Steroid hormone receptors in human salivary gland tumours

P-J LAMEY,* R E LEAKE,† S K COWAN,† D S SOUTAR,‡ I A MCGREGOR,‡
F M MCGREGOR§

From the *Department of Oral Medicine and Pathology, Glasgow Dental Hospital and School, †Department of Biochemistry, University of Glasgow, ‡Plastic Surgery Unit, Canniesburn Hospital, Bearsden, §Department of Pathology, Royal Infirmary, Glasgow, Scotland

SUMMARY Major salivary gland tumours were studied for the presence of hormone receptors for oestrogen and progesterone. Of the eight salivary gland tumours exhibiting varied histology, none showed high affinity receptors for oestrogen or progesterone. Salivary tissue from four patients with non-neoplastic salivary gland disease was also studied and found not to contain high affinity receptor sites. The absence of hormone receptors in these glands suggests that such tumours are not dependent on endocrine function.

Studies of human breast tumours¹ and human colon cancers² have shown the presence of steroid hormone receptors to oestrogen and progesterone in some cases. High affinity binding sites to other steroid hormones, such as dihydrotestosterone and glucocorticoid, may also be found in these tumours. Evidence is accumulating concerning other hormone dependent malignancies, including some types of acute leukaemia,³ cancer of the prostate,⁴ endometrial cancer⁵ and other solid tumours⁶. The sequence of events whereby steroid hormones interact with receptor proteins and induce protein production is not fully understood, but it is generally accepted that the presence of steroid receptors is crucial to the hormone responsiveness⁷ of target tissue.

The association of breast cancer and salivary gland tumours is well known in man⁸ and animals.⁹ Common aetiological factors for these two tumours have also been proposed.

This preliminary study shows that human salivary gland tumours do not contain steroid hormone receptor sites often associated with hormone dependent tumours.

Material and methods

Six men and six women with suspected neoplastic and non-neoplastic salivary gland release were selected for study. The age range of the patients was 29-80 years (mean 45.7 years). No patient was taking oestrogens

before surgery, and only one patient was post-menopausal.

At operation the affected salivary gland was removed and sampling of the tumour or non-tumour tissue undertaken. Care was taken to sample the salivary tissue for hormone analysis adjacent to the area to be subjected to routine histopathological examination. Of the patients with non-neoplastic salivary disease (three male and one female), three patients had chronic sialadenitis and one patient had normal parotid tissue. Table 1 gives the details of these patients and the histological diagnoses

Samples of tissue for steroid receptor assay were transported on ice to the laboratory and either assayed fresh or stored as previously described.¹⁰ Tissue was homogenised and separated into soluble and nuclear fractions by our standard procedure.⁷ Oestrogen receptor values were determined in both fractions by a 7-point saturation assay using tritiated oestradiol (range 0.2-3 nmol/l) either with or without a 200-fold excess of diethylstilboestrol to eliminate non-specific binding. Results were analysed by Scatchard analysis. Progesterone receptor values were determined in a similar assay which used tritiated ORG-2058 (Organon Synthetic Progestin) (range 0.5-5 nmol/l) with or without unlabelled ORG-2058 at 200-fold excess concentration. All buffers contained 15% glycerol for the progesterone receptor assay.

Receptor values were only considered to be positive when the "best-fit" line could be constructed using at least five of the points plotted after correction for

Table 1 Summary of clinical features of patients studied and histological diagnosis of their salivary gland lesions

Case No	Sex	Age	Site of tumour	Tumour histology
1	F	80	Left parotid	Pleomorphic salivary adenoma
2	M	34	Right parotid	Chronic sialadenitis
3	F	38	Left parotid	Pleomorphic salivary adenoma
4	F	45	Left parotid	Adenocarcinoma
5	M	41	Right parotid	Pleomorphic salivary adenoma
6	M	44	Left parotid	Mucoepidermoid
7	F	42	Left parotid	Pleomorphic salivary adenoma
8	F	48	Right parotid	Carcinoma ex-pleomorphic salivary adenoma
9	M	64	Left parotid	Adenocarcinoma
10	M	64	Left parotid	Normal tissue
11	F	20	Right submandibular	Chronic sialadenitis
12	M	29	Right submandibular	Chronic sialadenitis

non-specific binding. This approach to receptor assays helps to eliminate binding due to proteins other than the specific high affinity, saturable cellular receptors.¹¹ All assays are subject to strict quality control.¹²

Results

Scatchard analysis of high affinity receptor binding protein was undertaken on all specimens. Table 2 shows the results. None of the assays was positive for high affinity receptor sites from oestrogen and none of the patient's salivary tissue samples was progesterone receptor positive.

Discussion

Sexual dimorphism of murine salivary glands has been well documented.¹³ The submandibular glands of mice are particularly affected, and the histological changes seen generally entail granular tubule cells.¹⁴ This dimorphism is thought to be mediated by steroid sex hormones which are also known to have a role in the granular tubule cell content of growth factors—

namely, epidermal growth factor.¹⁵ These physiological differences between male and female murine salivary glands are probably established at or before puberty, and sex steroid responses mediated through the high affinity receptor probably do not occur in most salivary gland cells in mature adults. A small select group of cells may retain sex steroid receptors, but this would only be detectable using an immunocytochemical assay.¹⁶

An association between breast tumours and salivary tumours in man has been reported.¹⁸ In addition, experimental manipulation of sex hormones in mice induces secondary primary tumours of breast⁹ in animals which would normally only develop salivary gland tumours selectively.¹⁷ It is postulated that as the salivary tumours were well differentiated (pleomorphic salivary adenomas) they may produce epidermal growth factor and that this may be important in the subsequent breast tumour growth occurring *in vitro*.¹⁸ In practice raised values of epidermal growth factor receptors in breast tumours are associated with loss of oestrogen receptors.¹⁹

To our knowledge hormonal treatment has not been suggested or tried in patients with salivary gland

Table 2 Analysis of oestrogen and progesterone receptors in human salivary samples

Case No	Cytosol protein (mg/ml)	Nuclear DNA (mg/ml)	Oestrogen receptor assay	Progesterone receptor results
<i>Tumour</i>				
1	2.1	51	ND	ND
3	2.75	185	ND	ND
4	4.05	250	ND	ND
5	1.7	120	ND	ND
6	1.65	170	ND	ND
7	0.43	33	ND	ND
8	4.05	190	ND	ND
9	1.4	168	ND	ND
<i>Without tumour</i>				
2	1.0	39	ND	ND
10	1.15	120	ND	ND
11	2.95	120	ND	ND
12	2.4	250	ND	ND

*ND = not detectable; assay detects receptor in excess of 0.1 fmol/μg DNA.

tumours. The results of our study suggest that hormonal manipulation is unlikely to be effective, as salivary gland tumours do not contain high affinity oestrogen receptors.

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Requests for reprints to: Dr P-J Lamey, Department of Oral Medicine and Pathology, Glasgow Dental Hospital and School, 378 Sauchiehall Street, Glasgow G2 3JZ, Scotland.