HIGH INCIDENCE OF RENAL TUMORS INDUCED BY N-DIMETHYLNITROSAMINE IN ANALBUMINEMIC RATS

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Analbuminemic rats were found to be highly susceptible to induction of renal tumors. Thirty-nine weeks after N-dimethylnitrosamine administration, the incidence of renal tumors and average weight of kidneys (including tumors) were 76.0% and 10.8 ± 4.1 g in male analbuminemic rats, respectively, whereas they were 37.1% and 3.5 ± 0.1 g, respectively, in normal male SD rats.

Key words: Renal tumor — Analbuminemic rats — N-Dimethylnitrosamine

We established a mutant strain of analbuminemic rats (Nagase analbuminemic rats; NAR) from a stock of Sprague-Dawley (SD) rats.4) The effects of some carcinogens were compared in NAR and normal SD rats, because albumin is known to be a carrier of many endogenous and exogenous compounds, including bile acids, hormones, drugs, toxins and probably carcinogens.7) NAR showed extraordinarily high susceptibility to bladder cancer induced by N-butyl-N-(4-hydroxybutyl) nitrosamine,1) but the same susceptibility as controls to liver cancer induced by oral 3'-methyl-4-dimethylaminoazobenzene.8)

N-Dimethylnitrosamine (DMN) induces renal neoplasia, as well as having a hepatocarcinogenic effect. The prolonged feeding of low levels of DMN to rats results in a high incidence of hepatocellular carcinoma with no kidney tumor, while feeding of higher doses for short periods has the reverse effect.5, 3)

In the experiments reported here, it was found that NAR showed high susceptibility to induction of renal cancer by DMN. It is suggested that these rats may be useful for studying the mechanism of renal carcinogenesis and for investigating the function of albumin in carcinogenesis.

NAR and normal SD rats bred in the Sasaki Institute were used. At 6 weeks old, male NAR and normal SD rats were starved for 24 hr, and then given a single ip injection of DMN at a dose of 50 mg/kg body weight as a 3.0% solution in 0.9% NaCl solution. These rats were given commercial diet (CE-2, CLEA, Japan Inc., Tokyo) and tap water ad libitum. They were weighed once a week until week 39 after DMN administration. Then they were killed and the number of kidney tumors and weight of the kidneys (including tumors) were recorded. Each tumor was fixed in phosphate-buffered formaldehyde solution, embedded in paraffin and sectioned at 3 µm thickness, and sections were stained with hematoxylin-eosin for histological observation.

NAR are similar in external appearance to normal SD rats, but are smaller. Moreover, they show no significant pathological abnormalities. The initial and final body weights of NAR and normal SD rats are given in Table I. The body weight of NAR was less than that of SD rats, but changes in body weight in both strains not treated with DMN were similar to those of the experimental group.

The incidence of renal tumors in NAR was significantly higher than that in normal SD rats 39 weeks after DMN administration and the average weight of the kidneys, including tumors, was also higher in NAR than
in normal SD rats as shown in Table I. Histological findings on renal tumors are also summarized in Table I. A mixed type of adenoma-adenocarcinoma and mesenchymal tumor was found in 7 of 38 kidneys of NAR, but in no normal SD rats. Tumors were larger in NAR than in SD rats, and no hepatocarcinomas were found in either strain.

The mechanism by which DMN caused this high incidence of renal tumor in NAR is unknown. The in vitro metabolic activation by liver S9 of dimethylnitrosamine and other carcinogenic nitrosamines, such as diethyl-nitrosamine and methylamyl nitrosamine, is similar in normal SD rats and NAR.6) Though the morphology of the kidney is normal in NAR (Tanaka, H., personal communication) the molecular composition of the kidneys in NAR may be different from that of normal SD rats. Further studies to elucidate the mechanism of the high susceptibility of NAR to renal carcinogens are in progress.

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Table I. Summary of Renal Tumorigenesis in NAR and Normal SD Rats 39 Weeks after DMN Administration

<table>
<thead>
<tr>
<th></th>
<th>NAR</th>
<th>Normal SD rats</th>
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<tbody>
<tr>
<td>Body weight (g)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>111.7±18.4^a)</td>
<td>111.2±6.4</td>
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<tr>
<td>Final</td>
<td>414.2±63.6</td>
<td>572.9±82.7</td>
</tr>
<tr>
<td>Incidence</td>
<td>76.0% (19/25)^b)</td>
<td>38.7% (12/31)</td>
</tr>
<tr>
<td></td>
<td>76.0% (38/50)^e)</td>
<td>37.1% (23/62)</td>
</tr>
<tr>
<td>Weight^d) (g)</td>
<td>10.8±4.1</td>
<td>3.5±0.1</td>
</tr>
<tr>
<td>Histological type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenoma-adenocarcinoma</td>
<td>18^e)</td>
<td>16</td>
</tr>
<tr>
<td>Mesenchymal tumor</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>Mixed type</td>
<td>7</td>
<td>0</td>
</tr>
</tbody>
</table>

^a Mean±SD.
^b Number of rats with tumors/total number of rats examined.
^c Number of kidneys with tumors/total number of kidneys.
^d Mean±SE of the weights of kidneys including tumors.
^e Number of kidneys classified pathologically.

References