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PROGESTERONE AND ESTRADIOL CONCENTRATION IN HUMAN KIDNEY AND RENAL CELL CARCINOMA

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SUMMARY

Renal carcinoma and renal tissue, five each, were analyzed for their concentration of progesterone (P) and estradiol-17-β (E_2). Concentrations of these steroids were also measured in blood samples from each of the five patients. The mean plasma P and E_2 concentrations were 0.5 ng/ml and 44.8 pg/ml. The tissue concentrations of P were 8.2 ng/g and 5.9 ng/g for normal kidney and carcinoma tissue respectively. The difference between the two values was significant ($P < 0.025$). The difference between the E_2 concentrations in carcinoma (238 pg/g) and normal tissue (306 pg/g) was not significant. Although the biological significance of the relatively high concentrations of these steroids in renal tissue is not yet clear, the present data are consistent with recent findings of the presence of E_2 and P receptors in renal carcinoma and in normal kidney.

INTRODUCTION

It was shown over thirty years ago that prolonged estrogen treatment of male golden Syrian hamsters led to the development of kidney tumours [1, 2]. Recently, steroid hormone receptors have been demonstrated in the renal tissue of not only male golden hamsters [3] but also in mice [4] and humans [5, 6]. Furthermore, estradiol and progesterone receptors have been at least preliminarily demonstrated in human renal carcinoma [6, 7]. These observations suggest that renal tissue although classically a non-target tissue for estrogen and progesterone may have the capacity to concentrate these steroids from the peripheral plasma. We have in the present study determined the concentration of both estradiol 17β (E_2) and progesterone (P) in human renal tissue and renal cell carcinoma.

EXPERIMENTAL

Biological material

Samples were obtained from five patients, four men and one woman, 56–78 years old, with the diagnosis of renal cell carcinoma. The diseased kidney was removed at operation and tissue samples of carcinoma and of renal tissue with normal appearance, weighing about 1 g, were cut and placed in Krebs–Ringer medium as described previously [8]. After rinsing the tissue tnoroughly in cold saline it was blotted dry, weighed and frozen at −20°C. Venous blood (about 10 ml) was collected in heparinized glass tubes, centrifuged and the plasma stored frozen at −20°C until analysed.

Tissue digestion and extraction of steroids

The frozen tissues were thawed and then digested in 0.5 ml of a mixture containing 5% sodium dodecyl sulphate (SDS) and 0.5 N NaOH as described previously [8]. An aliquot of the digested material, usually 0.1 ml, was taken for protein and DNA determinations and the remainder was extracted three times with three volumes of ethyl acetate. The combined extracts were evaporated to dryness under air at 40°C. The dried extracts, however, contained a significant amount of SDS which had to be removed before radioimmunoassay. This was accomplished by Sephadex LH-20 chromatography and 6 ml of the eluate was collected [8, 9]. The recovery of radioactive steroids added into the digested tissue samples and measured in the eluate, was 94 and 99% for progesterone and estradiol-17β respectively.

Protein in the digested material was determined directly with Lowry's method [10] using bovine serum albumin, dissolved in digestion mixture, as a standard.

Radioimmunoassay

After evaporation of the collected (6 ml) eluate, the residue was dissolved in 1 ml of ethyl acetate and a suitable amount, depending on the predictive concentration of estradiol-17β (E_2) and progesterone (P), was taken for the respective radioimmunoassays of these steroids. The procedure for radioimmunoassay of E_2 was that described by Lindberg *et al.*[11], the reliability of which, for the determination of E_2 in tissue-extracts, has been previously checked by us [9]. The method for progesterone determination and other details have been described previously [8]. E_2 and P

Table 1. Progesterone (P) concentration in plasma (Pl), tissue (T- with and without carcinoma*) and tissue/plasma (T/Pl) ratios in 5 patients with renal carcinoma

Pat. No.	ngP/ml	Tissue with cancer ngP/g per w/w	T/Pl ratio	ngP/mg prot	Tissue without cancer ngP/g per w/w	T/Pl ratio	ngP/mg prot
1 (M)	0.6	5.13	8.55	0.045	7.54	12.57	0.053
2 (M)	0.5	3.86	7.72	0.024	7.38	14.76	0.058
3 (M)	0.4	8.13	20.33	0.052	8.28	20.70	0.070
4 (F)	0.8	5.45	6.81	0.045	9.99	12.49	0.058
5 (M)	0.3	6.99	23.30	0.054	7.61	25.37	0.051
Mean ± SE	0.52	5.91	13.34	0.044	8.16	17.18	0.058
	0.09	0.75	3.50	0.005	0.48	2.54	0.003

Male and female are indicated by M and F respectively.
* In each case tissue samples with and without carcinoma were obtained from the same kidney.

concentration in plasma were determined also by these radioimmunoassays.

RESULTS

Table 1 shows P concentrations in plasma, kidney and renal cell carcinoma. The tissue concentrations were determined on the basis of both wet weight and protein.

The mean plasma concentration of P was 0.5 ng/ml, whereas the tissue concentration was 8.16 ng/g and 5.91 ng/g for apparently normal and carcinoma tissues respectively. The uptake of P, expressed as tissue concentration per g tissue/plasma concentration per ml was 17.18 and 13.34 for the two kinds of tissue respectively. Progesterone concentration in renal carcinoma was significantly ($P < 0.025$) lower than in normal tissue.

The mean E_2 concentration in plasma and in renal tissue without carcinoma was 54 pg/ml and 306 pg/g respectively (Table 2). E_2 concentration in the carcinoma tissue was not significantly different from the tissue without carcinoma (mean 238 pg/E_2/g). The uptake of E_2 by the tissue (expressed as pg per g tissue/pg per ml plasma) did not differ significantly when tissues with (8.2) and without cancer (9.23) were compared (Table 2).

The mean P concentration expressed as ngP/mg protein was 0.058 for non-cancerous tissue and 0.044 for cancerous tissue (Table 1). The mean E_2 concentration in both cancerous and non-cancerous tissues was 2.2 pg/mg protein.

DISCUSSION

The present data have clearly demonstrated a high capacity for progesterone and estrogen accumulation by the human kidney. This was true for both normal renal tissue and for hypernephroma. These data are consistent with the recent findings of the presence of estrogen and progesterone receptors in the human renal tissues [5, 6].

The concentration of E_2 in plasma and in tissue as well as tissue E_2 uptake ability were in the range recently reported for the prolipherative endometrium [12]. Although plasma P concentration in the patients of the present study was slightly higher than that found in women in the prolipherative phase, the renal tissue concentration was in the same range as that found in the prolipherative endometrium [12]. The progesterone concentration in renal cancer tissue was lower than that of the normal renal tissue and accordingly the progesterone accumulating ability (tissue/plasma ratio) was lower in the carcinoma tissue.

The endogenous P concentration in the renal tissues reported here are similar or slightly higher than the P receptor concentrations published by Concolino

Table 2. Estradiol-17β (E_2) concentration in plasma (Pl), tissue (T- with and without carcinoma*) and tissue/plasma (T/Pl) ratios in 5 patients with renal carcinoma

Pat. No.	pgE_2/ml	Tissue with cancer pgE_2/g per w/w	T/Pl ratio	pgE_2/mg prot	Tissue without cancer pgE_2/g per w/w	T/Pl ratio	pgE_2/mg prot
1 (M)	40	300	8	3.0	160	4	1.0
2 (M)	43	120	3	1.0	390	9	3.0
3 (M)	88	260	3	2.0	360	4	3.0
4 (F)	43	300	7	3.0	430	10	3.0
5 (M)	10	210	21	2.0	190	19	1.0
Mean ± SE	54	238	8	2.2	306	9	2.2
	13	34	3	0.4	55	3	0.5

Male and female are indicated by M and F respectively.
* In each case tissue samples with and without carcinoma were obtained from the same kidney.

et al.[5–7]. This would suggest that the P receptors are saturated at the P levels occurring endogenously. Tissue E_2 concentration on the other hand were considerably lower than the concentration range reported for E_2 receptors [5–7]. It should, however, be pointed out that an estimate of the extent of the saturation of the receptor by the steroid concentration in the tissue assumes that the measured receptor concentrations are truly representative of those occurring endogenously. Another assumption that is implicit in these estimates is that, the total measured concentration of the steroid in the tissue is freely available for binding to the receptor.

Although the rationale for the use of progesterone therapy is not clear, progesterone has been used to treat renal carcinoma [13, 14]. An argument for the hormone dependence of human renal carcinoma has also been advanced [15]. Favourable results with tumour remission in renal carcinoma have been reported with progesterone therapy [13]. These observations together with the present data showing lower levels of progesterone in the carcinoma tissue than in normal renal tissue may form the basis for an argument that the lower progesterone accumulating ability of renal carcinoma may play a role in the genesis of renal carcinoma. However, since the number of tissues analysed in the present investigation was relatively small such an argument is considered purely speculative.

Although kidney is not considered classically a target tissue for sex steroid hormones, evidence has been presented that mouse kidney responds to androgen treatment with increased RNA and protein synthesis [16, 17].

The present results showing relatively high concentrating ability of renal tissue for estradiol and progesterone together with the data on the presence of receptors for these hormones lead to the question of the extent to which kidney is estrogen or progesterone-sensitive. It is interesting, however, to note that the kidney and the uterus have common embryonic origin namely, the mesonephric ridge. It is possible that, although the renal cells are able to accumulate estrogen and progesterone, these hormones do not in contrast to their effect on the uterus elicit immediate responses but are needed for normal cell kinetics.

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