Chemoprevention of Colon Carcinogenesis by Dietary Organoselenium, Benzylselenocyanate, in F344 Rats

Bandaru S. Reddy, S. Sugie, Hiroshi Maruyama, Karam El-Bayoumy, and Patrice Marra

ABSTRACT

The effect of feeding benzylselenocyanate (BSC) and its sulfur analogue, benzylthiocyanate (BTC), 2 wk before, during, and until 1 wk after carcinogen administration (initiation phase) on intestinal carcinogenesis induced by azoxymethane (CAS:25843-45-2) was studied in male F344 rats. Weanling rats were raised on a semipurified diet (AIN-76A diet; control diet). Beginning at 5 wk of age, groups of animals consuming the control diet were fed one of the diets containing 25 ppm BSC or BTC. An additional group was continued on the control diet. At 7 wk of age, all animals in 3 groups, except the vehicle-treated controls, were administered s.c. injections of azoxymethane (15 mg/kg body weight, once weekly for 2 wk). Animals were continued on the control diet and BSC and BTC diets until 1 wk after carcinogen treatment, when those groups receiving BSC and BTC diets were fed the control diet until termination of the experiment. Tissue and blood plasma glutathione peroxidase activity was measured in vehicle-treated animals fed the control diet and BSC and BTC diets for 5 wk. The results indicate that body weights were comparable among the various dietary groups. BSC in the diet significantly inhibited the incidence (percentage of animals with tumors) and multiplicity (tumors/animal) of adenosarcomas in the colon and multiplicity of adenosarcomas in the small intestine compared to those fed the control diet. BTC in the diet had no effect on colon and small intestinal tumors. Selenium-dependent glutathione peroxidase activity was significantly increased in kidneys and colon and small intestinal mucosae of animals fed the BSC diet compared to animals fed the BTC and control diets.

INTRODUCTION

Chemoprevention, which focuses on the inhibition of carcinogenesis by chemical agents, is a concept that certain agents, in particular, synthetic antioxidants and certain naturally occurring substances found in some foods, such as phenols, indoles, aromatic isothiocyanates, selenium, and several vitamins, to cite a few, could inhibit partially or totally the carcinogenic process or development of tumors (11).

Large bowel cancer is the neoplastic disease that strikes both men and women in the United States at high frequency (2). Epidemiological and animal model studies suggest that nutritional factors are of major importance in its etiology (3, 4). Epidemiological studies also suggest an increased incidence of large bowel cancer in humans in geographical regions where selenium is deficient (5–7). A large body of evidence in animal models indicates that supplementation of the diet or drinking water with inorganic selenium protects against cancer induced by a variety of chemical carcinogens, including cancer of the colon, mammary gland, pancreas, to cite a few (8–13). These data have resulted in considerable interest in the potential of selenium as a chemopreventive agent.

Although inorganic selenium has been shown to inhibit carcinogenesis, there is a concern about its toxicity. On a molar basis, selenium salts are the most toxic among the essential elements (14). Generally, chronic feeding of 5 to 10 ppm of selenium is toxic in animals. Toxic reproductive and teratogenic effects of selenium have been reported for both animals and humans (14).

Since selenium occurs predominantly as an organic form (selenomethionine) in cereals, vegetables, and grains, attention has been focused to study the effect of organic forms of selenium in carcinogenesis. In the methylnitrosourea-DMBA-induced mammary carcinogenesis, dietary inorganic selenium (4 to 6 ppm) provided greater inhibition of mammary carcinogenesis in female rats than did an equivalent amount of selenium in the form of selenomethionine (9). In addition, 6 ppm selenium in the form of selenomethionine caused liver damage as indicated by extensive necrosis and fibrosis (9). These observations show the need to identify and develop novel forms of organoselenium compounds that are least toxic and more effective than inorganic forms and that can be used effectively as chemopreventive agents. In addition, synthetic organoselenium compounds offer greater promise for the chemoprevention of cancer, in that their chemical structures can be altered to provide maximal chemopreventive efficacy with minimal toxicity.

To answer the question of identification of novel selenium compounds that are less toxic and possess tumor-inhibitory effect, we synthesized two organoselenium compounds, MBS and BSC, which were found to be effective inhibitors of benzo(a)pyrene-induced forestomach tumors in mice (15). The 50% lethal doses of MBS and BSC in mice were 370 and 18 mg/kg body weight, respectively. Feeding of 50 ppm MBS in a semipurified diet containing high fat 2 wk before, during, and 1 wk after carcinogen treatment inhibited AOM-induced colon, kidney, and hepatocarcinogenesis in rats (16, 17). In the present study, we have investigated the potential inhibitory activity of dietary BSC and its sulfur analogue, BTC, when fed during the initiation phase (before and during carcinogen treatment) of colon carcinogenesis in male F344 rats. The effect of these diets on tissue and blood glutathione peroxidase activiy (seleno-enzyme) was measured.

MATERIALS AND METHODS

Animals, Diets, and Carcinogen. A total of 177 weanling male F344 rats were purchased from Charles River Breeding Laboratories, Wilmington, MA. AOM (CAS:25843-45-2) was obtained from Ash Stevens, Detroit, MI, and BTC from Aldrich Chemicals, Milwaukee, WI. BSC was synthesized in the laboratory of Dr. Karam El-Bayoumy by a previously described procedure and added to the diet (15). AIN-76A diet was used throughout the study (18, 19). All diet ingredients were obtained from Dyets, Inc., Bethlehem, PA, and mixed in our laboratory.

The composition of this semipurified diet is as follows (18, 19): casein, 20%; dL-methionine, 0.3%; corn starch, 52.0%; dextrose, 13.0%; corn oil, 5%; Alphacel, 5%; mineral mix (AIN-76), 3.5%; water with inorganic selenium protects against cancer induced by a variety of chemical carcinogens, including cancer of the colon, mammary gland, pancreas, to cite a few (8–13). These data have resulted in considerable interest in the potential of selenium as a chemopreventive agent.

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2 To whom requests for reprints should be addressed.
vitamin mix (AIN-76A), 1%; and choline bitartrate, 0.2%. BSC or BTC was added to the semipurified diet at a level of 25 ppm. The AIN-76A (control) diet contains 0.1 ppm selenium as sodium selenite. The experimental BSC and BTC diets contain, in addition to 0.1 ppm inorganic selenium, 10 ppm and 0 ppm selenium, respectively. The incorporation of BSC or BTC into the semipurified diet was done with a V-blender after BSC or BTC was premixed with a small quantity of diet in a food mixer to ensure uniform distribution of these compounds. The stability of BSC and BTC in the diet during 10 min, 24 h, and 48 h at room temperature and during 2 wk at 4°C was confirmed by high-pressure liquid chromatography analysis (15). Control and experimental diets were prepared twice weekly.

Experimental Procedure. Male F344 rats received at weaning were quarantined for 10 days and had access to AIN-76A semipurified diet (control diet). They were then randomly allocated by weight to one of three dietary groups (control diet and 25 ppm BSC and 25 ppm BTC diets). Each dietary group was divided into AOM-treated (27 animals per subgroup) and vehicle-treated (12 animals per subgroup) subgroups and housed in plastic cages with filter tops in the animal holding room under controlled environmental conditions.

Beginning at 5 wk of age, groups of rats fed the control diet were transferred to diets containing 25 ppm BSC or 25 ppm BTC. At 7 wk of age, the contents of each group, except the vehicle-control group, were given two weekly s.c. injections of AOM at a dose level of 15 mg/kg body weight/wk. Vehicle controls were treated with an equal volume of normal saline. One wk after AOM or saline treatment, animals receiving the BSC and BTC diets were transferred to the control diet and continued on this diet until the termination of the experiment. The 1-wk delay before transferring to control diet was to ensure complete metabolism and excretion of the carcinogen. The animals receiving the control diet were continued on the same diet. The experiment was terminated 34 wk after the last AOM injection.

Body weights were recorded weekly until the animals reached 16 wk of age and then every 4 wk. Six vehicle-treated animals randomly chosen from each dietary group while they were consuming experimental and control diets were used for tissue and blood plasma glutathione peroxidase analysis.

As scheduled, both AOM- and vehicle-treated animals were sacrificed by CO₂ euthanasia. Following laparotomy, the entire stomach, small intestine, and large intestine were resected and opened longitudinally, and the contents were flushed with normal saline. The location, number, and size of colon and small intestinal tumors were noted grossly under the dissection microscope. All other organs, including liver and kidneys, were also examined grossly for tumors. Tissues were fixed in 10% buffered formalin, embedded in paraffin blocks, and processed by routine histological methods with the use of eosin and hematoxylin stains. The histological criteria used for tumor classification were as described previously (20).

Biochemical Determination. For the determination of tissue and blood plasma glutathione peroxidase activity, 6 vehicle-treated animals from each dietary group, while the animals were on experimental and control diets, were used. Before sacrificing the animals, blood was obtained under ether anesthesia by cardiac puncture with a syringe. They were then decapitated, and liver, kidneys, small intestine, and colon were rapidly removed. The liver was perfused with ice-cold normal saline. The small intestine and colon were slit open longitudinally and freed from all the contents, and the mucosa was scraped with a microscope glass slide. The liver and kidneys were trimmed free of connective tissue, minced with scissors, and homogenized for 10 s in 3 volumes of buffer, pH 7.3 (0.25 sucrose-10 mM EDTA-50 mM potassium phosphate) using a Brinkman Polytron at low speed. The colonic and small intestinal mucosal scrapings were immediately placed into 3 volumes of the same buffer and homogenized similarly. The homogenates were centrifuged in a Sorvall RC-2B centrifuge at 10,000 × g, 4°C, for 20 min. The supernatant was centrifuged in a Beckman Ultracentrifuge at 100,000 × g, 4°C, for 1 h. The resulting cytosol fraction was used for determination of glutathione peroxidase activity and protein.

Glutathione peroxidase activity was determined spectrophotometrically according to a modification of the enzyme-coupled assay procedure of Paglia and Valentine (21–23). The reaction mixture consisted of 50 mM potassium phosphate buffer (pH 7.0), 1 mM EDTA, 0.2 mM NADPH, 1 enzyme unit/ml oxidized glutathione-reductase, 1 mM glutathione, and 1.5 mM cumene hydroperoxide in a total volume of 1 ml. The cytosol was added to the above mixture and allowed to incubate 5 min at room temperature. Total glutathione peroxide was measured with cumene hydroperoxide as a substrate. Selenium-dependent glutathione peroxidase was measured with tert-butyl hydroperoxide. The reaction was started with the addition of substrate solution. Absorbance was measured at 340 nm, and activity was measured from the slope of the lines as amol NADPH oxidized/min/mg protein. Blank reactions without cytosol were run simultaneously. Protein concentration in the cytosol fraction was measured by the method of Lowry et al. (24) with bovine serum albumin as standard.

Statistical Analysis. The data on tumor incidence were analyzed statistically by the χ² method and Fischer’s exact probability test, and tumor multiplicity was analyzed by Student’s t test. Biochemical results were analyzed by Student’s t test.

RESULTS

General Observations. There was no evidence of toxicity in animals fed BSC and BTC diets. Body weights of animals fed the experimental and control diets and treated with AOM or vehicle were comparable (Table 1). However, as expected, the body weights of AOM-treated animals in all dietary groups were slightly lower than the vehicle-treated animals during the terminal part of the study because of tumor burden and consequent reduction in body weight.

Tumor Incidences. Table 2 summarizes AOM-induced colon tumor incidences (percentage of animals with tumors) and colon tumor multiplicity (number of tumors/animal). One animal from the BTC group died 2 wk after AOM treatment and was not included in the results. The incidences of AOM-induced total colon tumors as well as adenocarcinomas of the colon were significantly lower in rats fed the BSC diet than in those fed the control diet. There were no differences in colon tumor incidences between the animals fed the control diet and BTC diet. With regard to colon tumor multiplicity, the number of total colon tumors (adenomas and adenocarcinomas) in the dietary groups were not significant (P > 0.05), feeding of the BSC diet slightly reduced the incidence of small intestinal adenocarcinomas. Small intestinal tumor multiplicity was significantly inhibited in animals fed the BSC diet compared to those fed the control diet and BTC diet. Although there was a slight inhibition of multiplicity of adenomas in the BSC diet as compared to the control diet and BTC diet, the differences, however, did not reach statistical significance (P > 0.05).

Table 3 shows the incidence and multiplicity of small intestinal tumors and incidence of ear duct tumors. Although the differences in the incidence of small intestinal tumors among the dietary groups were not significant (P > 0.05), feeding of the BSC diet slightly reduced the incidence of small intestinal adenocarcinomas. Small intestinal tumor multiplicity was significantly inhibited in animals fed the BSC diet compared to those fed the BTC diet and control diet. A significant inhibition in the multiplicity of small intestinal adenocarcinomas was observed in animals fed the BSC diet compared to those fed the control diet. There was a slight but not significant difference in ear duct tumor incidences among the dietary groups. Two animals in the BSC diet group, 5 animals in the control diet group, and 5 animals in the BTC diet group developed ear duct tumors. Two animals in the control diet groups developed metastases in several organs, whereas none of the animals in BSC and BTC diet groups developed metastasis.

Biochemical Observations. Table 4 summarizes the selenium-dependent glutathione peroxidase activity in various tissues. Since there are no differences in the activity of non-selenium-
ORGANOSelenium INHIBITION OF COLON CANCER

Table 1. Body weights of male F344 rats fed the experimental diets

<table>
<thead>
<tr>
<th>Dietary group</th>
<th>No. of rats at start of experiment</th>
<th>Initial wk (Wk 0)</th>
<th>4</th>
<th>8</th>
<th>16</th>
<th>22</th>
<th>30</th>
<th>37 (at termination)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AOM treated</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>27</td>
<td>42 ± 3*</td>
<td>178 ± 10</td>
<td>285 ± 14</td>
<td>350 ± 19</td>
<td>388 ± 20</td>
<td>435 ± 21</td>
<td>454 ± 24</td>
</tr>
<tr>
<td>BSC diet</td>
<td>27</td>
<td>40 ± 4</td>
<td>174 ± 9</td>
<td>279 ± 15</td>
<td>348 ± 16</td>
<td>390 ± 21</td>
<td>430 ± 20</td>
<td>449 ± 22</td>
</tr>
<tr>
<td>BTC diet</td>
<td>27</td>
<td>40 ± 3</td>
<td>180 ± 10</td>
<td>281 ± 18</td>
<td>356 ± 21</td>
<td>394 ± 22</td>
<td>432 ± 24</td>
<td>459 ± 19</td>
</tr>
<tr>
<td>Vehicle treated</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>12</td>
<td>39 ± 3</td>
<td>184 ± 11</td>
<td>289 ± 16</td>
<td>361 ± 20</td>
<td>398 ± 21</td>
<td>442 ± 28</td>
<td>469 ± 20</td>
</tr>
<tr>
<td>BSC diet</td>
<td>12</td>
<td>41 ± 4</td>
<td>179 ± 12</td>
<td>284 ± 19</td>
<td>364 ± 19</td>
<td>402 ± 20</td>
<td>448 ± 26</td>
<td>467 ± 21</td>
</tr>
<tr>
<td>BTC diet</td>
<td>12</td>
<td>40 ± 3</td>
<td>182 ± 10</td>
<td>286 ± 18</td>
<td>362 ± 21</td>
<td>406 ± 22</td>
<td>449 ± 24</td>
<td>470 ± 24</td>
</tr>
</tbody>
</table>

* Mean ± SD.

Table 2. Effect of dietary benzylselenocyanate and benzylthiocyanate on azoxymethane-induced colon tumors in male F344 rats

<table>
<thead>
<tr>
<th>Dietary group</th>
<th>No. of animals/group</th>
<th>Colon tumor incidence (% of animals with tumors)</th>
<th>Colon tumor multiplicity (no. of tumors/animal)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Colon Adenoma Adenocarcinoma Colon Adenoma Adenocarcinoma</td>
<td>Total Adenoma Adenocarcinoma Total Adenoma Adenocarcinoma</td>
</tr>
<tr>
<td>Control</td>
<td>27</td>
<td>78 (21) 59 (16) 38 (10)</td>
<td>1.62 ± 1.2 (44) 1.18 ± 1.2 (32) 0.44 ± 0.6 (12)</td>
</tr>
<tr>
<td>BSC diet</td>
<td>27</td>
<td>48 (13) 44 (12) 11 (3)</td>
<td>0.81 ± 1.0 (32) 0.69 ± 1.0 (22) 0.70 ± 0.9 (19)</td>
</tr>
<tr>
<td>BTC diet</td>
<td>26</td>
<td>69 (18) 62 (16) 31 (9)</td>
<td>1.62 ± 1.3 (42) 1.27 ± 1.3 (33) 0.35 ± 0.4 (9)</td>
</tr>
</tbody>
</table>

* Animals were fed the control diet and BSC and BTC diets 2 wk before, during, and until 1 wk after carcinogen treatment, and then the animals on BSC and BTC diets were transferred to control diet.

Table 3. Effect of dietary benzylselenocyanate and benzylthiocyanate on azoxymethane-induced tumors in male F344 rats

<table>
<thead>
<tr>
<th>Dietary group</th>
<th>Small intestinal tumor incidence (% of animals with tumors)</th>
<th>Small intestinal tumor multiplicity (no. of tumors/animal)</th>
<th>% of animals with ear duct tumors</th>
<th>No. of animals with metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total Adenoma Adenocarcinoma Total Adenoma Adenocarcinoma</td>
<td>% of animals with ear duct tumors</td>
<td>No. of animals with metastasis</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>33 (9) 11 (3) 26 (7) 0.52 ± 0.5 0.15 ± 0.4 0.41 ± 0.7 29 (8) 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BSC diet</td>
<td>19 (5) 4 (1) 15 (4) 0.19 ± 0.3 0.04 ± 0.2 0.15 ± 0.3 7 (2) 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BTC diet</td>
<td>38 (10) 12 (3) 38 (10) 0.46 ± 0.6 0.12 ± 0.3 0.34 ± 0.6 19 (5) 0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Twenty-seven animals were used in the control diet and BSC and BTC diets and 26 animals in the BSC diet group.

Table 4. Effect of dietary benzylselenocyanate and benzylthiocyanate on selenium-dependent glutathione peroxidase activity in various tissues of male F344 rats

<table>
<thead>
<tr>
<th>Dietary group</th>
<th>Plasma</th>
<th>Liver</th>
<th>Kidney</th>
<th>Colon</th>
<th>Small intestine</th>
<th>μmol NADPH oxidized/min/mg protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.64 ± 0.20*</td>
<td>1.99 ± 0.40*</td>
<td>0.74 ± 0.24*</td>
<td>0.19 ± 0.04*</td>
<td>0.26 ± 0.02*</td>
<td></td>
</tr>
<tr>
<td>BSC diet</td>
<td>0.78 ± 0.14*</td>
<td>1.88 ± 0.60*</td>
<td>1.70 ± 0.29*</td>
<td>0.56 ± 0.14*</td>
<td>0.71 ± 0.13*</td>
<td></td>
</tr>
<tr>
<td>BTC diet</td>
<td>0.69 ± 0.16*</td>
<td>1.90 ± 0.66*</td>
<td>0.64 ± 0.30*</td>
<td>0.23 ± 0.06*</td>
<td>0.20 ± 0.10*</td>
<td></td>
</tr>
</tbody>
</table>

Weanling animals were raised on AIN-76A semipurified (control) diet. Starting at 5 wk of age, animals were transferred to diets containing BSC or BTC and fed for an additional 5 wk. AIN-76A semipurified (control) diet. Starting at 5 wk of age, animals were transferred to diets containing BSC or BTC and fed for an additional 5 wk.$^b$ Mean ± SE (n = 6).

dependent glutathione peroxidase activity among the dietary groups and for simplification of the data, only the values of selenium-dependent glutathione peroxidase activity have been reported in the present study. Selenium-dependent glutathione peroxidase activity of plasma and liver was not affected by various dietary treatments. There was, however, a significant increase in the enzyme activity in kidney and colonic and small intestinal mucosae of animals fed the BSC diet compared to that in those animals fed the BTC diet and control diet.

DISCUSSION

The results of the present study are of considerable interest because the synthetic organoselenium compound, BSC, but not its sulfur analogue, namely BTC, inhibited AOM-induced tumors in the colon and to a certain extent in the small intestine. BSC also inhibited AOM-induced metastasis in several organs. We are not aware of any previous study of a potential colon tumor-inhibitory effect by BSC. These results confirm our earlier study in which another form of synthetic organoselenium compound, namely MBS, inhibited AOM-induced colon carcinogenesis in rats (16). Our recent study indicated that dietary MBS and BSC, but not BTC, inhibited the development of benz(a)pyrene-induced forestomach tumors in mice (15). Wat-tenberg (25) demonstrated that administration of BTC 4 h prior to administration of carcinogen resulted in the inhibition of DMBA-induced mammary tumors but not DMBA-induced forestomach tumors. These studies together suggest that the
introduction of the element selenium into organic molecules can be utilized in the chemoprevention of certain types of cancer.

It was also demonstrated that the feeding of the BSC diet caused an increase in selenium-dependent glutathione peroxidase activity in the kidney, colon, and small intestine, whereas it had no effect on this enzyme activity in the liver and plasma. The reason for no increase in liver and plasma glutathione peroxidase activity of animals fed the BSC diet is not clear. Studies by Horvath and Ip (26) also indicated that the inorganic selenium supplementation (2.5 ppm) produced an insignificantly increase in the mammary pad and liver glutathione peroxidase activity in rats. However, in 10-wk-old virgin mice, in which the mammary tissue exhibited a rapid growth, increased levels of dietary selenium enhanced the glutathione peroxidase activity of the mammary gland (11). Since colonic and small intestinal mucosal cells proliferate actively, it is possible that the increase in glutathione peroxidase activity of colonic and small intestinal mucosa in animals fed the organoselenium diet can be related to active proliferation of mucosal epithelial cells.

The mechanism by which BSC affects AOM-induced carcinogenesis remains to be elucidated. In the present study, BSC was fed to rats during the initiation stage of colon carcinogenesis. The fact that dietary BSC but not BTC leads to increased levels of glutathione peroxidase activity in colon and small intestinal mucosa suggests that the tumor-inhibitory effect of BSC may be explained, at least in part, on the basis of an increased enzyme-dependent detoxifying system in these tissues. Alternatively, there is some evidence that selenium may act by altering the metabolism of carcinogens resulting in inactive metabolites of carcinogens as observed by Marshall (27). It is possible that, in the present study, the inhibitory effect of BSC may be related to some action of this compound on the metabolic activation and detoxification of AOM. The metabolic activation of AOM to a reactive species capable of alkylating DNA occurs in two steps: (a) the hydrolyzation of AOM to methylazoxymethanol and (b) the oxidation of methylazoxymethanol to methylazoxyformaldehyde (28–30). While the hydrolyzation of AOM to methylazoxymethanol was found mainly to occur in rat liver, probably by a cytochrome P-450-dependent pathway, there is some evidence that the compound may be activated to a limited extent in the colon mucosa (31). The oxidation of methylazoxymethanol to methylazoxyformaldehyde is affected by microsomes from both liver and colon (29), as well as by alcohol dehydrogenase from the cytosol of both of these organs (30). Whether the inhibition of AOM-induced colon carcinogenesis by BSC is due to alteration of metabolic activation and detoxification of AOM and/or to its ability to induce the selenoenzyme glutathione peroxidase activity remains to be investigated.

The results of this and our previous studies (15–17) may open new approaches to the development of effective and less toxic novel selenium-containing chemopreventive agents. There is also a possibility that the chemopreventive efficacy of these organoselenium compounds can be increased and optimized by systematically altering their molecular structures.

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