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Absence of Catecholamines in Malignant Tumors*

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Abstract—*Noradrenaline and adrenaline concentrations were measured in tissue specimens of malignant and non-malignant tumors as well as in adjacent normal tissue. Tissue specimens were obtained immediately after surgical excision. Noradrenaline and adrenaline were nearly absent from all malignant tumors examined. In specimens from 7 tumors from 6 different organs mean noradrenaline concentration averaged 1.7% of normal values. Several cases of leiomyoma of uterus examined similarly contained very small amounts of noradrenaline while other benign lesions such as serous cystadenoma of the ovary, hyperplasia of the prostate gland and fibroadenoma of the breast contained approximately normal amounts of noradrenaline.*

The very low noradrenaline concentrations in malignant and in some non-malignant tumors indicate, in all probability, lack of sympathetic innervation.

INTRODUCTION

IN RECENT years there have been considerable advances in the understanding of the vascularisation of tumors. Tumor vessels derive from preformed normal vessels and the growth of the vessels is stimulated by angiogenesis factors [1, 2]. Information regarding regulation of tumor circulation is sparse. Normal tissue contains considerable amounts of noradrenaline (approximately 1000 times the plasma concentration) which is located in the sympathetic nerve axon terminals. Centrally mediated changes in noradrenaline secretion constitute, together with local factors, the main regulation of the microcirculatory bed. The aim of the present study was to examine if malignant and non-malignant tumors contain noradrenaline.

PROCEDURE AND METHODS

Tissue specimens (approximately 200 mg) were removed after surgical excision from non-malignant and malignant tumors and in most cases also from the adjacent normal tissue. No post-mortem material was used. At least two specimens from each tumor and normal tissue were obtained and all results presented are the mean of at least two catecholamine determinations. All specimens were examined microscopically to verify the presence of tumor and normal tissue, respectively. Tumor tissue containing necrosis was excluded.

Tissue specimens were immediately cut into small pieces added to 10 volumes of iced perchloric acid (0.4 N) containing 2 mg/ml of ascorbic acid (*pro analysi*, Merck), homogenized and frozen until the analysis could be performed. Each sample was homogenized in 1 min periods for 15 min. Further homogenization did not increase the catecholamine content of the tissue specimens. Approximately 50 mg of tissue was used for each analysis.

Noradrenaline and adrenaline were determined by a double-isotope derivative technique [3, 4]. Reproducibility of noradrenaline determination in tissue specimens has been reported elsewhere [5].

Non-parametric tests (Wilcoxon) for paired and unpaired samples were used for statistical analysis [6].

RESULTS

Table 1 shows mean tissue noradrenaline concentration in a number of malignant tumors and in specimens of normal tissue obtained from the same organs. The noradrenaline concentration was relatively low in

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Table 1. Noradrenaline (ng/g of tissue) in 7 malignant tumors obtained from 6 different organs (2 cases of breast cancer) and adjacent normal tissue

Tumor	Malignant tissue (ng/g)	Normal tissue (ng/g)	Percentage
Carcinomatous hepatic metastasis	8	1097	0.7
Hypernephroma	5	476	1.1
Pyloric adenocarcinoma	6	430	1.4
Adenocarcinoma coli	4	110	3.6
Bronchogenic carcinoma	1	28	3.6
Breast carcinoma	0	11	0

normal lung and breast tissues. Noradrenaline was practically absent from the malignant tumors and averaged 1.7% (range 0–3.6%) of normal tissue concentration ($2P<0.05$).

The normal tissue contained small amounts of adrenaline, the concentration of which correlated with the noradrenaline concentration (Fig. 1, $r=0.96$, $2P<0.001$).

Very low tissue noradrenaline concentrations were also observed in specimens of other malignant tumors [serous cystadenocarcinoma of the ovary (0.8 ng/g); metastasis from an adenocarcinoma of the ovary (1 ng/g); seminoma of the testis (4 ng/g)].

Figure 2 shows the noradrenaline concentration in specimens of leiomyoma uteri obtained from 6 patients and in normal myometrium tissue obtained from the same patients (3 cases) and from 3 other subjects. The mean age averaged 46 yr in patients with leiomyoma uteri and 43 yr in the controls. In tissue from the normal myometrium the noradrenaline concentration averaged 280 ng/g (range 13–787 ng/g) and adrenaline averaged 3 ng/g (range 0–7 ng/g). The noradrenaline concentration was very low in leiomyoma uteri and averaged 4 ng/g [range 0–12 ng/g ($2P<0.01$)].

Relatively high concentrations of noradrenaline were found in serous cystadenoma of the ovary (84 ng/g, $n=1$); hyperplasia of the prostrate gland (305 ng/g, $n=1$); and in fibroadenoma of the breast (11 and 43 ng/g, $n=2$). Although the noradrenaline concentration was relatively low in fibroadenoma of the breast it is not different from the values obtained in normal breast tissue.

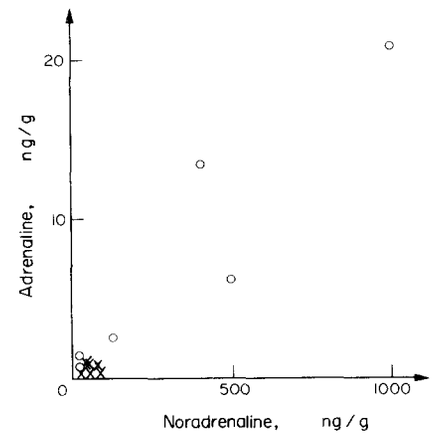

Fig. 1. Correlation between tissue noradrenaline and adrenaline concentrations (ng/g) in malignant (×) and normal tissue (○).

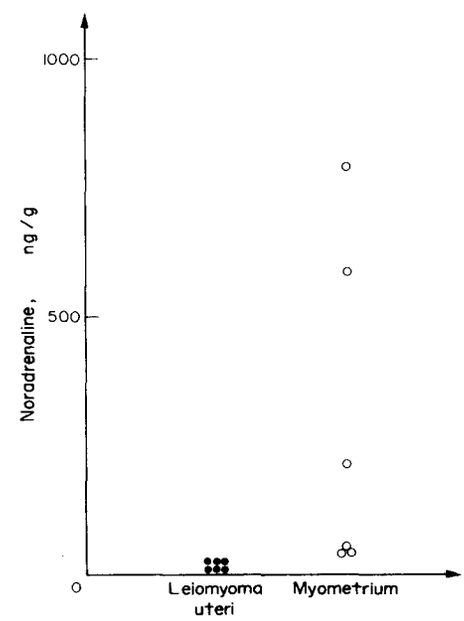

Fig. 2. Tissue noradrenaline concentration (ng/g) in 6 cases of leiomyoma uteri and in 6 cases of normal myometrium tissue.

DISCUSSION

The present study shows that noradrenaline was nearly absent from 10 malignant tumors obtained from 9 different organs. Although the material is relatively small the difference in noradrenaline concentrations between normal tissue and malignant tumors is pronounced.

The noradrenaline content of a tissue in part reflects the density of the sympathetic

innervation. Our results indicate lack of sympathetic innervation of tumor vessels. An increased turnover of noradrenaline in the tissues either due to increased release or enzymatic destruction may have reduced tissue noradrenaline concentration, but such mechanisms are unlikely to explain the extremely low noradrenaline concentrations observed in the present study.

Tumor vessels, which are of fundamental importance for tumor growth, arise from preformed normal vessels. The growth of the vessels is controlled by the tumor cell population by angiogenesis factors [1, 2]. Tumor vessels are relatively undifferentiated and are mainly composed of endothelium which lacks smooth muscle cells.

The present study indicates that malignant tumors in contrast to angiogenesis do not stimulate the growth of autonomic nerve fibers. To what extent this lack of innervation is due, to the relatively undifferentiated state of the tumor circulation or related to other factors, remains to be settled.

The lack of tumor catecholamines indicate that tumor circulation is not directly under central nervous control. Because tumor vessels arise from normal vessels vasodilatation and vasoconstriction in these vessels outside the tumor may of course indirectly influence tumor circulation.

Tumor blood flow has been reported to be supersensitive to the vasoconstrictor action of noradrenaline [7]. It has also been reported, however, that tumor vessles are unresponsive to catecholamines [8].

Further studies of the control of microcirculation in human tumors are warranted. If tumor circulation is relatively insensitive to the vasoconstrictor action of noradrenaline it may be possible by intravenous infusion of noradrenaline to direct chemotherapeutics more selectively into tumor cells as opposed to normal tissue.

Interestingly, a very low noradrenaline concentration was also found in leiomyoma uteri but not in other benign lesions such as serous cystadenoma of the ovary, hyperplasia of the prostate gland or in fibroadenoma of the breast. The reason for this difference is not clear. Hyperplasia of the prostate gland is of course not a solid and welldefined tumor in the same way as leiomyoma uteri.

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