incorporation into DNA indicated that the surface epithelium was replaced within 4 h without an increase in proliferative activity during this period. Rapid replacement of severely damaged frog and rodent gastric mucosa after exposure to ethanol (15, 16), aspirin (17), or hyperosmolar NaCl (18) has previously been reported. Replacement of surface cells within 8 h has also been demonstrated...
DOC ACTIONS ON COLONIC CELL LOSS AND PROLIFERATION

Table 2. Effect of phenidone and CuDIPS on basal and DOC induced loss of DNA into the colonic lumen and subsequent increases in DNA synthesis.

<table>
<thead>
<tr>
<th>Intracolonic instillation</th>
<th>Lumenal DNA (µg)</th>
<th>[3H]dThd incorporation into mucosal DNA (cpm/µg DNA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. 1 (t = 0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saline</td>
<td>48 ± 2</td>
<td>10 ± 2</td>
</tr>
<tr>
<td>CuDIPS</td>
<td>52 ± 7</td>
<td>12 ± 2</td>
</tr>
<tr>
<td>Phenidone</td>
<td>43 ± 5</td>
<td>11 ± 2</td>
</tr>
<tr>
<td>No. 2 (t = 30 min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saline DOC</td>
<td>859 ± 94*</td>
<td>28 ± 4*</td>
</tr>
<tr>
<td>CuDIPS DOC</td>
<td>762 ± 86*</td>
<td>11 ± 1</td>
</tr>
<tr>
<td>Phenidone DOC</td>
<td>862 ± 104*</td>
<td>9 ± 1</td>
</tr>
</tbody>
</table>

* P < 0.05 compared to corresponding value in rats exposed to saline at t = 0 and t = 30.

in rat colon damaged by a bolus of p.o. administered fat (19). Analogous to the results of the present study, gastric mucosal surface epithelium was restored, despite the continued presence of the damaging agent in the lumen, by migration of existing gastric pit cells (15–18). Moreover, surface restoration did not require new cell division (15–18). Thus, restoration of the damaged gastric mucosal surface epithelium was observed within 4–6 h without an increase in [3H]dThd incorporation into DNA within that time (16–18). The present observations are consistent with studies of cell cycle kinetics which have demonstrated that 19 h is required for rat colonic epithelium to complete a cell cycle (20). Moreover, they support previous studies which have shown that cells in G1 or G0 can migrate out of the proliferative zone and differentiate into mature cells without a concurrent increase in proliferative activity (20).

In the present study, the initial increase in luminal DNA content and surface cell loss was closely correlated with subsequent increases in proliferative activity as a function of DOC dose. The relationship between DOC induced surface cell loss and the subsequent increase in proliferative activity has previously been observed by Wargovich, et al. (5, 21). In the latter studies intrarectal administration of DOC or fatty acids caused damage to the mouse colonic mucosa and induced an increase in [3H]dThd incorporation into DNA. Calcium supplementation p.o. prevented both these actions of DOC (5, 21). These observations raise the possibility that the acute loss of surface epithelium induced by DOC might alone trigger the subsequent increase in colonic mucosal ODC and [3H]dThd incorporation into DNA. In this regard, it has been speculated that the increase in colonic proliferative activity which is seen in patients at a high risk for colon cancer may be related to mucosal injury caused by increased fecal bile acid and fat excretion (22, 23). However, in the present studies removal of DOC from the colonic lumen after a 1-h exposure completely prevented the subsequent increase in proliferative activity, despite the fact that surface cell loss was maximal after 1 h of exposure to DOC. Loss of the proliferative response to DOC did not appear to be due to a shift in the time course of new DNA synthesis within the time frame studied. Thus, no subsequent increase in [3H]dThd incorporation into mucosal DNA was observed in colon instilled with DOC (5, 21). DOC induced increases in mucosal ODC or [3H]dThd incorporation into DNA was observed in colons exposed to DOC for 1 h and DNA synthesis was observed at 12, 24, 36, or 48 h after instillation of DOC. Since the loss of surface epithelium was maximal by 1 h after DOC exposure, this observation clearly indicates that loss of surface epithelium alone was not sufficient to initiate the later increase in proliferative activity observed in response to DOC. It is also of interest that removal of DOC from the colonic lumen at any time after 4 h did not influence the magnitude of the subsequent increase in [3H]dThd incorporation into DNA observed at 12–24 h. Taken together these results suggest that the continuous exposure of colonic mucosa to DOC for 4 h is required to induce an optimal increase in ODC. However, once this increase in ODC has occurred, the bile acid can be removed without influencing the subsequent increase in DNA synthesis.

Studies with phenidone, an antioxidant and radical scavenger, and CuDIPS, a small lipopholic molecule with superoxide dismutase activity (24), also implied that the DOC induced loss of surface epithelium alone was not sufficient to initiate the subsequent increases in mucosal ODC or [3H]dThd incorporation into DNA. Studies with phenidone, an antioxidant and radical scavenger, and CuDIPS, a small lipopholic molecule with superoxide dismutase activity (24), also implied that the DOC induced loss of surface epithelium alone was not sufficient to initiate the subsequent increases in mucosal ODC or [3H]dThd incorporation into DNA. Thus, phenidone and CuDIPS block the DOC induced increase in mucosal proliferative activity without influencing the earlier loss of surface epithelium in response to DOC. These findings indicate that events in addition to surface cell loss are involved in the expression of bile acid action to stimulate the proliferative activity of colonic mucosa. The concentrations of phenidone and CuDIPS used in the present studies were previously shown to completely abolish increases in reactive oxygen induced by 5 mM DOC in colonic mucosa in vitro (2). Accordingly, the current findings appear to suggest that DOC induced increases in reactive oxygen are involved in expression of the action of the bile acid to increase the proliferative activity of colonic mucosa but may not mediate DOC induced increases in surface cell loss. Alternatively, it is possible that damage to the epithelial cells occurs at lower concentrations of reactive oxygen than are required to stimulate the proliferative response or that the reactive oxygen moiety which mediates DOC effects on surface cell loss differs from that which may mediate increased proliferative activity. In this regard hydroxyl radical (OH) produced by the reaction of O₂⁻ with H₂O₂ has been implicated in the mediation of ischemic injury in the small intestine (25). In separate studies, we have identified several inhibitors of reactive oxygen formation which block both surface cell loss and the proliferative response to DOC (2, 26). Moreover, we have demonstrated that intracolonic instillation of the O₂⁻ generating system xanthine-xanthine oxidase induces both surface cell loss and a proliferative response. Both these actions of xanthine-xanthine oxidase are blocked by superoxide dismutase (2, 26). This area clearly requires further investigation.

Previous studies in rodent colon perfused with bile acids at concentrations similar to those used in the present study (8, 9, 27) have demonstrated marked structural and functional alterations including cell sloughing, ballooned absorptive cells, shortened villi, inhibition of water transport, and increased mucosal permeability. The potency of several bile acids as inducers of these changes is related to their surface properties as determined by critical micelle concentration and surface tension reduction (27). It is thus also possible that the action of bile acids to induce loss of surface epithelium is directly related to their detergent activity.

It should also be emphasized that our results are consistent with the notion that the initial surface cell loss may be an event necessary to the subsequent enhancement of proliferative activity observed in response to DOC. Indeed, in the present study, no conditions were found in which DOC enhanced proliferative activity without causing a prior loss of surface epithelium. Moreover, our results do not address the role of other forms of colonic mucosal injury, aside from surface cell loss, in the expression of the proliferative response to DOC. Events such as DNA strand breakage would not be detected by the procedures used and might account for the inhibitory effects of

* Unpublished observations.
CuDIPS or phenidone on bile acid stimulation of proliferative activity (28). In this regard, phorbol ester tumor promoters are known to increase O$_2^-$ production, induce DNA single strand breaks, increase proliferative activity, and promote tumor growth (28).

However, even with these limitations, the current observations indicate that events in addition to surface epithelial loss are necessary for the ultimate expression of the action of bile acids to stimulate proliferative activity. In contrast to DOC induced surface cell loss, these additional events require the continuous exposure of colonic mucosa to the bile salt for 4 h. In this regard, it is notable that the studies of Deschner and Raicht (29) have supported a regulatory action of bile salts on mucosal proliferative activity which appears to be independent of any action of bile salts on mucosal integrity. Thus, proliferative activity was reduced in the colonic mucosa of bile fistula rats, a model for bile salt diversion (29). These investigators have also observed stimulation of the proliferative activity of colonic mucosa in response to chronic cholic acid ingestion in the absence of any evidence of surface cell loss (6).

The precise mechanism(s) by which DOC increases colonic mucosal proliferative activity remain to be delineated. In view of the evidence implicating reactive forms of oxygen in the mediation of DOC effects on proliferative activity, it is of some interest that several studies have demonstrated increased phosphoinositide breakdown with consequent activation of protein kinase C in the mediation of a variety of receptor mediated cellular responses, including enhanced O$_2^-$ production (30-32) and increases in cellular proliferative activity induced by phorbol ester tumor promoters (33-35). Our earlier studies have shown that DOC increases release of free arachidonate from colonic mucosa, and the synthesis of both cyclooxygenase and lipoxygenase products in this tissue (1). These processes are often accompanied by increased reactive oxygen formation, activation of the phosphoinositide pathway, and activation of protein kinase C (33). In this regard, recent studies from our laboratory have implicated enhanced phosphoinositide turnover and protein kinase C activation in the expression of the stimulatory effects of bile salts on the proliferative activity of colonic mucosa (36).

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REFERENCES


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Relationship between Loss of Rat Colonic Surface Epithelium Induced by Deoxycholate and Initiation of the Subsequent Proliferative Response

Patricia A. Craven, James Pfanstiel, Reisuke Saito, et al.


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