Effect of Sex Hormones on Carcinogenesis in the Stomachs of Rats

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ABSTRACT

We have been investigating possible effects of sex hormones on the carcinogenesis of stomach cancer in Wistar rats that were given \( N \)-methyl-\( N' \)-nitro-\( N \)-nitrosoguanidine in drinking water (50 \( \mu \)g/ml) for 4 months. The incidences of stomach cancer in intact male, intact female, castrated male, and castrated female rats at Month 4 of the experiment were 5, 0, 0, and 0%, respectively; and those at Month 8 were 40, 10, 0, and 0%, respectively; indicating that the incidence in intact males was much higher than in the other groups. The difference in the incidence became more evident when the animals were sacrificed at Month 12 of the experiment (81, 0, 29, and 5%, respectively). Hypertrophy and dissociation of the lamina muscularis mucosae which are considered to occur in the carcinogenic process were observed only in the male rats at the earlier months, but not in female nor in castrated rats. In \( N \)-methyl-\( N' \)-nitro-\( N \)-nitrosoguanidine carcinogenesis, female and castrated rats had a lower incidence of gastric cancers with less change in the lamina muscularis mucosae than did the nontreated male rats. These findings, therefore, suggest that, in addition to the suppressive action of female hormones, male hormones facilitate carcinogenesis.

INTRODUCTION

It is known that the incidence of stomach cancer in women is as low as one-half the incidence in men (2, 10), and that stomach cancers of linitis plastica type are found more frequently in women than in men. These facts led us to infer that sex hormones, female hormones in particular, might play an important role in carcinogenesis.

We reported in a previous paper (3) that the administration of a carcinogenic agent, MNNG, to rats produced stomach cancer with a very high incidence in the male rats, while there was little onset of such a cancer in the female rats. In the present study, for the purpose of further investigating the cause of such a difference in sex, male and female rats were castrated and the carcinogenic process was observed 4, 8, and 12 months after the start of the experiment.

The results thus obtained are presented here.

MATERIALS AND METHODS

Male and female Wistar rats, 4 weeks old, weighing about 70 g, were used. MNNG (Wako Pure Chemical Industries, Ltd., Osaka, Japan) was dissolved in water to give a final concentration of 50 \( \mu \)g/ml, and polyoxyethylenemonostearate (Ishizu Pharmaceutical Co., Ltd., Osaka, Japan) was added to give final concentration of 0.04%. This solution was administered to the animals as a carcinogen (hereafter referred to as NG) for the first 4 months instead of drinking water. Male and female rats were divided into the following 4 groups and sacrificed 4, 8, and 12 months after the start of the experiment: Group 1, intact male rats (effective number: 4 months, 20; 8 months, 10; 12 months, 32); Group 2, intact female rats (4 months, 11; 8 months, 10; 12 months, 20); Group 3, castrated male rats (4 months, 25; 8 months, 10; 12 months, 21) and Group 4, castrated female rats (4 months, 20; 8 months, 12; 12 months, 20). The stomachs were removed and fixed in 10% formalin, and sectioned in 1 mm widths. These specimens were then stained with each of hematoxylin and eosin, periodic acid-Schiff, and Alcian blue so that they could be submitted to pathological examinations. The criteria used for histological diagnosis of cancer in this study were the presence of glandular proliferation with cellular atypism invading the submucosal layer or deeper. Statistical analysis was done using Fisher's exact probability test.

RESULTS

The incidence of cancer, the mucosal atypia which is considered as a cancer associated lesion, and the hypertrophy of lamina muscularis mucosae which is thought to be a transient process of erosion were subjected to the present investigation. The incidences of cancer at Month 4 of the experiment, that is, immediately after the completion of NG feeding, were 5, 0, 0, and 0% for Groups 1, 2, 3, and 4, respectively (Table 1). The incidences after 8 months were 40, 10, 0, and 0%; and those after 12 months were 81, 0, 29, and 5%. The mucosal atypias were observed in 36, 0, 0, and 0% of the animals sacrificed after 4 months for Groups 1, 2, 3, and 4, respectively; in 40, 20, 0, and 0% after 8 months; and in 59, 5, 52, and 8% after 12 months. The hypertrophy of the lamina muscularis mucosae was found in 73, 27, 30, and 30% of the animals after 4 months; in 60, 0, 42% after 8 months; and in 3, 0, 5, and 0% after 12 months. These findings were more pronounced in the earlier months.

Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>Time of observation (months)</th>
<th>Effective no.</th>
<th>No. of rats with gastric cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Intact</td>
<td>4</td>
<td>20</td>
<td>1 (5)%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8</td>
<td>10</td>
<td>4 (40)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12</td>
<td>32</td>
<td>26 (81)</td>
</tr>
<tr>
<td>2</td>
<td>Intact</td>
<td>4</td>
<td>11</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8</td>
<td>10</td>
<td>1 (10)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12</td>
<td>20</td>
<td>0 (0)%</td>
</tr>
<tr>
<td>3</td>
<td>Castrated</td>
<td>4</td>
<td>25</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8</td>
<td>10</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12</td>
<td>21</td>
<td>6 (29)%</td>
</tr>
<tr>
<td>4</td>
<td>Castrated</td>
<td>4</td>
<td>20</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8</td>
<td>12</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12</td>
<td>20</td>
<td>1 (5)%</td>
</tr>
</tbody>
</table>

*All rats were given MNNG (50 \( \mu \)g/ml) in drinking water for 4 months after each treatment.*

*1 To whom requests for reprints should be addressed.

*2 The abbreviation used is: MNNG, \( N \)-methyl-\( N' \)-nitro-\( N \)-nitrosoguanidine.*

Received May 25, 1982; accepted August 8, 1982.
DISCUSSION

Although many investigations concerning MNNG-induced stomach cancer use male rats (8), neither female rats nor castrated rats have been used for such investigations. In the present study, the incidence of stomach cancer 1 year after MNNG administration was remarkably high (81%) in male Wistar rats, whereas that in female rats was surprisingly low (0%). Castration of the male rats resulted in a reduction in the incidence to 29%, while castrated female rats showed an incidence of 5%. Such a difference in the incidence of stomach cancer among the groups was less evident in the earlier phase of the experiment (4 and 8 months). The sex difference was also noted in the case of mucosal atypia which is considered a cancer-associated change. Hypertrophy and dissociation of the lamina muscularis mucosae, which is thought to represent a transient step to the erosion, were observed only in the group of male rats during the earlier phases, but not in any of the other groups. These findings, therefore, suggest that the onset of cancer at the later phases reflects the presence of the erosion during the earlier phases. The significance of erosion as a precancerous lesion was pointed out by Iwanaga et al. (4). In fact, Saito et al. (7) and Tabuchi et al. (9) presented supporting experimental evidence by demonstrating the increased onset of cancer after erosion in animals when a carcinogenic agent was administered. However, since only male animals were used in their experiments, no information on the sex difference in the formation of erosion can be obtained.

In terms of the influence of female hormones upon stomach cancer, it is known that highly malignant Borrmann 4-type cancers (so-called ‘Scirrhus’) are most frequently observed in young women (6). In such cases, the involvement of female sex hormones may be strongly suggested. And there is a report stating the presence of estrogen receptors in stomach cancer tissue (5). However, unlike the breast, it is difficult to recognize the stomach as a target organ of 17β-estradiol. Moreover, even if the stomach cancer were estrogen receptor positive, it is still unknown whether or not 17β-estradiol may induce the proliferation of cancer.

Although the incidence of cancer in male rats was markedly reduced by castrating at the age of 4 weeks, it was still higher than that for the intact female rats. On the other hand, when female rats were castrated, the incidence of cancer was increased, although only slightly. These findings, therefore, may suggest that, in addition to the suppressive action of female hormones, male hormones facilitate carcinogenesis. Such facilitating action of male hormones might play a more important role than did suppressive action of female hormones on the development of stomach cancer in rats. As far as we know, there is no previous literature describing possible interrelation between male hormones and stomach cancer.

To investigate more details on the effects of sex hormones on carcinogenesis, it will be necessary to study the acquired hormonal environment and, moreover, to treat animals at an earlier stage of sex differentiation (1).

REFERENCES

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