Genetic Control of Susceptibility of Rats to Gastric Carcinoma

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ABSTRACT

Genetic control of the induction of gastric tumors by N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) was studied in susceptible ACI rats, resistant Buffalo rats, and their F1 and F2 offspring. Both sexes of all strains, initially 7 to 9 weeks old, were given MNNG at a concentration of 83 μg/ml in their drinking water for 32 weeks and were sacrificed at experimental Week 72. The incidence of gastric adenocarcinoma in ACI rats was 80% in males and 47% in females; in Buffalo rats, the incidence was 18% in males and 0% in females. F1 hybrids showed the same resistance to MNNG as did Buffalo rats; the incidence of gastric adenocarcinoma was 17% in males and 8% in females. These results suggest that resistance to induction of gastric adenocarcinoma by MNNG is a dominant characteristic. The incidence of gastric adenocarcinoma in the F2 generation was 36% in males and 14% in females, which is close to the 3:1 ratio expected from the segregation of a single resistant gene. In ACI and Buffalo strains and their hybrids, males were more susceptible than females to induction of gastric carcinoma by MNNG. Intestinal tumors were observed mainly in the duodenum and jejunum in both strains and their hybrids, and the incidences were as follows: ACI: males, 67% and females 42%; Buffalo: males, 12% and females, 18%; F1: males, 18% and females, 15%; and F2: males, 15% and females, 19%. Thus, there seems to be a common genetic basis for both gastric and intestinal carcinogenesis by MNNG.

INTRODUCTION

Administration of MNNG3 in the drinking water produces gastric and intestinal tumors at high frequency in rats, hamsters, and dogs (34). In particular, gastrocarcinogenesis in rats has been extensively studied. Randomly bred Wistar rats have been used most frequently (35). Donryu (31), Sprague-Dawley (19), ACI (16), Wistar/kob (18), BD IX, and BN rats (22) developed gastric tumors at a high frequency in response to MNNG. However, it is difficult to make an exact comparison of the susceptibility to MNNG among these strains, since the criteria for histological diagnosis of the tumors, the dose of MNNG, and the duration of treatment differed in each experiment. Bralow et al. (4) found that susceptibility to induction of gastric carcinoma by MNNG varied in different strains of rats. Administration of MNNG at a concentration of 83 μg/ml for 52 weeks induced gastric adenocarcinoma in 50% of randomly bred Wistar rats, but in no inbred Buffalo-Mai rats.

In humans, environmental factors, especially eating habits, are thought to be important in the induction of gastric cancer (6, 15). However, reports on familial clustering of gastric cancer (9, 17, 20, 21, 37) suggest that not only environmental factors but also genetically determined susceptibility to environmental carcinogens may contribute to the occurrence of this disease.

In this work, we studied the genetic control of susceptibility to induction of gastric carcinoma by MNNG, using susceptible ACI and resistant Buffalo rats and their F1 and F2 offspring.

MATERIALS AND METHODS

Test Strains and Hybrids. ACI rats, in which a single dose of MNNG has been reported to be gastrocarcinogenic (16), were purchased from Fuji Animal Farm, Yamanashi, Japan. This strain of rats originated from the inbred ACI/N strain from the NIH, Bethesda, Md., and was transferred to Fuji Animal Farm in 1972 and 1979. Since then, it has been maintained in a closed colony. Buffalo rats, which have been reported to be resistant to MNNG (4), were kindly provided by the National Cancer Institute, Bethesda, Md., in 1963 and maintained by brother-sister mating in our institute.

F1 hybrids of ACI × Buffalo and Buffalo × ACI rats were obtained by reciprocal mating between these 2 strains. The experiment with the F1 hybrids was performed twice (Experiments 1 and 2). ACI × Buffalo F2 rats were obtained by crosses between ACI × Buffalo F1 hybrids; and Buffalo × ACI F2, by crosses between Buffalo × ACI F1 hybrids. For the studies on the ACI and Buffalo strains and their F1 (Experiment 1) and F2 offspring, ACI rats of the 18th generation after transfer from NIH to Fuji Animal Farm in 1972, and Buffalo rats of the 38th generation after transfer to this institute were used. For this study on the F1 hybrid (Experiment 2), ACI rats of the third generation after the transfer from NIH to Fuji Animal Farm in 1979, and Buffalo rats of the 42nd generation were used. All the rats of both sexes were 7 to 9 weeks old at the beginning of the experiments.

Treatment with Carcinogen. MNNG, purchased from Aldrich Chemical Co., Inc., Milwaukee, Wis., was dissolved in deionized water at a concentration of 830 μg/ml and kept in the dark as a stock solution. A solution of 83 μg of MNNG per ml was prepared from the stock solution just before use and given to rats for 32 weeks ad libitum in place of drinking water. Thereafter, rats were maintained on tap water until Week 72. The rats were weighed once per month, and water intake was measured 3 times/week. Rats were maintained on a basal diet (CE-2; CLEA Japan, Inc., Tokyo, Japan).

Histological Examination. Complete autopsies were performed on all rats when they died or became moribund during the experiment or when they were sacrificed at Week 72. The stomach was opened along the greater curvature, pinned flat on a cork board, and fixed with 15% neutralized formalin. Two- to 3-mm-wide step sections were made along the lesser curvature, and sections were stained with hematoxylin and eosin. The intestine was opened longitudinally, and the Swiss roll technique was used for its histological examination.

Definition of Gastrointestinal Tumors. Tumors in the gastrointestinal tract were classified as adenocarcinomas, adenomas, and sarcomas.
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Adenocarcinomas were defined as tumors with excessive glandular hyperplasia with structural and cellular atypia invading the submucosa, the muscularis propria, or the serosa. Adenomas were defined as tumors with expansive proliferation with slight atypia remaining in the submucosa. Sarcomas were classified as spindle cell sarcomas, pleomorphic with expansive proliferation with slight atypia remaining in the submucosa, muscularis propria, or the serosa. Adenomas were defined as tumors with structural and cellular atypia invading the submucosa. Adenocarcinomas were defined as tumors with excessive glandular differentiation in tumor cells. Statistical Analysis. The $\chi^2$ test was used for statistical analysis of differences in tumor incidence.

RESULTS

Coat Color. The coat color of ACI rats is agouti (Irish), and that of Buffalo rats is albino. $F_1$ rats are agouti (Irish), and coat color phenotypes in $F_2$ rats segregated to: agouti, 38%; albino, 27%; black, 17%; agouti hooded, 14%; and black hooded, 4%. The observed ratio of coat color segregation in $F_2$ rats is close to the theoretical ratio ($0.25 < p < 0.5$) if it is assumed that 4 loci are related to coat color phenotypes (12).

Body Weight. There was no difference in the body weights of female rats of the 2 strains and their hybrids, but the average body weight of male ACI rats was about 80% of that of male Buffalo rats throughout the course of the experiment. On the average, $F_1$ males weighed the same as did Buffalo rats, whereas $F_2$ males were intermediate between male ACI and Buffalo strain rats.

Carcinogen Intake. The average daily water intake per rat by $F_1$ hybrids was almost the same as that by ACI rats of both sexes; that by male Buffalo rats was 3.8 to 4.0 ml less than that by male ACI or $F_1$ hybrid rats; that by female Buffalo rats was 4.2 to 5.2 ml less than that by female ACI or $F_1$ hybrid rats; and, that by $F_2$ rats was intermediate between that by ACI and Buffalo rats of both sexes.

Tumors in the Glandular Stomach. The incidence of tumors in the stomach is summarized in Table 1. Most gastric tumors induced by MNNG were adenocarcinomas, but a few adenomas and sarcomas were found in each strain. Gastric adenocarcinoma developed at high incidence in ACI rats of both sexes. Of the Buffalo rats, only 18% of the males and none of the females developed gastric adenocarcinoma. Male Buffalo strain rats did not show complete resistance to gastric carcinogenesis by MNNG in this experiment. However, the incidence of gastric adenocarcinoma in Buffalo rats was significantly lower than that in ACI rats in both sexes (male, $p < 0.001$; female, $p < 0.001$). The incidence of adenocarcinoma in $F_1$ hybrids was similar to that in Buffalo rats in both Experiments 1 and 2. There is no statistically significant difference between $F_1$ hybrids and the same incidence as Buffalo rats. There is no statistically significant difference between ACI × Buffalo $F_2$ and Buffalo × ACI $F_2$ in the development of gastric adenocarcinoma. These results show that susceptibility to MNNG is controlled genetically and that the resistance of the Buffalo strain is autosomal dominant. The incidence of gastric adenocarcinoma in the $F_2$ generation was 36% in males and 14% in females. Assuming that the genotypes of the ACI and Buffalo strains are $rr$ and RR, respectively, the genotype of $F_2$ is $rr$, and the genotypes of $F_2$ segregate into $1rr:2rR:1RR$ by the Mendelian law. Assuming that the $rr$ genotype shows the ACI phenotype, and the $rR$ and RR genotypes both show the phenotype of Buffalo rats, the incidence of gastric adenocarcinoma in the $F_2$ generation is calculated to be 34% in males and 12% in females. These theoretical values are very close to the observed ones. There is no statistically significant difference between the incidence of gastric adenocarcinoma in ACI × Buffalo $F_2$ and that in Buffalo × ACI $F_2$ rats. The incidence of adenocarcinoma in $F_2$ rats of each coat color was not related to the susceptibility to MNNG.

In all strains, male rats tended to be more susceptible to MNNG gastrocarcinogenesis than females, but a statistically significant difference in incidence in both sexes was found only in $F_2$ rats ($p < 0.01$).

Macroscopically, most of the adenocarcinomas were located in the pyloric region. The mean diameters (mm; mean ± S.D.) of adenocarcinomas in each strain were as follows. ACI: males,

<table>
<thead>
<tr>
<th>Strain</th>
<th>Sex</th>
<th>Initial no.</th>
<th>Effective no.</th>
<th>Adenocarcinoma</th>
<th>Adenoma</th>
<th>Sarcoma</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Observed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Expected</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACI</td>
<td>M</td>
<td>20</td>
<td>15</td>
<td>12 (80 ± 20)</td>
<td>0</td>
<td>0</td>
<td>12 (80)</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>20</td>
<td>19</td>
<td>9 (47 ± 22)</td>
<td>3</td>
<td>0</td>
<td>12 (63)</td>
</tr>
<tr>
<td>Buffalo</td>
<td>M</td>
<td>20</td>
<td>17</td>
<td>3 (18 ± 18)</td>
<td>2</td>
<td>0</td>
<td>5 (29)</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>20</td>
<td>17</td>
<td>0 (0)</td>
<td>0</td>
<td>1</td>
<td>1 (6)</td>
</tr>
<tr>
<td>$F_1$</td>
<td>M</td>
<td>31</td>
<td>31</td>
<td>6 (19 ± 14)</td>
<td>2</td>
<td>3</td>
<td>11 (35)</td>
</tr>
<tr>
<td>Experiment 1</td>
<td>F</td>
<td>35</td>
<td>32</td>
<td>1 (3 ± 6)</td>
<td>1</td>
<td>1</td>
<td>3 (9)</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>58</td>
<td>45</td>
<td>7 (16 ± 11)</td>
<td>6</td>
<td>1</td>
<td>14 (31)</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>58</td>
<td>52</td>
<td>6 (12 ± 9)</td>
<td>3</td>
<td>1</td>
<td>10 (19)</td>
</tr>
<tr>
<td>Total</td>
<td>M</td>
<td>93</td>
<td>76</td>
<td>13 (17 ± 8)</td>
<td>14 (18)</td>
<td>8</td>
<td>25 (33)</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>93</td>
<td>84</td>
<td>7 (8 ± 6)</td>
<td>0 (0)</td>
<td>4</td>
<td>13 (15)</td>
</tr>
<tr>
<td>$F_2$</td>
<td>M</td>
<td>57</td>
<td>53</td>
<td>19 (36 ± 14)</td>
<td>18 (34)</td>
<td>12</td>
<td>34 (64)</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>65</td>
<td>59</td>
<td>8 (14 ± 9)</td>
<td>7 (12)</td>
<td>6</td>
<td>17 (29)</td>
</tr>
</tbody>
</table>

* Effective rats are defined as those surviving for more than 244 days, when the first gastric tumor was found in a male $F_2$ rat.

* Theoretical incidence obtained on the assumption that the difference in susceptibility to MNNG of the ACI and Buffalo strains is controlled by a single gene and that resistance to MNNG in the Buffalo strain is autosomally dominant.

* Ninety-five% confidence limit.

* Numbers in parentheses, percentages.
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10.0 ± 5.8 and females, 8.3 ± 4.6; Buffalo: males, 5.3 ± 3.8 and females, 5.6 ± 3.7; and F2: males, 6.0 ± 2.9 and females, 6.6 ± 2.0. The average size of the adenocarcinomas in the susceptible ACI rats was larger than in the resistant Buffalo or F1 hybrid rats. Histologically, in male ACI rats, 75% of the adenocarcinomas were seen to have invaded the muscularis propria and the serosa. However, in the other groups, more than 50% of the adenocarcinomas remained in the submucosa. One gastric adenocarcinoma induced in a male ACI rat invaded the pancreas directly, and one in an F1 hybrid rat invaded the liver directly. No metastasis was found in any rat.

The days on which the first gastric adenocarcinoma was found in each strain were as follows. ACI: males, 356 and females, 305; Buffalo: males, 399; F1: males, 367 and females, 481; and F2: males, 244 and females, 423. As shown in Chart 1, gastric adenocarcinomas were observed earlier in the susceptible ACI strain than in the Buffalo strain in both sexes. The cumulative incidence of gastric adenocarcinoma in F1 hybrids is almost the same as that in the Buffalo strain. This finding shows that F1 rats are the same as Buffalo rats, not only in the incidence but also in the latent period of induction of gastric adenocarcinoma.

Table 1. Cumulative incidence of gastric adenocarcinoma induced by MNNG in ACI (A), Buffalo (O), F1 (C), and F2 (D) rats. Gastric adenocarcinomas were found earlier in the ACI strain than in the resistant Buffalo or F1 hybrid rats.

<table>
<thead>
<tr>
<th>Strain</th>
<th>Sex</th>
<th>Effective no.</th>
<th>Adenocarcinoma</th>
<th>Adenoma</th>
<th>Sarcoma</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACI</td>
<td>M</td>
<td>15</td>
<td>2</td>
<td>0</td>
<td>8</td>
<td>10 (67)</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>19</td>
<td>0</td>
<td>0</td>
<td>8</td>
<td>8 (42)</td>
</tr>
<tr>
<td>Buffalo</td>
<td>M</td>
<td>17</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2 (12)</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>17</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>3 (18)</td>
</tr>
<tr>
<td>F1</td>
<td>M</td>
<td>31</td>
<td>5</td>
<td>0</td>
<td>4</td>
<td>9 (29)</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>32</td>
<td>2</td>
<td>0</td>
<td>5</td>
<td>7 (22)</td>
</tr>
<tr>
<td>F2</td>
<td>M</td>
<td>45</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>5 (11)</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>52</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>6 (12)</td>
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<tr>
<td>Total</td>
<td>M</td>
<td>76</td>
<td>9</td>
<td>1</td>
<td>4</td>
<td>14 (18)</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>84</td>
<td>5</td>
<td>1</td>
<td>7</td>
<td>13 (15)</td>
</tr>
<tr>
<td>F2</td>
<td>M</td>
<td>53</td>
<td>5</td>
<td>1</td>
<td>3</td>
<td>8 (15)</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>59</td>
<td>6</td>
<td>0</td>
<td>5</td>
<td>11 (19)</td>
</tr>
</tbody>
</table>

Gastric adenocarcinoma was induced in F2 males earlier than in males of the ACI strain, but the cumulative incidence for both sexes of F2 rats was intermediate between that of the ACI and of the Buffalo strains.

Non tumorous Regions in the Glandular Stomach. Ulcération and gastritis were observed in the stomachs of most rats of all strains. Irregular regenerative glands, atrophy of the pyloric glands, and cystic dilatation of the fundic glands were found in many rats, but no strain differences in their incidence were observed. Focal intestinal metaplasia in the pyloric region and pyloric gland metaplasia in the fundic region were observed in the stomach of some rats of each strain.

Tumors in the Intestine. Intestinal tumors were induced by MNNG principally in the duodenum and jejunum. A tumor of the large intestine was found in one male F1 rat, one female Buffalo rat, one female ACI rat, and one female F2 rat. Histologically, most of the tumors of the intestine were adenocarcinomas or sarcomas. The incidence of intestinal tumors induced by MNNG is summarized in Table 2. ACI rats were susceptible to both gastro- and intestinal carcinogenesis, and Buffalo rats were resistant to both. The incidence of intestinal tumors in F1 hybrids is lower than that in the ACI strain. Most sarcomas showed spindle cell or pleomorphic cell figures, but a few showed round cell figures. The ratio of the number of adenocarcinomas to sarcomas and the histological types of sarcomas are not statistically different in different strains.

DISCUSSION

The incidence of gastric adenocarcinoma induced by MNNG was significantly different between ACI and Buffalo rats under the same experimental conditions. Results with F1 and F2 showed that the gene(s) controlling resistance to MNNG was autosomal in the Buffalo strain and was inherited dominantly by F1 and F2 offspring.

There are some reports indicating that familial factors may influence the incidence of human gastric cancer (9, 17, 20, 21, 37). However, since members of a family live under similar environmental conditions, it is difficult to determine whether genetic factors are actually involved in human gastric carcinogenesis. In this work, we have shown experimentally that sus-
ceptibility to a chemical carcinogen is genetically controlled in gastric carcinogenesis in rats.

The phenotype(s) that determines resistance to induction of gastric adenocarcinoma by MNNG in Buffalo rats has not been clarified. Berman et al. (2) reported that Buffalo rats are also resistant to the induction of intestinal tumors by methyl(acetoxyethyl)nitrosamine. However, Buffalo rats are not resistant to all chemical carcinogens; mammary tumors can be induced in them by N-nitrosomethylurea (14), kidney tumors by N-4-(4'-fluorobiphenyl)acetamide (28), esophageal tumors by diethylnitrosamine (30), and colon tumors by methylazoxymethanol acetate (29). Moreover, there is no marked difference between the induction of gastric tumors in the ACI and in the Buffalo strains by p.o. administration of N,N'-2,7-fluorenylenebisacetamide (24, 33), although the incidence of gastric tumors is very low in both strains.

In this study, susceptible ACI rats consumed 20 to 30% more MNNG than did resistant Buffalo rats because of a difference in their daily water intake. However, the marked difference in susceptibility shown in this experiment cannot be explained by this difference in carcinogen intake, since resistant F1 hybrid rats consumed as much MNNG as did ACI strain rats. MNNG acts directly on gastric epithelial cells, causing methylation of nucleic acids and proteins (35). It has been reported that alkylation of macromolecules in gastric tissue by MNNG may be enhanced by glutathione (3). MNNG is rapidly converted to N-methyl-N'-nitroguanidine, which is not mutagenic or carcinogenic under the acidic conditions in the stomach or by enzymes in gastric epithelial cells (23, 36). Excess MNNG may reach the duodenum and, under alkaline conditions, MNNG is converted to diazomethane, which is a strong methylating agent (35).

In view of the characteristics which are specific to MNNG, some possible mechanisms for protection against MNNG in Buffalo rats can be postulated. (a) Lower pH of the gastric juice and a larger quantity of mucin which protects the gastric mucosa might prevent MNNG from reaching the gastric mucosa of Buffalo rats. (b) A smaller amount of glutathione in the gastric mucosa and stronger activity of the enzyme that converts MNNG to N-methyl-N'-nitroguanidine might protect Buffalo rats against modification of DNA by MNNG. (c) There are 2 types of cell strains, Mnr and Mer, that show different abilities to repair DNA after treatment with MNNG as reported by Day et al. (7). Buffer rats may be able to repair DNA modified by MNNG without error. (d) In the present work, we observed a difference between ACI and Buffalo rats not only in the incidence of gastric adenocarcinoma but also in the size of the adenocarcinomas and in their latent period. These findings suggest the possibility that there is a mechanism of protection against carcinoma induction by MNNG in Buffalo rats in the stage of promotion or progression of initiated cells.

Buffalo rats did not show complete resistance to MNNG, and a few gastric adenocarcinomas were induced, probably because the mechanism of protection against gastric carcinoma induction by MNNG in Buffalo rats is not complete. Damage to the gastric mucosa by MNNG and reaction to the damage were observed in nontumorous regions of the glandular stomach in resistant Buffalo strain rats and F1 hybrid rats as well as in ACI strain rats. It remains to be clarified whether the frequencies of these changes in the early stage of the experiment are different in the ACI and Buffalo strains.

A correlation was found between carcinogenesis in the stomach and in the intestine. ACI rats were susceptible to both gastric and intestinal carcinogenesis by MNNG, whereas the Buffalo strain and F1 hybrid rats showed resistance to both. Thus, genetic susceptibility to MNNG seems to be common to the stomach and intestine. However, it is also possible that the amounts of MNNG reaching the small intestine were different in each strain because of a difference in the degradation of MNNG in the stomach.

In all countries, mortality from gastric cancer is higher in men than in women (8, 32). In this experiment, the incidence of gastric adenocarcinoma in ACI and Buffalo rats and their F1 and F2 offspring was higher in males than in females. Furukawa et al. (13) studied the influence of sex hormones on induction of gastric tumors by MNNG. Castrated male rats and male rats given estradiol showed a lower incidence of adenocarcinoma of the stomach than did intact male rats after administration of MNNG. The influence of sex hormones might be the main factor in the sex difference found in gastric carcinogenesis by MNNG.

Strain differences in susceptibility have been observed with some other carcinogens (1, 10, 25). 1,2-Dimethylhydrazine is one of the compounds which have been studied extensively with regard to strain-dependent susceptibility: ICR/Ha mice are susceptible, whereas DBA/2 and C57BL/Ha mice are resistant (10), and Sprague-Dawley rats are susceptible (1, 26), whereas Lobund Wistar rats are resistant (1).

Evans et al. (11) studied the genetic control of colon carcinogenesis induced by 1,2-dimethylhydrazine in susceptible ICR/Ha mice, resistant C57BL/Ha mice, and their hybrids. In this case, high susceptibility to the carcinogen was dominant. It has been reported that metabolic activation of this chemical is related at least partially to strain differences in susceptibility in both mice (5) and rats (27).

It is important to try to determine the reason why Buffalo strain rats show resistance to the potent carcinogen MNNG, because clarification of the mechanism of their resistance might be helpful in prevention of human cancer. Thus, studies of the ACI and Buffalo strain rats should provide useful information on not only the genetic background of gastric carcinogenesis but also the prevention of human gastric cancer.

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