Formation of Histamine in Transplants from a Rat Mammary Carcinoma

A high rate of histamine formation has been recognized as part of various types of normal rapid tissue growth[1]. The rat embryo, during a certain phase of growth, exhibits a high histamine forming capacity (HFC) as a result of activation of histidine decarboxylase[2,3]. Embryonic growth can be arrested by enzyme inhibition[4]. In reparatively growing tissues of healing skin wounds, the HFC was 50–60 times the level in control skin[5]. The rate of wound healing in rats, as measured by the tensile strength of the wound, could be retarded or enhanced by measures which depressed or elevated the HFC[5]. The rate of collagen formation in healing skin wounds could be increased by elevating the HFC[6]. Extracellular histamine derived from injected 'long-acting-histamine' (histamine dipicrate) had no effect on the rate of healing or collagen formation[6]. The histamine content of these tissues with a high HFC was very low, and mast cells were largely absent. In man the histidine decarboxylase activity is higher in blood containing immature myeloic cells, capable of mitosis, than in blood where these cells are few or absent[7].

Once the relationship between histidine decarboxylase and normal rapid tissue growth was recognized, it appeared likely that a similar association would be found also in malignant growths. Accordingly, in rats bearing a subcutaneously implanted hepatoma, a high rate of histamine formation was found which fell to normal on removal of the tumour; the histidine-decarboxylase activity was high in homogenates of hepatoma tissue and low in normal rat liver[8].

The object of the present study was to determine the HFC of a rat cancer tissue *in vitro* by a sensitive method permitting the use of low, physiological concentrations of histidine. The tumour tissue was obtained from female albino rats bearing subcutaneous transplants of the Walker rat mammary carcinoma 256. Portions of 1 g of minced cancer tissue. after suspension in 3 ml of 0.1 *M* phosphate buffer of pH 7.3, were incubated with 40 µg ^{14}C-histidine for 3 h at 37°C under nitrogen. The amount of ^{14}C-histamine formed during the incubation was determined by isotope dilution with histamine dihydrochloride as carrier according to SCHAYER, by the standard procedures as described in detail[9]. The cancer tissue produced histamine at considerable rates. In 4 determinations on 4 separate tumours respectively 0.094, 0.096, 0.139, and 0.154 µg ^{14}C-histamine (in terms of the base) was formed per g tissue in 3 h. The histidine decarboxylase activity of the tumour tissue was considerably increased by the addition of pyridoxal-5-phosphate. In normal rat mammary tissue, excised from pregnant rats 20–21 days after mating, the rate of histamine formation was too low to permit exact determinations. The histamine content of the malignant and normal mammary tissue was very low, in the range of 2 µg/g (base). Mastcells were not found in the tumour tissue investigated. A similar discrepancy between high HFC and low histamine content is characteristic of embryonic and granulation tissue where the high HFC is non-mast cell in nature.

The present observations are in line with reports from this institute which suggest that rapidly formed intracellular histamine actively and locally promotes certain types of tissue growth.

Zusammenfassung. Tumorgewebe von Ratten mit subcutan transplantiertem Walker-Milchdrüsencarcinom 256 produzierte ^{14}C-Histamin mit beträchtlicher Geschwindigkeit bei Inkubation des Krebsgewebes mit ^{14}C-Histidin. Zusatz von Pyridoxal-5-phosphat aktivierte die Histidindecarboxylase des Krebsgewebes. In normalem Milchdrüsengewebe lag die Histaminbildung ausserhalb des Messbereichs. Der Histamingehalt des Krebsgewebes war sehr niedrig und Mastzellen wurden keine gefunden. Der Histaminmetabolismus des Carcinoms 256 ist demjenigen im Rattenembryo und im Granulationsgewebe heilender Hautwunden ähnlich.

R. HÅKANSSON

Institute of Physiology, University of Lund (Sweden), March 27, 1961.

[1] G. KAHLSON, Lancet *1960/I*, 67.
[2] G. KAHLSON, E. ROSENGREN, and H. WESTLING, J. Physiol. *143*, 91 (1958).
[3] G. KAHLSON, E. ROSENGREN, and T. WHITE, J. Physiol. *151*, 131 (1960).
[4] G. KAHLSON and E. ROSENGREN, Nature *184*, 1238 (1959).
[5] G. KAHLSON, K. NILSSON, E. ROSENGREN, and B. ZEDERFELDT, Lancet *1960/II*, 230.
[6] N. SANDBERG, to be published.
[7] S. LINDELL, H. RORSMAN, and H. WESTLING, to be published.
[8] D. MACKAY, P. MARSHALL, and J. RILEY, J. Physiol. *153*, 31P (1960).
[9] G. KAHLSON, E. ROSENGREN, H. WESTLING, and T. WHITE, J. Physiol. *144*, 337 (1958).

In vitro Uncoupling of Oxidative Phosphorylation in Normal Liver Mitochondria by Serum of Sarcoma-Bearing Rats

In previous reports (NANNI[1]), an uncoupling of oxidative phosphorylation was observed in liver and kidney mitochondria of sarcoma-bearing rats. Treatment *in vivo* with, and addition *in vitro* of, extracts of cortical or of necrotic central parts of this tumour cause in liver mitochondria of normal animals an evident uncoupling of phosphorylations from oxidations, greater in the first case than in the second. In the case of kidney mitochondria, treatment with the two kinds of extracts does not modify oxidative phosphorylation. It would therefore seem that a substance (or several substances) forming the soluble phase of cortical zone neoplastic cells is able to act on mitochondria containing enzymes of oxidative phosphorylation, producing an uncoupling of phosphorylation from oxidation. Work by many authors has demonstrated that neoplastic tissues give out substances which pass into the circulation (SHERMAN et al.[2]); FUKUOKA and NAKAHARA[3] have shown a thermostable protein in the serum of sarcoma-bearing animals. Other authors demonstrated inhibitive actions on many enzymatic activities by tumour-elaborated substances (ELLIOT[4], DIANZANI[5], EMMELOT and

[1] G. NANNI, Lo Sperimentale, in press.
[2] C. D. SHERMAN, J. J. MORTON, and G. B. MIDER, Canc. Res. *10*, 371 (1950).
[3] F. FUKUOKA and W. NAKAHARA, Gann. *44*, 1 (1953).
[4] K. A. C. ELLIOT, Biochem. J. *34*, 1134 (1940).
[5] M. U. DIANZANI, Tumori *36*, 304 (1950).