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
However, in the historical data for untreated control F344 rats from carcinogenicity studies performed in our laboratory\textsuperscript{2-9} and in the literature historical data on control F344 rats\textsuperscript{10-12} used for carcinogenicity studies, no spontaneous occurrences of SCCs in the salivary gland are recorded. Therefore, the incidence of SCCs in the 1000 ppm

| Table I. Chemical Intake and Incidences of Histopathological Lesions in the Salivary Glands of Rats Given Water Containing Potassium Iodide for 2 Years |
|-----------------------------------|
| Male                             | Female                        |
|-----------------------------------|--------------------------------|
| Chemical intake (mg/kg/day)       | 0  | 10 | 100 | 1000 (ppm) |
| Submandibular gland              |    |    |     |            |
| Lobular atrophy and ductular proliferation | 0  | 1  | 0   | 31         |
| Squamous cell carcinoma          | 0  | 0  | 0   | 4          |
| Parotid gland                    |    |    |     |            |
| Lobular atrophy and ductular proliferation | 1  | 1  | 1   | 4          |
| Sublingual gland                 |    |    |     |            |
| Lobular atrophy and ductular proliferation | 0  | 0  | 0   | 1          |

Fig. 1. A squamous cell carcinoma observed in the submandibular gland of a male rat given 1000 ppm KI in the water for 2 years. Tumor cells exhibit nuclear atypia. HE staining, ×130.

Fig. 2. Ductular proliferation observed in the submandibular gland of a male rat given 1000 ppm KI in the water for 2 years. Only few acini are evident in this lesion. HE staining, ×210.
Iodide-associated Salivary Gland Tumors

Although there have been no previous reports of SCCs of the salivary gland in animals treated with iodine-containing chemicals, there are some references to support the group in the present study can not be ignored, and the possibility must be entertained that the SCCs are related to the treatment with large amounts of KI.
possibility that SCCs can be induced in the salivary gland. For example, they can be caused in rats by DMBA-treatment,10, 11 being preceded by the development of duct-like structures and dilated excretory ducts, concomitantly with elevation of cell proliferation and squamous metaplasia.12

In addition, squamous metaplasia is well known to occur in other non-squamous tissues, such as the mammary gland13 and bronchi14 in man. It has also been reported that squamous metaplasia arises in respiratory and olfactory epithelia subjected to prolonged or continuous injury by irritants or infectious inflammation, with occasional cellular atypia suggestive of a preneoplastic nature.15

Squamous metaplasia of ductules or ducts is probably a feature of salivary glands suffering repeated injury associated with inflammation. Metaplasias may, for example, occur in sialadenitis caused by conditions blocking secretion, such as sialolithiasis,16 and in hyperplastic ductal epithelia with inflammation in the cases of sialolithiasis after fine-needle aspiration in humans.17 In the present study, epithelia with inflammation in the cases of sialolithiasis after elevation of cell proliferation and squamous metaplasia.13

structures and dilated excretory ducts, concomitantly with inflammation. Metaplasias may, for example, occur in sialadenitis caused by conditions blocking secretion, such as sialolithiasis,18 and in hyperplastic ductal epithelia with inflammation in the cases of sialolithiasis after fine-needle aspiration in humans.19 In the present study, ductular proliferation in lobules appeared to be a reaction to acinar atrophy. However, it was unclear whether the acinar change was caused by direct injury or was secondary to disturbed excretion due to interlobular duct lesions.

Chemicals containing iodine have in fact been reported to impair salivary gland function in man and rats. In human beings, I-131 used for thyroid tumor therapy has been demonstrated to cause sialadenitis in the submandibular or parotid glands with reduction of serous cell numbers and duct proliferation.20 Contrast media may also induce so-called iodide mumps, characterized by swelling of submandibular, sublingual or parotid glands and/or sialadenitis.21, 22 In rats, sodium iodide induces inflammatory lesions and squamous metaplasia of ducts in the submandibular gland23 that are in line with those seen in the present study. Moreover, treatment with iodinated glycerol is associated with focal atrophy and squamous metaplasia of the salivary glands.24 Based on these reports, it can be considered that the salivary gland of the human and the rat is one of the major target organs of compounds containing iodine, and acinar atrophy, inflammatory lesions, duct proliferation or squamous metaplasia are induced by these compounds.

In the present study, the observed SCCs clearly originated in the duct system, in association with ductular proliferation and metaplasia. However, since KI has been found to be negative in genotoxicity tests,25, 26 the underlying mechanisms are presumably epigenetic. The 1000 ppm dose of KI applied in the present study is about 2500 times the maximum tolerable daily intake (1.0 mg iodine/day) settled by FAO/WHO Joint Expert Meeting on Food Additives.27 with the average human body weight assumed to be 50 kg. The fact that the lower doses employed (10 and 100 ppm) were not associated with tumor development is a clear pointer to a non-genotoxic carcinogenic potential for the salivary glands in rats. The risk to humans can therefore be considered negligible except in cases of excessive exposure to iodine compounds.

A full report on the 2-year carcinogenicity study of this chemical will be presented in the near future.

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