Chemoprevention of Colon Carcinogenesis by the Synthetic Organoselenium Compound 1,4-Phenylenbis(methylene)selenocyanate

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Divisions of Nutritional Carcinogenesis [B. S. R., N. K.], Experimental Pathology and Toxicology [A. R.], and Chemical Carcinogenesis [P. U., K. E.-B.], American Health Foundation, Valhalla, New York 10595

ABSTRACT

The chemopreventive effect of 40% and 80% maximum tolerated dose (MTD) levels of 1,4-phenylenbis(methylene)selenocyanate (p-XSC) administered in the diet during the initiation phase (2 weeks before, during, and up to 3 days after carcinogen administration) and the postinitiation phase (3 days after carcinogen treatment until termination) of azoxymethane (AOM)-induced colon carcinogenesis was studied in male F344 rats. The MTD of p-XSC was determined in male F344 rats and found to be 50 ppm. Beginning at 5 weeks of age, all animals were divided into various experimental groups (42 rats/group) and fed the high-fat semipurified diet or diets containing 20 (40% MTD) and 40 (80% MTD) ppm p-XSC. At 7 weeks of age, all animals (30 rats/group except the vehicle-treated group [12 rats/group]) were administered s.c. injections of AOM (15 mg/kg body weight; Ref. 22) for 2 weeks). Three days after the second injection of AOM or vehicle (normal saline), groups of animals fed the p-XSC diets and control diet were transferred, respectively, to control diet and p-XSC diets and continued on these diets until the termination of the study. All animals were necropsied during the 36th week after AOM treatment. Colonic mucosal prostaglandin E2 and selenium-dependent glutathione peroxidase were measured in animals fed the control and p-XSC diets at the termination of the study. The results indicate that 40 ppm p-XSC administered during the initiation phase significantly inhibited the colon tumor incidence (percentage of animals with tumors). Dietary p-XSC administered at 20 and 40 ppm levels during the initiation phase significantly inhibited colon tumor multiplicity (tumors/animal and tumors/tumor-bearing animal). Colon tumor incidence and multiplicity were significantly reduced in groups fed 20 and 40 ppm p-XSC diets at the postinitiation phase of carcinogenesis. Colonic mucosal selenium-dependent glutathione peroxidase activity was increased, and prostaglandin E2 was reduced in animals fed the p-XSC diet compared to animals fed the control diet. Whereas the precise mechanisms of p-XSC-induced inhibition of colon carcinogenesis remain to be elucidated, it is likely that the effect during the initiation and postinitiation phases may be due to alteration in carcinogen metabolism and to modulation of prostaglandin synthesis and selenium-dependent glutathione peroxidase activity.

INTRODUCTION

Epidemiological studies indicate an increased incidence of colorectal cancer in humans in geographic regions where selenium is deficient (1–3). Case-control studies suggest an inhibitory effect of selenium on cancer mortality (4, 5). Prospective studies also appear to provide a clear reflection of the association between the levels of selenium and colon cancer (4, 5). Beginning with the work of Clayton and Baumann (6), a series of experiments were conducted in laboratory animals which demonstrate that selenium supplementation in the diet or in drinking water inhibits initiation and/or postinitiation stages of pancreas, liver, colon, and mammary gland carcinogenesis (7–12).

Although inorganic selenium compounds have been shown to inhibit colon carcinogenesis, their toxicity is of concern (13). Since human exposure to selenium occurs primarily through ingestion of the organic form, which occurs predominantly in the form of selenomethionine in cereals, grains, and vegetables, investigators have focused on the inhibitory effect of organic forms of selenium. Ip and White (14) found no significant differences in the tumor-inhibiting potential of the inorganic (e.g., selenate, selenite, selenium dioxide) and organic (e.g., selenomethionine and selenocysteine) selenium compounds in DMB3-induced mammary carcinogenesis. Thompson et al. (15) also showed that selenite was more potent and less toxic than selenomethionine in DMBA-induced mammary tumorigenesis during the postinitiation stage. In fact, selenomethionine at 6 ppm (as selenium) caused liver damage in rats. Milner and Hsu (16) reported that the inorganic selenium compounds were more effective than either selenomethionine or selenocysteine. It is apparent from these studies that the naturally occurring organoselenium compounds do not provide an advantage over inorganic selenium compounds as protective agents in carcinogenesis.

During the last decade it was our goal to develop novel synthetic organoselenium compounds with optimal chemopreventive potency and yet with low toxicity (17). Experiments conducted in our laboratory indicate that synthetic organoselenium compound, BSC, but not its sulfur analogue, benzyl thiocyanate, inhibited AOM-induced colon carcinogenesis when administered during the initiation or postinitiation stage of carcinogenesis, whereas the inorganic form of selenium, sodium selenite, inhibited colon carcinogenesis only during the postinitiation stage (18). Although BSC was less toxic than Na2SeO3 on the basis of its acute 50% lethal dosage (BSC, 125 mg/kg body weight; Na2SeO3, 35 mg/kg body weight), animals fed both agents gained less weight and consumed less food compared to those on the control diet, suggesting that these agents exerted a systemic toxic effect (18). Because of these side effects, additional organoselenium compounds were synthesized in an effort to design more effective chemopreventive agents with minimal toxic side effects. Based on mechanistic and metabolism studies (19), we modified the structure of BSC to develop a more effective and less toxic chemopreventive agent.

Among these novel compounds, p-XSC (Fig. 1) was less toxic than BSC and Na2SeO3, based on 50% lethal dosage and subchronic studies (50% lethal dosage of p-XSC, 1000 mg/kg body weight; Ref. 20). Selenium is an important component of GSH-Px, the biochemical function of which is to protect cells from oxidative

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2 The abbreviations used are: DMBA, 7,12-dimethylbenz[a]anthracene; BSC, benzylselenocyanate; AOM, azoxymethane; GSH-Px, selenium-dependent glutathione peroxidase; PGE2, prostaglandin E2; MTD, maximum tolerated dose; MAM, methylazoxymethanol; p-XSC, 1,4-phenylenbis(methylene)selenocyanate.
The stability of \( \text{p-XSC} \) in the diet at room temperature was confirmed by high-performance liquid chromatography analysis (20). \( \text{p-XSC} \) was extracted with ethyl acetate. The extract was dried with MgSO\(_4\) and evaporated to dryness. A known volume of tetrahydrofuran was added to the residue, and an aliquot was analyzed by high-performance liquid chromatography for \( \text{p-XSC} \) as described above. The recovery of \( \text{p-XSC} \) was more than 97% under the bioassay feeding conditions.

### Determination of Maximum Tolerated Dose of \( \text{p-XSC} \)

The aim of this study was to determine the MTD of \( \text{p-XSC} \), which is defined as the highest dose that causes no more than 10% body weight reduction (as compared to those fed the control diet) and does not induce mortality or external clinical signs of toxicity that would be predicted to shorten the natural life span of the animal. At 35 days of age, groups of male F344 rats (10/group) were fed the high-fat control diet (Table 1) and high-fat diets containing 20, 40, 50, 75, and 100 ppm \( \text{p-XSC} \). All animals were examined daily for any symptoms of toxicity. Body weights were recorded twice weekly for 10 weeks. After 10 weeks on the experimental diets, all animals were sacrificed, and tissues were examined grossly under the dissection microscope for any abnormalities that can be attributed to toxicity of the test agents. The body weights of animals fed the diets containing 20, 40, and 50 ppm of \( \text{p-XSC} \) were comparable to those fed the control diet. Animals fed 75 and 100 ppm of \( \text{p-XSC} \) showed a decline in body weight by about 12 and 20%, respectively. The results of this study thus suggest that the MTD of \( \text{p-XSC} \) is 50 ppm.

### Experimental Procedure

Experiments were designed to study the efficacy of two levels (80% and 40% MTD) of \( \text{p-XSC} \) administered in the high-fat diet during the initiation and postinitiation phases of AOM-induced intestinal carcinogenesis in male F344 rats. The dose levels, respectively representing 80% and 40% MTD, were 40 and 20 ppm. The high-fat control diet contained about 0.1 ppm selenium as Na\(_2\)SeO\(_3\). The experimental 20 and 40 ppm \( \text{p-XSC} \) diets contained about 10 and 20 ppm selenium, respectively.

Male F344 rats received at weaning were quarantined for 10 days. At 5 weeks of age, all animals were divided at random into various experimental groups (27 animals/group) using formal randomized methods (Table 2) and were fed the control or one of the experimental diets containing \( \text{p-XSC} \) (Table 1). At 7 weeks of age, all animals (30/group) except the vehicle-treated received a s.c. injection of AOM at a dose level of 15 mg/kg body weight/week for 2 weeks. Vehicle-treated groups (12 animals/group) received an equal volume of normal saline. Three days after the second injection of AOM or normal saline, groups of animals receiving the experimental diets containing 20 and 40 ppm \( \text{p-XSC} \) were transferred to the control diet and continued on this diet until termination of the experiment (initiation stage). Additional subgroups fed the control diet were transferred to the experimental diets containing 20 and 40 ppm \( \text{p-XSC} \) and continued on these diets until the termination of the study (postinitiation stage). The 3-day delay before feeding the experimental diets was meant to ensure complete metabolism and excretion of AOM. All animals were fed their respective experimental diets and continued on this regimen until the termination of the experiment. Body weights were recorded every 2 weeks until the study was terminated. At 35 days after weaning, groups of animals were killed for histological examination.
INHIBITION OF COLON CANCER BY ORGANOSELENIUM

Table 2 Experimental design

<table>
<thead>
<tr>
<th>Dietary groups</th>
<th>No. of animals/group</th>
<th>Levels of p-XSC</th>
<th>No. of animals/group</th>
<th>Levels of p-XSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>AOM-treated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control diet</td>
<td>30</td>
<td>0</td>
<td>30</td>
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</tr>
<tr>
<td>80% MTD, p-XSC</td>
<td>30</td>
<td>20 ppm</td>
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<td>20 ppm</td>
</tr>
<tr>
<td>40% MTD, p-XSC</td>
<td>30</td>
<td>40 ppm</td>
<td>30</td>
<td>40 ppm</td>
</tr>
<tr>
<td>Saline-treated</td>
<td></td>
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<td></td>
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<tr>
<td>Control diet</td>
<td>12</td>
<td>0</td>
<td>12</td>
<td>0</td>
</tr>
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<td>80% MTD, p-XSC</td>
<td>12</td>
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<td>12</td>
<td>40 ppm</td>
<td>12</td>
<td>40 ppm</td>
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</tbody>
</table>

* Animals were fed the diets containing 0, 20, and 40 ppm p-XSC 2 weeks before, during, and 3 days after the carcinogen or saline treatment and then transferred to control diet.

Analysis of PGE2 and GSH-Px.

Animals intended for PGE2 and GSH-Px analysis were sacrificed by CO2 euthanasia. Colon was rapidly removed, cut open longitudinally, and rinsed with ice-cold normal saline to free them of all contents. They were then laid flat on a glass plate, and the mucosal layer was scraped with a microscope slide. The samples were quickly frozen in liquid nitrogen and stored at -80°C. The samples were homogenized in 0.1 M Tris-HCl buffer (pH 7.4) containing 0.1 M phosphate buffer and 0.1 M dithiothreitol in 20% glycerol. Samples were centrifuged at 105,000 x g for 1 h to separate the cytosol fraction. GSH-Px was determined spectrophotometrically according to a modification of the enzyme-coupled assay procedure (32-34).

RESULTS

General Observations.

Food intake measured at 12 weeks on experimental diets indicated no significant differences in food consumption between the groups fed the control and p-XSC diets. On the average, the daily food consumption of animals in the control diet group, 20 ppm p-XSC group, and 40 ppm p-XSC group was about 14.2, 13.9, and 13.8 g, respectively.

Table 3 summarizes the body weights of animals fed the control and experimental diets. Using analysis of variance, it was found that differences between the means were tested by using Student’s t test as well as analysis of variance. The analyses were carried out on a VAX 11/750 computer using the SAS package.

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was found that the differences in body weights from week 0 to week 36 among the dietary groups (AOM-treated and saline-treated animals) were not significant ($P > 0.05$). AOM-treated animals weighed slightly less than those treated with saline in all dietary groups.

Table 4 shows the AOM-induced colon tumor incidence (percentage of animals with adenocarcinomas) and multiplicity (adenocarcinomas/animal and tumor-bearing animal). In the present investigation, colon tumor classification was based on studies of Elwell and McConnell (30) and Pozharisski (29). According to this classification, more than 90% of colon tumors in the present study were adenocarcinomas and the rest were adenomas. There were no differences in the incidence of adenomas among the dietary groups. Therefore, Table 4 summarizes only the results of adenocarcinomas. There was no evidence of tumors in animals not treated with AOM and fed p-XSC. The incidence of colon adenocarcinomas was significantly inhibited in animals fed 40 ppm p-XSC during the stage of initiation. The diet containing 20 ppm p-XSC also decreased the colon tumor incidence during the stage of initiation, but the differences did not reach a statistical significance ($P > 0.05$). Colon tumor multiplicity (tumors/animal and tumors/tumor-bearing animal) was significantly inhibited in animals fed 20 and 40 ppm during the stage of initiation. Feeding of 20 and 40 ppm p-XSC during the postinitiation stage significantly suppressed colon tumor incidence and multiplicity.

Table 5 summarizes PGE$_2$ and GSH-Px levels in the colon mucosa. The results indicate that 40 ppm p-XSC in the diet significantly decreased the colonic mucosal GSH-Px. Also, dietary p-XSC at 20 and 40 ppm feeding significantly increased (about 3-fold) the colonic mucosal GSH-Px activity.

DISCUSSION

The purpose of the current study was to investigate the efficacy of dietary organoselenium, p-XSC, when fed during the initiation or postinitiation stage of AOM-induced colon carcinogenesis in F344 rats. The results of the present study are of considerable interest because to our knowledge, this is the first report showing that p-XSC can effectively reduce colon carcinogenesis when administered during the initiation or postinitiation phase. There are limited reports on the chemopreventive effects of p-XSC in laboratory animal models. Recently, El-Bayoumy et al. (35) and Ip et al. (36) demonstrated that dietary BSC, an analogue of p-XSC, significantly induces the hydroxylation of AOM (38, 39). The metabolic activation of AOM to a reactive metabolite takes place in two steps, i.e., the hydroxylation of AOM to MAM and the oxidation of MAM to methylazoxymethanol, which is highly unstable (38, 39). While the hydroxylation of AOM to MAM takes place in the liver, the oxidation of MAM to methylazoxymethanol is modulated by microsomes of both rat liver and colon (39). Fiala et al. (40) demonstrated that dietary BSC, an analogue of p-XSC, significantly induces the hydroxylation of AOM and the oxidation of MAM in the rat liver. Recently El-Bayoumy et al. (35) also demonstrated that p-XSC reduces DMBA-DNA binding in the target organ, i.e., mammary gland. Therefore, an increase in the rates of AOM and MAM metabolism in the liver due to enzyme induction by organoselenium may result in the decreased delivery of MAM to the colon via the bloodstream.

The general mechanisms of tumor inhibition by selenium include the inhibition of lipid peroxidation, peroxide decomposition, free radical scavenging, repair of molecular damage, and incorporation into enzymes with protective functions for the cell, i.e., GSH-Px (17, 21, 22). Selenium has an essential role in the functions of GSH-Px, an enzyme that is responsible for preventing oxidative damage due to peroxidation. Our results demonstrate that the feeding of p-XSC causes an increase in colonic mucosal GSH-Px activity. It is therefore possible that inhibition of colon carcinogenesis by dietary p-XSC can also be related to an increase in Se-GSH-Px activity in the colon.

### Table 4

**Table 4** Azoxymethane-induced colon carcinogenesis in male F344 rats fed different levels of p-XSC during initiation and postinitiation phases

<table>
<thead>
<tr>
<th>Experimental diets fed during*</th>
<th>% animals with colon adenocarcinomas</th>
<th>Multiplicity of colon adenocarcinomas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incidence (%)</td>
<td>Inhibition (%)</td>
</tr>
<tr>
<td>Initiation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control diet</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>20 ppm p-XSC</td>
<td>63</td>
<td>21</td>
</tr>
<tr>
<td>40 ppm p-XSC</td>
<td>50c</td>
<td>38</td>
</tr>
<tr>
<td>Control diet</td>
<td>20 ppm p-XSC</td>
<td>40c</td>
</tr>
<tr>
<td>Control diet</td>
<td>40 ppm p-XSC</td>
<td>37c</td>
</tr>
</tbody>
</table>

* No. of animals in each group, 30.

b $\pm$ SD.

Significantly different from the control diet group; $P < 0.05$.

### Table 5

**Table 5** Effect of dietary p-XSC on colonic mucosal PGE$_2$ and selenium-dependent glutathione peroxidase activity in AOM-treated rats

<table>
<thead>
<tr>
<th>Dietary regimen (n = 6)</th>
<th>PGE$_2$</th>
<th>GSH-Px</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control diet</td>
<td>13 ± 6.4$^{ab}$</td>
<td>102 ± 54$^a$</td>
</tr>
<tr>
<td>20 ppm p-XSC</td>
<td>11 ± 2.9</td>
<td>278 ± 46$^d$</td>
</tr>
<tr>
<td>40 ppm p-XSC</td>
<td>9 ± 4.6$^d$</td>
<td>280 ± 61$^d$</td>
</tr>
</tbody>
</table>

* Values are means ± SD.

a $\pm$ SD.

b Significantly different from the control diet group; $P < 0.05$. $\%$ nmol NADPH oxidized/min/mg protein.
In the present study, dietary supplementation of p-XSC at 40 ppm significantly suppressed colonic mucosal PGE2 levels. Prostaglandins are known to be one of the regulators of tumor growth and spread (24, 25, 40). Increased prostaglandin production by tumors has been associated with aggressive tumor progression (41, 42). Furthermore, the suppression of immune responses in patients and laboratory animals bearing tumors may be due to tumor-derived factors such as PGE2 (43–45). Recent studies have shown that the administration of indomethacin or piroxicam, inhibitors of prostaglandin synthesis, suppresses colon carcinogenesis in rats (46). It has been shown that Se-GSH-Px may be involved in the regulation of fatty acid hydroperoxides generated during the production of prostaglandins, leukotrienes, and related compounds via cyclooxygenase and lipoxygenase pathways (26). Whether this may partially account for the inhibitory action of p-XSC during the postinitiation phase of colon carcinogenesis remains to be determined.

Another possible mechanism of tumor inhibition by synthetic organoselenium may be explained on the basis of pharmacokinetics and tissue distribution. Sohn et al. (47), who examined the excretion and tissue distribution of BSC, an analogue of p-XSC, reported that selenium in animals fed BSC is excreted very slowly and is retained in the organs for a much longer period compared to rats given Na2SeO3. The persistence of total selenium in the colon with BSC suggests that BSC or its selenium-containing metabolites may be bound to tissue components, probably proteins, which may influence the normal cellular functions such as rate of cell turnover, enzyme activities, and degradation and/or synthesis of various enzymes. Whether the prolonged retention of selenium in colons of rats fed BSC (or p-XSC) is associated with tumor inhibition is yet to be investigated.

In conclusion, the results of this study demonstrate that dietary p-XSC inhibits colon carcinogenesis at both the initiation and postinitiation phases. The inhibitory effect of p-XSC on AOM-induced colon carcinogenesis during the initiation phase may be partly explained by its ability to alter the metabolic activation of carcinogen. Although the exact mechanisms involved for its protective effect during the postinitiation phase, however, are not clearly understood at present, the results from colonic GSH-Px and PGE2 should provide a stimulus to design additional studies to investigate the mechanism of colon tumor inhibition of p-XSC.

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REFERENCES


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