76. *Atrophy of Salivary Glands and Pancreas of Rats fed on Diet with Amino-methyl-a-carboline*

By Shozo TAKAYAMA,*¹,*** Yoko NAKATSURU,*² Hiroko OHGAKI,*³ Shigeaki SATO,**¹ and Takashi SUGIMURA, M. J. A.**¹

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Introduction. 2-Amino-3-methyl-9H-pyrido[2,3-b]indole (MeAaC) and 2-amino-9H-pyrido[2,3-b]indole (AaC) were found to be mutagenic heterocyclic amines in soybean globulin pyrolysate,¹ and their carcinogenicity in mice has been established.²,³ During the long-time feeding experiments of these compounds in rats we found that MeAaC induced severe atrophy of the salivary glands and pancreas, the result of which is reported here. The result on AaC is also described.

Materials and methods. Six-week-old F344 rats of both sexes were obtained from Charles River Japan Inc., Kanagawa, Japan. They were housed 4 to a plastic cage. Their body weights were measured once a month. Food and tap water were given ad libitum.

Synthetic MeAaC acetate and AaC acetate were obtained from Nard Institute, Osaka, Japan. The purities of these compounds were confirmed by high performance liquid chromatography and by their mass and infrared spectra, and melting points. MeAaC acetate and AaC acetate were added to the pellet diet, each at a concentration of 0.08%. The presence of more than 83% of the added MeAaC and AaC in the diet was confirmed by high performance liquid chromatography after extraction of the compounds with methanol.

Groups of 20 rats of each sex, initially 8 weeks old, were given diets containing MeAaC acetate and AaC acetate, while control groups to 50 rats of each sex were given basal diet only. Autopsies were performed when animals died or were killed in a moribund state. All surviving rats were killed on day 730 and autopsied. Organs were fixed in 10% neutralized formalin, and embedded in paraffin, processed, and stained with hematoxylin and eosin.

Results and discussion. The average intakes of food and carcinogens per day per rat, respectively, were as follows: males on a diet with MeAaC, 12 g and 10 mg; females on a diet with MeAaC, 9 g and 7 mg; males on a diet with AaC, 14 g and 11 mg; and females on a diet with AaC, 9 g and 7 mg. The rats on the MeAaC diet showed a slight decrease in body weight, but those on the AaC diet showed nearly the same increase in body weight as control rats in both sexes. Until day 210, the survival rates of male and female rats on the MeAaC and AaC diets were similar. However, subsequently the survival rate of rats fed MeAaC decreased sharply.

On day 230, a female rat in the MeAaC group was killed due to severe

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*¹ Department of Experimental Pathology, Cancer Institute, Kami-Ikebukuro, Toshima-ku, Tokyo 170, Japan.
**¹ Biochemistry Division, National Cancer Center Research Institute, Tsukiji, Chuo-ku, Tokyo 104, Japan.
***¹ Present address: National Cancer Center Research Institute, Tsukiji, Chuo-ku, Tokyo 104, Japan.
Fig. 1. Macroscopic appearance of remarkable atrophy of the major salivary glands in a female rat in MeAαC diet group.

Fig. 2. Histological picture of the submandibular gland shown in Fig. 1. Marked atrophy of mucous alveoli and duct dilatation are seen.

emaciation. At the autopsy, remarkable atrophy of the major salivary glands (Fig. 1) and pancreas were found. From this time until the end of the experiment on day 266, the severe and moderate atrophy of both the salivary glands and pancreas was found in 10 of 19 males and 11 of 20 females fed MeAαC. In addition, severe and moderate atrophy of the salivary glands only was recorded in 3 of 19 male and 3 of 20 female rats. Pancreas atrophy alone was found in 2 of the male and 1 of 20 female rats. However in all other animals slight atrophy was noticed.

Histologically, the atrophy of the salivary glands showed a variable pattern. Marked atrophy of the cells in mucous and serous alveoli was most prominent. Dilatation of intralobular ducts and secretory ducts was occasionally observed (Fig. 2). No atrophy of lacrimal gland was detected.

In the pancreas, remarkable atrophy of acinar cells, islets of Langerhans and pancreatic ducts was also found. Compared with the control, the amount of eosinophilic zymogen granules in acinar cells in the MeAαC diet group also decreased (Fig. 3).

In other organs, no remarkable changes were observed in both sexes.

In the rats given AαC, no atrophy of the salivary glands and pancreas was
Fig. 3. Atrophy of acinar cells and islet of Langerhans in a male rat given MeAaC.

observed. Surviving rats were killed on day 730 and examined histologically. There was no significant difference in the incidences of tumors in experimental and control groups. Thus under these experimental conditions, the carcinogenicity of AaC in rats was not established.

It is reported that selective resection of the auriculotemporal nerve and removal of the superficial cervical ganglion in rats caused atrophy of the parotid gland. Concerning the atrophy of the pancreas, it has been reported that the acinar cells in the rat pancreas were selectively destroyed by penicillamine and a copper-deficient diet. Destruction of pancreatic acinar cells, and atrophy of pancreatic lobuli in rats were also produced by a single intraperitoneal injection of L-arginine. Recently, a selenium deficient diet was proven to induce pancreatic atrophy in chicks.

The mechanisms of the atrophy of salivary glands and pancreas by MeAaC are not clear. No atrophy of these organs was detected in mice fed this compound. These atrophies have not been observed in rats treated with 2-amino-6-methylidipryrido[1,2-α:3',2'-d]imidazole, 2-aminodipyrido[1,2-α:3',2'-d]imidazole and 2-amino-3-methylimidazo[4,5-f]quinoline.

MeAaC and AaC have been found in grilled beef, grilled chicken, and also in grilled Chinese mushrooms and cigarette smoke condensates in rather high amounts compared to other heterocyclic amines. In this context also, the hazardous effect of these materials on human should be carefully evaluated. Experiments with a lower dose and shorter exposure of MeAaC in rats are in progress.

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References