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Induction of Squamous Cell Carcinomas in the Salivary Glands of Rats by Potassium Iodide

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In a 2-year carcinogenicity study of potassium iodide (KI) in F344/DuCrj rats, squamous cell carcinomas (SCCs) were observed in the salivary glands of 4/40 males and 3/40 females receiving 1000 ppm KI in the drinking water. Ductular proliferation with lobular atrophy was observed at high incidence in the submandibular glands of the high-dose animals, and squamous metaplasia was frequently evident within the proliferative ductules and the larger interlobular ducts. A transition from metaplasia to SCC was apparent. The results suggest that squamous metaplasia in proliferative ductules, occurring secondarily to lobular impairment induced by KI, may develop into SCCs via a non-genotoxic, proliferation-dependent mechanism.

Key words: Squamous cell carcinoma — Salivary gland — Potassium iodide — Rat

In a carcinogenicity study of potassium iodide (KI), squamous cell carcinomas (SCCs) derived from the salivary gland were observed in several male and female rats given water containing excess amounts of KI. However, there have been no reports of salivary gland carcinogenesis by chemical substances containing iodine. In order to elucidate the pathogenesis of the SCC induction, further detailed morphological examinations were performed in the present study.

Four-week-old male and female F344/DuCrj rats were purchased from Charles River Japan Inc. (Atsugi), and divided into 4 groups consisting of 40 rats each at 5 weeks of age. They were given potassium iodide in the water at concentrations of 0, 10, 100 and 1000 ppm for 2 years. The highest dose has been reported to result in pronounced physiological effects in experimental animals.[1)] KI intakes of rats during the treatment period were calculated from the water consumption. After the termination of treatment, all animals were killed under ether anesthesia and dissected. Salivary glands and tissue masses observed macroscopically in the subcutis of the neck were fixed in neutral-buffered 10% formalin, routinely processed for production of sections stained with hematoxylin-eosin (HE), and examined histopathologically. In addition, immunohistochemistry to identify cells positive for the proliferating cell nuclear antigen (PCNA) was performed. PCNA labeling indices of epithelial cells in normal ducts and proliferative lesions were determined as percentage of PCNA-positive cells in more than 500 cells counted.

Histopathological examination revealed SCCs in 4/40 male and 3/40 female rats receiving 1000 ppm of KI. The lesions were all considered to be derived from the salivary glands rather than the Zymbal's gland, based on their anatomical locations and histological patterns (Fig. 1, Table I). Ductular proliferation accompanied by lobular atrophy was also frequently observed in submandibular glands of both sexes of the 1000 ppm group, the incidence being 31/40 in males and 34/40 in females (Fig. 2, Table I). These ductular proliferative lesions were well-circumscribed and triangular in shape, with no or only a few acini in association, and appeared to be restricted to single lobules. These lesions were usually multiple in the bilateral submandibular glands, and frequently featured squamous metaplasia within the proliferating ductules (Figs. 3 and 4). In addition, the interlobular ducts draining the affected lobules also generally featured squamous metaplasias (Fig. 3). The lesions were usually associated with various degrees of inflammatory cell infiltration. Similar changes were also observed in the sublingual and parotid glands of the 1000 ppm group, although at much lower incidences and without squamous metaplasia. There was a morphological continuum from squamous metaplasia of proliferating ductules to SCCs. As compared with normal ductules, PCNA labeling indices were elevated in proliferating ductules, squamous metaplasias and SCCs, the values for SCCs being highest (Table II). PCNA labeling indices for interlobular ducts exhibiting squamous metaplasia were also higher than those of normal ducts from control rats. The histological findings and cell kinetics suggest that squamous metaplasia originating from either proliferating ductules in lobular atrophy or interlobular ducts might progress to SCCs.

The incidences of SCC in the 1000 ppm group, 4 of 40 males and 3 of 40 females, were not statistically significant as compared to those in the concurrent control group.

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