DEMONSTRATION OF CARCINOGENICITY IN F344 RATS OF 2-AMINO-3-METHYLIMIDAZO[4, 5-f]QUINOLINE FROM BROILED SARDINE, FRIED BEEF AND BEEF EXTRACT

Shozo Takayama,*1 Yoko Nakatsuru,*1 Mitsunobu Masuda,*1 Hiroko Ohgaki,*2 Shigeaki Sato*2 and Takashi Sugimura*2

*1 Department of Experimental Pathology, Cancer Institute, Kami-Ikebukuro 1-37-1, Toshima-ku, Tokyo 170 and *2 Biochemistry Division, National Cancer Center Research Institute, Tsukiji 5-1-1, Chuo-ku, Tokyo 104

The mutagenic compound 2-amino-3-methylimidazo[4, 5-f]quinoline, originally isolated from broiled sardines and also present in cooked beef and beef extract, is being tested for carcinogenicity in F344 rats of both sexes. High incidences of tumors of the Zymbal gland, colon, small intestine and liver in males have been observed in the first 300 days of the experiment.

Key words: 2-Amino-3-methylimidazo[4,5-f]-quinoline — Carcinogenicity — Rats

A series of new mutagenic heterocyclic amines has been isolated from amino acid and protein pyrolysates, broiled fish, fried beef and commercial beef extract.14-20 Among these heterocyclic amines, 3-amino-1,4-dimethyl-5H-pyrido[4,3-b]indole and 3-amino-1-methyl-5H-pyrido[4,3-b]indole from a tryptophan pyrolysate, 2-amino-6-methyldipyrido[1,2-a:3',2'-d]imidazole (Glu-P-1) and 2-aminodipyrido[1,2-a:3',2'-d]imidazole (Glu-P-2) from a glutamic acid pyrolysate, and 2-amino-9H-pyrido[2,3-b]indole and 2-amino-3-methyl-9H-pyrido[2,3-b]indole from soybean globulin pyrolysate have been found to be carcinogenic to mice.9,11,20 Glu-P-1 and Glu-P-2 have also been shown to be multipotent carcinogens in F344 rats when given orally.21

More recently, it was observed that 2-amino-3-methylimidazo [4, 5-f] quinoline (IQ), isolated first from broiled sardines,5,7 and then from cooked beef1,4 and beef extract3,4,22 is carcinogenic to CDF1 mice when given continuously in the diet.10 We report here that IQ is also a multipotent carcinogen to rats, inducing tumors of the Zymbal gland, colon, small intestine, liver, skin, clitoral gland and oral cavity when given in the diet.

Synthetic IQ was obtained from Nard Institute, Osaka. The purity of this compound was confirmed by high performance liquid chromatography, and mass and infrared spectroscopies. IQ was incorporated

<table>
<thead>
<tr>
<th>Initial No. of rats</th>
<th>No. of rats examined by day 300</th>
<th>Zymbal gland Carcinoma</th>
<th>Colon</th>
<th>Small intestine</th>
<th>Liver</th>
<th>Skin</th>
<th>Oral cavity</th>
<th>Clitoral Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Adenoma</td>
<td>Adenocarcinoma</td>
<td></td>
<td>Carcinoma</td>
<td>Carcinoma</td>
</tr>
<tr>
<td>M 40</td>
<td>20</td>
<td>18c</td>
<td>2</td>
<td>7</td>
<td>5</td>
<td>8</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>F 40</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

a) Squamous cell carcinoma.
b) Hepatocellular carcinoma.c) One had metastases to the lung and thyroid.
S. TAKAYAMA, ET AL.

Three tumors are seen in the colon of a male rat killed on day 255. (B) Histological picture of an adenocarcinoma of the colon illustrated in (A) showing a typical glandular pattern with pleomorphic nuclei. Hematoxylin and eosin stain. × 150.

Six-week-old F344 rats of both sexes were obtained from Charles River Japan Inc., Kanagawa. Forty rats of each sex were given diet containing 300 ppm of IQ from the age of 8 weeks. A control group of 50 rats of each sex of the same age was given basal diet only. Animals that became moribund due to
tumor formation were killed and autopsied. All organs were fixed in 15% neutralized formalin, embedded in paraffin, processed and stained with hematoxylin and eosin.

The mean body weights of rats of both sexes given IQ were consistently less than those of the control group. The average intakes of the diet and IQ per day per rat by day 300 of the experiment were as follows: males on diet containing IQ, 14.0 g and 4.2 mg; females on diet containing IQ, 10.0 g and 3.0 mg; males on basal diet, 16.5 g; females on the basal diet, 10.0 g. During this period, 20 of 40 males, and 4 of 40 females in the experimental group were killed. The numbers of rats with tumors in various organs are shown in Table I. Tumors were frequently found in the Zymbal gland, colon, small intestine and liver of male rats. In the Zymbal gland, tumors were squamous cell carcinoma, and the first one was found in a male rat on day 165.

The first tumor of the colon was found in a male rat on day 255. These tumors were usually located 5 to 22 cm above the anorectal junction and some of them were multiple as shown in Fig. 1A. The first small intestinal tumor was found in a male rat on day 239. Most tumors of the small intestine were found in the terminal ileum, and in some cases they were also multiple tumors. The tumors of the colon and small intestine were identified as adenomas and adenocarcinomas (Fig. 1B). The first hepatic tumor was found in a male rat on day 288 and later, hepatic tumors were found in 8 of 20 male rats. These tumors were hepatocellular carcinomas.

Tumors were also found in the skin of the lower abdomen of male rats and the clitoral gland of female rats. Squamous cell carcinomas of the oral cavity also developed in male rats. No externally visible tumors were observed in the control group, as reported previously.\(^1, 3, 6, 12\)

IQ has been found together with 2-amino-3,8-dimethylimidazo[4,5-f]quinoline and/or 2-amino-3,4-dimethylimidazo[4,5-f]quinoline in foods cooked under ordinary conditions.\(^1, 3, 4, 6, 7, 12\)

On the basis of the dose used and the latent periods for appearance of tumors, the carcinogenic potency of IQ in F344 rats is higher than those of Glu-P-1 and Glu-P-2. The present experiment is still in progress and rats will be given IQ-diet for a total of 104 weeks. The results will be reported in detail when the experiment is finished.

This work was supported by Grants-in-Aid for Cancer Research from the Ministry of Education, Science and Culture and the Ministry of Health and Welfare and by a grant from the Toyota Foundation.

(Received April 6, 1984; Accepted May 10, 1984)

REFERENCES

S. TAKAYAMA, ET AL.


