Effect of Aspirin on Urinary Bladder Carcinogenesis Initiated with N-[4-(5-Nitro-2-furyl)-2-thiazolyl]formamide in Rats

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ABSTRACT

N-[4-(5-Nitro-2-furyl)-2-thiazolyl]formamide (FANFT), a potent urinary bladder carcinogen, is metabolically activated in vitro by a variety of enzyme systems including aerobic cooxidation by prostaglandin H synthase which is present in the rat bladder mucosa. In a previous experiment, aspirin coadministered with FANFT for 12 weeks inhibited FANFT-induced bladder carcinogenesis and enhanced forestomach carcinogenesis. To further evaluate the effects of aspirin on FANFT carcinogenesis, male F344 rats were fed either FANFT (0.2% of the diet) for 12 weeks (Group 4), aspirin (0.5% of the diet) simultaneously with FANFT for 12 weeks (Group 2), aspirin simultaneously with FANFT for 12 weeks and then subsequently to the end of the experiment (Group 1), or FANFT only followed by aspirin (Group 3). The incidence of bladder carcinoma was significantly higher when aspirin was fed after FANFT treatment (87%) compared to FANFT followed by control diet (48%) and was higher in rats given aspirin plus FANFT followed by aspirin (73%) compared to aspirin plus FANFT followed by control diet (47%). Aspirin alone given for 13 weeks (Group 6) or throughout the experiment (68 weeks) (Group 5) did not induce bladder cancer. However, in all groups administered aspirin long-term, renal papillary necrosis and renal pelvic hyperplasia and atypia were frequently observed. Only a single forestomach tumor was observed. In the present experiment, aspirin appeared to exhibit promoting activity for bladder carcinogenesis in the rat.

INTRODUCTION

FANFT is a potent urinary bladder carcinogen in rats and other species (1, 2). It is metabolized by a variety of enzyme systems including microsomal and nonmicrosomal nitroreductases (3), xanthine oxidase (3), and PHS (1, 4, 5). Rat and rabbit urinary bladder epithelium contain substantial PHS activity (1, 6).

Aspirin inhibits fatty acid cyclooxygenase, one of the enzymatic activities of PHS, by acetylation of a serine moiety (7). It significantly reduced rat bladder prostaglandin E synthesis (1), and prevented bladder PHS-catalyzed metabolism of FANFT and ANFT, the deformylated metabolite of FANFT (1, 7). Aspirin appears in the urine after oral administration (8). In a previous study, aspirin inhibited FANFT-induced bladder carcinogenesis in the rat when coadministered with FANFT for 12 weeks followed by control diet for 56 weeks, but enhanced the induction of forestomach tumors (9). FANFT alone induced a low incidence of forestomach tumors, whereas ANFT, a metabolite of FANFT, was a more potent forestomach carcinogen in rats (2).

Bladder carcinogenesis in rats can be divided into two stages, initiation and promotion (10, 11). Initiation can be induced by short-term administration of bladder carcinogens, such as FANFT, whereas subsequent promotion can be induced by high doses of a variety of substances, such as sodium saccharin. We have previously demonstrated that initiation of bladder carcinogenesis in rats by FANFT and promotion by sodium saccharin can be inhibited by coadministration of either substance with high doses of aspirin in the diet (12). Although the effect of aspirin on FANFT initiation and carcinogenesis may be by inhibiting the metabolic activation of ANFT (1, 4, 5, 9), such a mechanism is not possible for aspirin's effect on sodium saccharin. Saccharin is excreted in the urine in its anionic form, and it is not metabolized (13–15). Substances which inhibit arachidonic acid metabolism, such as aspirin and indomethacin, have been shown to have complex effects on promotion in other model systems, such as mouse skin and rat intestine (16, 17). The present experiment was designed to further evaluate the effects of aspirin on the promotion phase of bladder carcinogenesis in the rat.

MATERIALS AND METHODS

FANFT (Lot 811009) was obtained from Saber Laboratories, Inc., Morton Grove, IL, and aspirin (Lots 53F-0520 and 99C-0226) from Sigma Chemical Co., St. Louis, MO. FANFT and aspirin were mixed in powdered Prolab 3200 chow (Agway, Inc., St. Marys, OH) at doses of 0.2 and 0.5%, respectively, by weight into the same diet or separately, and the diets were pelleted. Male F344 rats (Charles River Breeding Laboratories, Inc., Kingston, NY), 5 weeks old at the beginning of the experiment, were housed in plastic cages with corn cob bedding in an air-conditioned room at 24°C and 50% humidity on a 12-h light/dark cycle.

Rats were randomly divided into seven groups as illustrated in Fig. 1. Groups 5 and 7 in the present experiment are the same animals as Groups 8 and 9, respectively, reported previously by Sakata, et al. (12). The two experiments were performed simultaneously with one shipment of rats. The groups that received aspirin with FANFT (Groups 1 and 2) were fed diet containing aspirin without FANFT for 2 days prior to FANFT administration to be sure that the enzyme system was inhibited by the time FANFT was fed (3). The time FANFT administration was begun was considered time zero of the experiment. FANFT was administered for a total of 12 weeks. In Group 2, rats were fed aspirin for 7 days after coadministration with FANFT and then fed control diet until the end of the experiment. The rats in Group 3 were fed aspirin beginning 7 days after cessation of FANFT administration to allow for elimination of FANFT from the rat (3). Appropriate control groups were administered diets as shown in Fig. 1. The rats in Groups 5 and 6 were also fed aspirin for the 2 days before Day 0 of the experiment, and in Group 6, it was continued through 13 weeks. During the period without treatment of aspirin and/or FANFT, rats were fed pelleted basal chow (Agway, Inc.). Food and tap water were available ad libitum. Rats were weighed and food consumption was determined periodically. Water consumption was measured during Week 63 of the experiment, and urinary pH was measured during Week 50 on freshly voided urine using a microelectrode (M1-410 Micro-combination pH probe, Microelectrodes, Inc., Londonderry, NH).

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Effect of aspirin on FANFT urinary bladder carcinogenesis

Table 1. Growth, chemical consumption, water intake, urinary pH, and liver weights in rats administered various combinations of FANFT and/or aspirin

<table>
<thead>
<tr>
<th>Group</th>
<th>Week 0</th>
<th>Week 12</th>
<th>Week 68</th>
<th>FANFT (g/rat)</th>
<th>Aspirin (g/rat)</th>
<th>Water intake at Week 63 (ml/day)</th>
<th>Urinary pH at Week 50</th>
<th>Liver weight (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>81 ± 10* A</td>
<td>270 ± 13</td>
<td>432 ± 26</td>
<td>2.7</td>
<td>45.9</td>
<td>40.6</td>
<td>6.67 ± 0.32 (30)</td>
<td>12.9 ± 0.9° (25)</td>
</tr>
<tr>
<td>2</td>
<td>79 ± 8  B</td>
<td>274 ± 12</td>
<td>454 ± 26</td>
<td>3.0</td>
<td>8.0</td>
<td>27.6</td>
<td>6.73 ± 0.24 (30)</td>
<td>14.9 ± 2.1 (21)</td>
</tr>
<tr>
<td>3</td>
<td>84 ± 7  C</td>
<td>288 ± 17</td>
<td>429 ± 26</td>
<td>3.0</td>
<td>39.9</td>
<td>39.6</td>
<td>6.61 ± 0.31 (30)</td>
<td>12.5 ± 1.4° (18)</td>
</tr>
<tr>
<td>4</td>
<td>88 ± 8  D</td>
<td>287 ± 16</td>
<td>456 ± 25</td>
<td>2.7</td>
<td>0</td>
<td>26.0</td>
<td>6.59 ± 0.31 (28)</td>
<td>15.0 ± 1.2 (25)</td>
</tr>
<tr>
<td>5</td>
<td>81 ± 8° E</td>
<td>290 ± 12</td>
<td>429 ± 34</td>
<td>0</td>
<td>48.8</td>
<td>38.8</td>
<td>6.52 ± 0.40 (29)</td>
<td>12.8 ± 1.1° (29)</td>
</tr>
<tr>
<td>6</td>
<td>81 ± 8° F</td>
<td>291 ± 14</td>
<td>462 ± 27</td>
<td>0</td>
<td>8.3</td>
<td>25.9</td>
<td>6.50 ± 0.30 (30)</td>
<td>15.2 ± 1.8 (30)</td>
</tr>
<tr>
<td>7</td>
<td>86 ± 7  G</td>
<td>325 ± 16</td>
<td>462 ± 23</td>
<td>0</td>
<td>0</td>
<td>24.6</td>
<td>6.45 ± 0.29 (30)</td>
<td>14.6 ± 1.3 (36)</td>
</tr>
</tbody>
</table>

* Mean ± SD.
* Significantly different from control (Group 7) at P < 0.05 by t test.
° Significantly different from control (Group 7) at P < 0.01 by t test.
* Numbers in parentheses, number of animals killed at the end of the experiment after 68 weeks.
° Numbers in parentheses, number of animals examined.

All surviving rats were killed at the end of Week 68 of the experiment. At autopsy, the skin, s.c. tissues, and organs in the thoracic and abdominal cavities were macroscopically examined. The urinary bladder was inflated with 10% phosphate buffered formalin, pH 7.4, in situ and later cut into eight strips. The stomach was also inflated with formalin. The kidneys were bisected transversely and fixed, other tissues with grossly visible pathological alterations were also fixed. The tissues were embedded in paraffin, sectioned, and stained with hematoxylin & eosin. Tissues were evaluated by the pathologists without knowledge of treatment. Statistical comparisons were by Fisher's exact test with correction for continuity and Student's t test (18).

RESULTS

The average body weights of the rats were significantly reduced during aspirin treatment (Table 1). At Day 0, the rats in Groups 1, 2, 5, and 6, which had already been fed aspirin for 2 days, showed significantly lower body weights than the control group. By 12 weeks, FANFT treatment also resulted in reduced body weight gain, and the rats given both aspirin and FANFT for 12 weeks (Groups 1 and 2) showed the lowest body weights. However, in the rats fed control diet after Week 13 (Groups 2, 4, and 6), the body weights were similar to the controls by the end of the experiment. Food consumption of rats given FANFT or FANFT plus aspirin was slightly less than the controls during the first week, but it was similar to the control level by the 3rd week. The cumulative doses of chemicals were proportional to the periods of the respective treatments (Table 1). Water intake, measured at Week 63, was increased by aspirin feeding. Aspirin did not change the urinary pH compared to control rats (Table 1).

At the end of the experiment, the liver weight was significantly lower in rats fed aspirin during the last 55 or more weeks of the experiment (Table 1). Except for the body and liver weights, no changes or lesions were observed grossly at autopsy attributable to aspirin administration.

The changes in the kidneys (Table 2) were similar to those described previously (19). Grading of the severity of renal papillary necrosis was according to the criteria of Henry et al. (20). Groups fed aspirin for long-term (Groups 1, 3, and 5) had high incidences of renal papillary necrosis, renal pelvic hyperplasia and nuclear atypia, and columnar metaplasia (Figs. 2 and 3). A few renal pelvic transitional cell carcinomas were observed in Groups 2–4 (Figs. 4 and 5). Groups fed FANFT without subsequent aspirin administration (Groups 2 and 4) had similar lesions but less frequently and less severe. There was no significant synergistic interaction between FANFT and aspirin administration in the kidney lesions. Also, brief aspirin administration followed by control diet (Groups 2 and 6) did not produce significant incidences of the renal lesions. As observed previously (19), long-term administration of aspirin inhibited the appearance of the nephropathy observed in aging male rats.

The first urinary bladder tumor was identified in a rat which died during Week 50 of the experiment. Rats dying or killed...
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Table 2. Type and incidence of kidney lesions in the different groups of rats

<table>
<thead>
<tr>
<th>Group</th>
<th>Effective no. of rats</th>
<th>Renal pelvic hyperplasia</th>
<th>Carcinoma*</th>
<th>CM*</th>
<th>Atypia*</th>
<th>Rate nephropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>14</td>
<td>4</td>
<td>1</td>
<td>24</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>3</td>
<td>7</td>
<td>2</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>10</td>
<td>7</td>
<td>2</td>
<td>21</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>29</td>
<td>4</td>
<td>14</td>
<td>4</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>13</td>
<td>4</td>
<td>1</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>30</td>
<td>13</td>
<td>4</td>
<td>1</td>
<td>12</td>
<td>+</td>
</tr>
<tr>
<td>7</td>
<td>36</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>8</td>
<td>++</td>
</tr>
</tbody>
</table>

* Transitional cell carcinoma.
* CM, columnar metaplasia of pelvic epithelium.
* Nuclear atypia of renal pelvic epithelium.
* RPN, renal papillary necrosis.

because of marked weight loss and/or hematuria after this time were included in the effective number of rats for calculating incidences. The cause of death in the rats fed FANFT was related to cachexia secondary to hematuria and advanced urinary bladder carcinoma. The mortalities before the terminal sacrifice in the groups treated with FANFT were as follows: Group 1, 5 of 30 (17%); Group 2, 9 of 30 (30%); Group 3, 12 of 30 (40%); and Group 4, 5 of 30 (17%). The mortality rate in Group 3 was significantly higher than in Group 1 or 4 (P < 0.05). The bladder lesions were histologically classified into simple hyperplasia, nodular or papillary hyperplasia, papilloma, and carcinoma as described previously (21). The carcinomas were all transitional cell (urothelial) carcinomas, some having foci of squamous cell differentiation. The results are summarized in Table 3. Each rat is tabulated on the basis of the most advanced lesion found in the bladder. An inhibitory effect of coadministered aspirin on FANFT carcinogenesis (initiation) was not detected in the present experiment (Group 2 compared to Group 4, and Group 1 compared to Group 3). However, aspirin administration after treatment with FANFT resulted in a significantly increased incidence of carcinoma compared to FANFT administration followed by control diet (Groups 1 and 3 compared to Groups 2 and 4, respectively). This increase occurred whether aspirin was also administered concurrently with FANFT or not. Aspirin alone (Group 5) induced one papilloma, but no other lesions were observed in this group or in rats fed aspirin for only 13 weeks (Group 6), not even simple hyperplasia.

Tumor lesions in tissues other than the urinary bladder are...
ASPIRIN EFFECTS ON FANFT-INDUCED CARCINOGENESIS

Table 3 Lesions in the urinary bladder in the different groups of rats

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>No. of rats</th>
<th>Normal</th>
<th>Simple hyperplasia</th>
<th>Nodular or papillary hyperplasia</th>
<th>Papilloma</th>
<th>Total</th>
<th>Noninvasive</th>
<th>Invasive</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F + A → A</td>
<td>30</td>
<td>0</td>
<td>2 (7)</td>
<td>4 (13)</td>
<td>2 (7)</td>
<td>22 (73)</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>F + A → C</td>
<td>30</td>
<td>2 (7)</td>
<td>6 (20)</td>
<td>6 (20)</td>
<td>2 (7)</td>
<td>14 (47)</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>F → A</td>
<td>30</td>
<td>0</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>2 (7)</td>
<td>14 (47)</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>F → C</td>
<td>30</td>
<td>1 (3)</td>
<td>5 (17)</td>
<td>2 (7)</td>
<td>3 (10)</td>
<td>14 (48)</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>A → A</td>
<td>30</td>
<td>28 (97)</td>
<td>0</td>
<td>0</td>
<td>1 (3)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>A → C</td>
<td>30</td>
<td>30 (100)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>C → C</td>
<td>40</td>
<td>36 (100)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* F, 0.2% FANFT; A, 0.5% aspirin; C, control diet.
* All rats surviving beyond Week 50 are included.
* Numbers in parentheses, percentages of effective number of rats in the group.
* Significantly different from Group 2 at P < 0.05 by Chi-square test.
* Significantly different from Group 4 at P < 0.01 by Chi-square test.

shown in Table 4. The stomach showed chronic gastritis of the glandular epithelium in rats fed aspirin until the end of the experiment. Only one tumor (papilloma) of the forestomach was observed (in Group 2).

At Week 68 of the experiment, 50% of rats fed control diet for a long period had interstitial cell tumors in one or both testes as observed grossly. Aspirin feeding inhibited the incidence of testicular tumors, even in rats fed the chemical for only the first 13 weeks of the experiment (Group 6).

DISCUSSION

In the present experiment, aspirin at high doses (0.5% of the diet) appeared to enhance (promote) the urinary bladder carcinogenicity of FANFT when administered after the FANFT. However, caution needs to be exercised in interpreting these results since the incidence of bladder cancer in the rats fed FANFT followed by control diet (Group 4) in the present study was only 48% in contrast to an incidence of 86% in our previous study (9).

The mechanism for the apparent enhancing (promoting) effect of aspirin is unclear. Clearly, the dose of aspirin that was used was toxic, as evidenced by a decreased weight gain during the period of administration of aspirin, either at the beginning of the experiment or during the second, longer phase of the experiment. Examination of the urine did not reveal any appreciable increase or decrease in pH compared to the controls, nor was there an increase in sodium, potassium, or calcium. However, for reasons that are not clear, aspirin administration led to an increased consumption of the drinking water and a consequent increase in urinary volume. There was no evidence of increased microcrystalluria or calculus formation in the bladders of the rats administered aspirin. Thus, aspirin does not fit into any of the previously indicated categories of urinary bladder tumor promoters (11). It is not a sodium salt, such as sodium saccharin or sodium ascorbate with the consequent urinary changes associated with the feeding of such compounds; it is not a compound resulting in calculus formation, such as uracil or biphenyl; nor does it appear to be associated with any of the amino acids that have been related to increased bladder tumor formation in rats.

Aspirin has an involvement in arachidonic acid metabolism, being a potent inhibitor of cyclooxygenase activity of the PHS enzyme (7). Aspirin, as well as other modifiers of arachidonic acid metabolism, especially indomethacin, have previously been shown to have effects during the promoting stage of carcinogenesis (16) in mouse skin (22), and to a lesser extent in the rat colon cancer model (17) and rat leukemia model (23). These effects appear to be highly variable, occasionally being associated with increased promoting activity and, in other circumstances, related to an inhibitory effect. Because of the very complex interaction of these compounds with the multiple arachidonic acid metabolic pathways, not just with one aspect of it, it is not too surprising that these variable effects have been reported. It is not even clear that the effects of these compounds in tumor promotion is directly related to their effects on arachidonic acid metabolism.

Aspirin at these high doses has been shown in the present experiment and previously (19) to have significant effects on the kidney, including the induction of papillary necrosis and...
significant urothelial hyperplasia. The relationship of these changes in the kidney to the development of urothelial lesions in the urinary bladder are not apparent, but are possibly related to the mechanism of action of aspirin as a urothelial tumor promoter.

Many chemicals known to be tumor promoters have a cyto-toxic effect on the target tissue, even without prior initiation (11). In the present study, we did not see evidence of urothelial damage in the urinary bladder following aspirin administration, but animals were not examined early in the experimental period. However, marked changes in the urothelium and other parts of the kidney were observed in response to aspirin administration in this experiment, as well as reported previously (19, 24). Similarly, other analgesics which have effects on cyclooxygenase, such as acetaminophen and phenacetin, have been reported to have effects on the urothelium and kidney in experimental animals. In a study in mice, the coadministration of aspirin, phenacetin, or caffeine did not result in tumor formation, but the urinary bladder epithelium showed vacuolization, focal desquamation, and subepithelial thickening (25). Four of 77 mice administered phenacetin demonstrated these lesions, none of the 86 mice administered aspirin alone showed these effects, but 24 of 75 mice administered phenacetin plus aspirin showed these changes in the urothelium. In addition, acetaminophen has been demonstrated to have renal toxic effects in rats and weak tumor-promoting activity on the rat kidney (26). Phenacetin, known to be associated with the development of renal papillary necrosis in urothelial cancers in humans (27), is also a potent tumor promoter for the rat urinary bladder (28) and renal pelvis (29), and can by itself induce renal papillary alterations (30) and cancer (31, 32) in the rat.

We have previously shown that aspirin coadministered with FANFT inhibits its carcinogenicity (9) and specifically its initiating activity (12). Similarly, when aspirin was coadministered with high doses of sodium saccharin in the diet, it acted as an inhibitor of promoting activity (12). Aspirin administered after FANFT, as in the present experiment, now appears to have weak tumor-promoting activity for the urothelium. Such variable behavior by a compound when administered under different circumstances is not unique in chemical carcinogenesis studies. For example, phenobarbital coadministered with a variety of hepatocarcinogens, such as 2-acetylaminofluorene, inhibits tumor formation, whereas when it is administered after such a compound, it is clearly a potent tumor-promoting compound (33, 34). The inhibitory effect of these compounds when coadministered with carcinogens is probably related to effects on their metabolism (33). Other compounds are also known to have variable effects on tumor induction, depending on circumstances of their administration. For example, butylated hydroxyanisole, a well-known antioxidant, inhibits carcinogenesis in a wide variety of animal tumor models, involving several different tissues (35). In contrast, it promotes forestomach and urinary bladder carcinogenesis initiated by methylnitrosourea in rats (36), and is a complete carcinogen in rats and hamsters for the forestomach when administered at high doses (37). Clearly, species, strain, dose, time of administration, and coadministration with other compounds are critical factors in determining the effects of these compounds in the carcinogenic process. In the case of aspirin and FANFT, Zenser et al. (4) have provided considerable evidence that aspirin inhibits the coactivative activation of the urinary metabolite of FANFT, 2-amino-4-(5-nitro-2-furyl)thiazole. The effect on the initiating and promoting phases of carcinogenesis by compounds such as aspirin are likely to be by totally different mechanisms.

In the present experiment, no inhibition was observed during the period of coadministration of aspirin with FANFT on bladder carcinogenesis. The reasons for this are unclear, but the incidence of tumors in the group treated only with FANFT (48%) was considerably less than in the previous (9) experiment (87%). Also, only one forestomach tumor was seen in the present experiment, compared to an incidence as high as 26% in the previous experiment. Also, we have previously demonstrated that the inhibitory effect on cell proliferation of coadministration of aspirin with FANFT at these doses is lost before 12 weeks of administration (38). Thus, although there is an inhibition of the proliferative activity secondary to FANFT administration in the urinary bladder and forestomach after 4 weeks of administration, this is not seen by 12 weeks of coadministration of these compounds.

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