Ornithine Decarboxylase Activity in the Rat and Human Colon

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ABSTRACT

We have investigated the effect of age, a high-fat diet, sodium deoxycholate, and the ornithine analogue α-difluoromethylornithine on ornithine decarboxylase (ODC) activity in the rat colon. The relative levels of ODC activity were also determined in normal mucosa and tumor tissue from rat and human colon.

The colonic ODC activity induced by intrarectal instillation of sodium deoxycholate in male Sprague-Dawley rats was highest in young animals, and it decreased with increasing age. A high level of dietary fat caused both an increase in basal colonic ODC activity and enhanced ODC induction by deoxycholate. α-Difluoromethylornithine given in drinking water inhibited, in a dose-dependent fashion, deoxycholate-induced ODC activity. The frequency of azoxymethane-induced intestinal tumors was also significantly reduced by α-difluoromethylornithine.

Since colonic ODC activity is increased in carcinogenesis by known promoting agents and decreased by tumor inhibitors, this short-term assay may provide a useful system for identifying colon tumor promoters and inhibitors. The ODC activity in colon tumors of Sprague-Dawley rats was found to be significantly higher than in normal-appearing mucosa in the same animals. Similarly, ODC activity in human colon cancer was found to be higher than that of the normal-appearing mucosa in the same specimen. These results strengthen the utilization of the rat model for studies, the results of which may apply to the human situation.

INTRODUCTION

The induction of ODCβ (EC 4.1.1.17) has been suggested to play a significant role in the phenomenon of tumor promotion. Initial studies in the mouse skin model showed an excellent correlation between the induction of ODC activity and the tumor-promoting ability for a variety of substances (3, 16). Subsequent studies have shown that tumor promoters in other organ systems will also increase ODC activity in their respective target tissues (12, 22). However, there are studies which do not support the correlation between ODC induction and tumor promotion (11). These data suggest that the relationship between the 2 phenomena is not necessarily straightforward, which has led some investigators to describe ODC induction as necessary but not sufficient for tumor promotion. This characterization seems to describe quite well the important but incompletely understood relationship between ODC and tumor promotion.

Colonic carcinogenesis has been shown to be a multistep process similar to that in the mouse skin (5). A variety of agents, such as high dietary fat, i.r.-instilled bile salts, or certain drugs, will increase the tumor yield in animals treated with colon carcinogens (13, 15, 17–19). The bile salts have also been reported to increase colonic ODC activity in doses which promote tumorigenesis (20). The relationship between ODC induction and tumor promotion has been suggested to be useful for short-term screening of potential inhibitors of tumorigenesis (25). Although this relationship is not absolute, there are enough data indicating a correlation between the 2 processes to justify further investigation, especially when one considers the relative ease and low cost of short-term testing versus long-term tumorigenesis studies.

The present studies were undertaken to: (a) determine characteristics of colonic ODC induction; (b) ascertain the effect of high levels of dietary fat on ODC activity; (c) determine the relationship between the inhibition of ODC by DFMO and the potential reduction in tumorigenesis; and (d) determine the levels of ODC in the normal colonic mucosa and tumors in rats and humans.

MATERIALS AND METHODS

Animals and Diets. Male Sprague-Dawley CD rats weighing 100 to 125 g (approximate age, 33 days) were obtained from Charles River Breeding Laboratories, Wilmington, MA. Animals were housed individually in suspended wire mesh cages in a light- (12 hr/day) and temperature- (24°) controlled room. Rats were given water and a standard semisynthetic diet ad libitum. The main ingredients of the standard diet (14) in weight percentage were: dextrose, 45.2; corn starch, 19.0; casein (vitamin free), 20.0; cellulose, 5.0; mineral mix (Bernhardt-Tomarelli salt mix, modified; Dyets No. 200030), 3.6; vitamin mix (Dyets No. 300150), 2.0; and ω-methionine, 0.2. The diet was prepared weekly in our laboratory. In the high-fat diet, 30% beef fat was introduced at the expense of dextrose. Dextrose was purchased from a bakery supply house. Beef fat was donated by the Belmont Packing Co., Detroit, MI, and was rendered in the laboratory. Other dietary components were obtained from Dyets, Inc., Bethlehem, PA.

Chemicals. Reagent grade chemicals were obtained from standard sources. [1-14C]Ornithine (50 mCi/mmol) was purchased from New England Nuclear, Boston, MA. DFMO (MDL 71,782) was a gift from Dr. Peter P. McCann, Merrell-Dow Pharmaceuticals, Inc., Cincinnati, OH. AOM was obtained from Ash-Stevens Co., Detroit, MI, and was prepared as an aqueous solution for injection.

ODC Assay: Treatment of Rats, Tissue Preparation, and Enzyme Assay. Animals were routinely starved (water allowed) for 24 hr prior to the i.r. instillation of sodium deoxycholate. Instillation of deoxycholate was done by injecting the solution (1.0 ml, 6 to 24 mm deoxycholate in 0.9% NaCl solution) with a 1-ml syringe through a No. 8F Foley catheter. The balloon was inflated after insertion to occlude the rectal opening. In small rats, occlusion was achieved simply by pinching the anus around the catheter without inflating the balloon. We tested both methods using 1 ml of methylène blue solution and found that the solution traversed the entire colon to the cecum. After instillation, the rats were restrained in a horizontal (supine) position for 1 min to expose the entire length of colon to the instillate. After the catheter was removed, rats were placed in cages and provided with drinking water. Where indicated DFMO was added to the drinking water for 4 days before deoxycholate treatment.
Three hr after deoxycholate instillation, rats were killed by decapitation, and the colons were removed, rinsed with cold 0.9% NaCl solution, and scraped with a razor blade. The scraped mucosa from 2 rats were pooled and immediately homogenized in 5 ml of cold homogenizing buffer (0.25 M sucrose in 50.0 mM Tris-HCl, ultrapure, pH 7.5 at 25°C, containing also 0.1 mM EDTA, 0.4 mM pyridoxal 5'-phosphate, and 1.0 mM dithiothreitol). Homogenates were centrifuged for 75 min at 100,000 g and 4°C; supernatant fluids were frozen immediately at −80°C.

In the rat tumor ODC studies, rats (fed 30% fat diet) received weekly s.c. injections of AOM (8 mg/kg of body weight) for 12 weeks. In this system, 100% of colon tumors are adenocarcinomas (5). Control rats received sterile water injections. Twenty-six weeks after the first AOM injection, animals were killed by decapitation, and colons were rinsed with cold 0.9% NaCl solution, stretched on ice-cold glass plates, and examined for the presence of tumors. Tumors were carefully freed of surrounding tissue, pooled for each rat, minced in homogenizing buffer, homogenized, and processed as described above. Normal-appearing intestinal mucosa were collected by scraping with a razor blade and were homogenized immediately.

Human specimens were obtained at local hospitals. Immediately after excision, the specimen was placed on ice. About 0.5-g samples of the actively growing area of tumor and normal-appearing mucosa were placed in cryotubes containing 1 ml of homogenizing buffer. The tubes were sealed and transported in liquid nitrogen to the laboratory for processing as described above for the rat tissue. The malignancy of tumors was established by the pathology reports.

ODC activity in colon mucosa was determined by a modification of the method of Russell and Snyder (21). The standard assay contained 1 mM EDTA, 1 mM dithiothreitol, 0.05 mM pyridoxal 5'-phosphate, 50 mM 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (pH 7.4), 0.02 mM L-ornithine, 0.25 μCi of [1-14C]ornithine (40 to 60 μCi/mmol) in 0.01 M HCl, and 0.5 to 3.5 mg of protein in a total reaction volume of 2.0 ml. Reactions were run in 25-ml Erlenmeyer flasks equipped with rubber stoppers supporting polyethylene center wells ( Kontes Scientific Glassware, Vineland, NJ; Catalogue Nos. K-882310-0000 and 882320-0000). All components of the system except enzyme were agitated for 10 min at 37°C. After addition of enzyme, the mixture was shaken for 60 min at 37°C. The reaction was stopped by addition of 1 ml of 2 M citric acid, and liberated 14CO2 was collected for 60 min in 0.2 ml of Hyamine hydroxide (New England Nuclear) suspended in the center well. Center wells were removed and placed in vials containing 2.0 ml of ethanol and 10 ml of toluene-based Omnifluor (98% PPO, 2% p-bis-(O-methylstyryl)benzene; New England Nuclear) scintillation fluid. All determinations were performed in duplicate, and control incubations without enzyme were done with each experiment. Protein concentration of the enzyme preparation was determined spectrophotometrically by the Lowry procedure (10) using bovine serum albumin as a standard. One enzyme unit is defined as one pmol of CO2/hr/mg of protein. Results were plotted as mean ± S.D.

Human tissues were analyzed by the same procedure used for rat tissues, except that human tissues were incubated at 4 different concentrations of L-ornithine, and Vmax was determined for greater reliability when making comparisons between specimens. Student's t test was used to analyze the significance of results.

**DFMO Tumorigenesis Study.** At the beginning of the experiment, rats were divided into 4 groups of 25 each, and all were fed the standard 5% fat diet throughout the study. The control group was given double-distilled deionized drinking water; the other groups received water supplemented with 0.01, 0.1, or 1.0% (w/v) DFMO. All rats received weekly s.c. injections of AOM (8 mg/kg of body weight) for 8 weeks. Body weights and water consumptions were recorded weekly, and food consumptions were determined every 4 weeks. After 12 weeks of treatment, 4 animals in each group were killed for determination of deoxycholate-induced ODC activity. After 26 weeks, all animals were killed, necropsies were performed, and all tissues were examined grossly for tumors. The number, size, and location of intestinal tumors were recorded.

**RESULTS**

**Induction of Colonic ODC Activity with a Bile Salt.** Using a slightly modified procedure of Takano et al. (22), in which we eliminated anesthesia during the instillation of the bile salt, we have verified their findings that sodium deoxycholate causes stimulation of ODC activity in the rat colon mucosa in a dose-dependent fashion. In addition, we have found that, when deoxycholate was instilled at a fixed concentration, there was no effect of volume on ODC induction in the range tested (1.0 to 3.0 ml of 18 mM solution; data not shown). Furthermore, we have demonstrated an age dependence of deoxycholate-induced ODC activity, as shown in Chart 1. There are 2 distinct rates of decline. In young rats, the rate of decline is rapid; in older rats, it is more gradual. The change in rate coincides with the onset of puberty (2), which suggests the influence of hormones in these male rats, rather than an age or body weight effect. There was essentially no effect of age on the basal level of colonic ODC activity [mean, 0.0008 ± 0.0005 (S.D.) nmol/hr/mg].

**Effect of High-Fat Diet on Colonic ODC Activity.** The promotional effect of a high-fat diet in the rat colon has been demonstrated in our laboratory (5). Now we report that a 30% fat diet also causes an elevation in ODC activity in the rat colon, as shown in Chart 2. The high-fat effect is evident as an increase in both the basal level of ODC as well as an increased response to i.r. instillation of deoxycholate. In addition, the same phenomena were observed in rats fed ad libitum as well as in animals starved for 24 hr prior to killing.

**Effect of DFMO on Bile Salt-induced ODC Activity in the Rat Colon.** The effect of DFMO on basal (normal) and deoxycholate-induced ODC activity in the rat colon is shown in Chart 3. The basal level of ODC activity is relatively unaffected by 0.25% DFMO. However, there is a dose-dependent inhibition of deoxycholate-mediated ODC induction from 0.005 to 0.1% DFMO. The highest dose of DFMO (0.25%) does not produce significant inhibition above that achieved with 0.10%. Addition of 200 nmol of DFMO to the incubation mixture caused a 96% inhibition of ODC activity.

**Effect of DFMO on AOM-induced Tumorigenesis.** The effect of DFMO on AOM-induced intestinal tumorigenesis and ODC activity is shown in Table 1. There was a dose-dependent decrease in intestinal tumor frequency with increasing doses of

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DFMO. The inhibition due to DFMO was evident in all segments of the intestinal tract. At the lowest level of DFMO tested (0.01%), the inhibition was not statistically significant, but the trend was evident.

![Chart 2](image2)

Chart 2. Effect of high-fat diet on basal and deoxycholate (DOX)-induced ODC activity in rat colon. Rats were fed either 5 or 30% fat diet for 6 weeks. Animals (approximate age, 76 days; body weight, 307 ± 43 S.D.) g were instilled with 1 ml of 18 mw deoxycholate or 0.9% NaCl solution. All bars (S.D.) represent pools of 2 rat colons except the starved, deoxycholate-induced, 5% fat (6 colons) and 30% fat (4 colons) colons. There is a significant difference between ODC activity of rats fed 5% fat and rats fed 30% fat (p < 0.05), except for basal levels of the enzyme in the starved animals.

![Chart 3](image3)

Chart 3. Effect of DFMO administered in drinking water for 4 days on deoxycholate-induced ODC. Bile salt was instilled i.r. at a 6 mm concentration. Body weight was 164 ± 14 (S.D.) g; approximate age was 43 days. Each bar (S.D.) represents a pool of 2 rat colons. All levels of DFMO significantly (p < 0.01) inhibited deoxycholate-induced ODC activity. There was also a significant difference between ODC activity of rats fed 5% fat and rats fed 30% fat (p < 0.05), except for basal levels of the enzyme in the starved animals.

Table 1

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Small bowel</th>
<th>Large bowel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal ODC</td>
<td>DOX* reduced ODC (pmol of CO₂/hr/mg of protein)</td>
<td>Tumor frequency</td>
</tr>
<tr>
<td>Basal ODC</td>
<td>DOX* induced ODC (pmol of CO₂/hr/mg of protein)</td>
<td>Tumor frequency</td>
</tr>
<tr>
<td>Control</td>
<td>163</td>
<td>452</td>
</tr>
<tr>
<td>0.01% DFMO</td>
<td>94</td>
<td>575</td>
</tr>
<tr>
<td>0.1% DFMO</td>
<td>293</td>
<td>22.1</td>
</tr>
<tr>
<td>1% DFMO</td>
<td>27</td>
<td>73.2</td>
</tr>
<tr>
<td>1% DFMO</td>
<td>42</td>
<td>152</td>
</tr>
<tr>
<td>1% DFMO</td>
<td>94</td>
<td>575</td>
</tr>
<tr>
<td>0.1% DFMO</td>
<td>293</td>
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<tr>
<td>0.01% DFMO</td>
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<td>575</td>
</tr>
<tr>
<td>Control</td>
<td>163</td>
<td>452</td>
</tr>
</tbody>
</table>

*DOX, deoxycholate.
\(a\) 5 mm DOX via i.r. instillation 3 hr before killing; 12th week of the experiment.
\(b\) At 26th week of the experiment.
\(c\) Mean ± S.D.
\(d\) p < 0.025 compared to controls.
\(p\) < 0.005 compared to controls.

Rats consuming 1% DFMO had reduced food consumption and lower body weights compared to the other 3 groups. The 1% DFMO rats weighed an average of 392 g at the end of 26 weeks, compared to an average of 502 g in the other groups. The toxicity of DFMO at the 1% level may be partially responsible for the reduction in tumor frequency. There was no difference between the other treatment groups and the control group with respect to body weight or food consumption.

The effect of i.r. instillation of 6 mm deoxycholate on ODC activity in the small and large intestines are also shown in Table 1. In the large bowel, there was a substantial reduction in ODC induction after 12 weeks of treatment with DFMO. This reduction was dose dependent, and it correlated with the reduction of tumorigenesis. In the small intestine, there was an increase in ODC activity due to deoxycholate instillation in the colon. This was unexpected, but it could have been due to absorption of deoxycholate from the colon, followed by delivery to the small intestine via the blood stream. The effect of DFMO in the small bowel was evident, but it did not correlate strongly with the respective dose levels.

Table 2

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of rats</th>
<th>ODC activity (pmol of CO₂/hr/mg protein)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>10</td>
<td>15 ± 5(e)</td>
</tr>
<tr>
<td>Normal-appearing colon</td>
<td>11</td>
<td>173 ± 146</td>
</tr>
<tr>
<td>Adenocarcinomas</td>
<td>11</td>
<td>930 ± 615(f)</td>
</tr>
</tbody>
</table>

* 20 µM substrate concentration.
\(e\) Mean ± S.D.
\(f\) From rats with colon tumors.
\(p\) < 0.001 versus normal-appearing colon in the same rats.

The activity of ODC in human colon tissue is shown in Table 3. Significantly higher enzyme activity was found in both malignant colon tumors and in colonic polyps relative to the normal-appearing mucosa of the respective tumor-bearing rats. The activity of ODC in human colon tissue is shown in Table 3. Significantly higher enzyme activity was found in both malignant colon tumors and in colonic polyps relative to the normal-appearing mucosa of the respective tumor-bearing rats. The mean value of polyp ODC activity was intermediate between that of tumors and normal-appearing colon; however, the limited number of tumors and normal-appearing colon; however, the limited number
whereby dietary fat exerts its effect, we have reported that direct

determining the extent of ODC induction. Furthermore, we have

depended response of older rats to treatment with a tumor-
lum. While bile salts have been suggested to be the agents

which may be present simultaneously in the colonie

tissue to dietary fat is the same as that produced by more direct

application of fats will increase colonic DNA synthesis (4). This

raises the possibility that components of the fats themselves

may act to enhance tumorigenesis, in addition to the effects of

bile salts.

The persistence of the increased ODC activity throughout the

24-hr starvation period suggests a change in the tissue with

respect to this enzyme as neoplasia progresses. Such a pro-

gression has been noted in the mouse skin where ODC activity

increases from normal skin through papillomas up to the highest

levels which are found in carcinomas (16). We have noticed a

similar progression in both the rat and human colon.

Since ODC induction is related to tumor promotion, it seems

reasonable that agents which inhibit this induction should be

able to inhibit, at least in part, tumor promotion. Such a rela-

tionship has been established in at least 2 studies in mouse skin. A

series of retinoids has been shown to inhibit both 12-O-tetradec-

anoilphorbol-13-acetate-mediated tumor promotion and ODC

induction (25). Similar data were also obtained with DFMO, an

enzyme-activated irreversible inhibitor of ODC activity (23). It is

important to realize, however, that there are steps in the tumor

promotion process, other than ODC induction, at which inhibitors

could act and still be effective (9).

The results of our studies on colonic ODC activity have pro-

duced 3 basic sets of information. (a) A level of dietary fat which

enhances colonic tumorigenesis will also cause an increase in

colonie ODC activity and increase the response of the colon to

a tumor-promoting bile salt. The latter observation may indicate

the existence of an interaction between promoting agents. (b) We

have demonstrated a dose-dependent inhibition of AOM-

induced intestinal tumor formation by DFMO. The reduction in

tumorigenesis was accompanied by a similar inhibition of deox-

ycholate-induced ODC activity. Similar results have also been

reported for the rat mammary, mouse colon, and mouse skin

systems (7, 8, 23). These reports serve to strengthen the asso-

ciation between ODC induction and the phenomenon of tumor

promotion. While, as mentioned earlier, the relationship between

ODC and tumor promotion is not absolute, it is reasonable to

suggest that potent inhibitors of ODC make good candidates for

tumorigenesis inhibitors, as demonstrated by the data presented.

(c) These studies describe yet another system in which ODC

levels are raised in the malignant state. This indicates additional

similarities between the animal model commonly used to study

colon cancer and the disease as it occurs in humans.

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deoxythymidine incorporation in the colon of rats treated intrarectally with bile

Table 3

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of samples</th>
<th>ODC activity [pmol CO2/hr/mg of protein (Vmax)]</th>
<th>ODC activity at 20 µm substrate concentration [pmol CO2/hr/mg of protein (Vmax)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal-appearing colon*</td>
<td>22</td>
<td>172 ± 241*</td>
<td>111 ± 157</td>
</tr>
<tr>
<td>Polyps†</td>
<td>6</td>
<td>886 ± 644†</td>
<td>462 ± 382</td>
</tr>
<tr>
<td>Adenocarcinomas</td>
<td>14</td>
<td>1121 ± 544†</td>
<td>715 ± 412</td>
</tr>
</tbody>
</table>

* From patients with colon tumors.
† Mean ± S.D.
*p < 0.05 versus normal-appearing colon in same patients.

DISCUSSION

The multistep nature of intestinal carcinogenesis has been
reported numerous times (5, 13, 17-19). A variety of agents has
been shown to enhance tumorigenesis when given after expo-
sure to a carcinogen. The promotional stimuli include increased
fat intake, oral administration of certain drugs, and i.r. instilla-
tion of bile salts. More recently, the biochemical response of the
intestinal epithelia to treatment with these agents has been
studied. In those situations examined, these agents elicit the
same response in their target tissue as do classical tumor promotor
mice skin initiation-promotion model (1, 5, 16, 22).

Takano et al. (22) have shown that i.r. instillation of tumor-
promoting bile salts will increase colonic ODC activity. In the
present study, we have verified their results with respect to the
time course and dose response for ODC induction. In addition,
we have found that the concentration of the instilled bile salt
solution and not its total dose (volume), is the important factor
determining the extent of ODC induction. Furthermore, we have
noted a decreased deoxycholate induction of ODC activity with
increasing age of the animals. Therefore, these data reflect a
decreased response of older rats to treatment with a tumor-
promoting bile salt. These findings emphasize the need for age-
matched animals (or taking into account age difference) when
doing comparative studies in colonic carcinogenesis.

High levels of dietary fat will enhance carcinogenesis, as has
been shown by both human epidemiological studies and numer-
ous experiments with laboratory animals (6). In many organs,
including skin, breast, pancreas, and colon, this effect occurs
during the promotional phase (5, 6, 20, 24). In this study, we
report that feeding a 30% fat diet for 6 weeks caused an increase
in colonic ODC activity both in rats fed and in those starved 24
hr before killing. These data show that the response of the target
tissue to dietary fat is the same as that produced by more direct
application of tumor-promoting agents (22). Furthermore, this fat
effect is evident in the increased responsiveness of the colon to
i.r. treatment with deoxycholate. Therefore, these results raise
the possibility of interaction between different tumor-promoting
agents which may be present simultaneously in the colonic
lumen. While bile salts have been suggested to be the agents
whereby dietary fat exerts its effect, we have reported that direct

of polyp specimens obtained precluded the demonstration of a
statistically significant difference.

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