Magnesium concentration variations during carcinogenesis

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Human and experimental animal tumors present a decreased ability of their phospholipid fraction to bind divalent cations, specially Mg^{2+}, which seems to be related to changes in the ionic permeability of the cell membrane. This event is presumably involved in the biochemical changes leading to the neoplastic development.

Magnesium is known to be an essential factor for the growth of living cells [11] and it plays an important role in the regulation of cell metabolism. It has been suggested that changes of the Mg^{2+}/Ca^{2+} ratio are a way of regulating that metabolism [4].

In spite of the fact that an extensive literature exists describing the importance of divalent cations (Ca^{2+} and Mg^{2+} in regulating membrane permeability [1], much less is known about the possible role of them in determining the peculiar characteristics of the tumor cell membrane. Since experimental evidence indicates that neoplastic cells present an altered permeability which permits the efflux of intracellular molecules [6], the study of the membrane binding characteristics for divalent cations and the intracellular distribution of cations which is regulated by the permeability of the cell membrane, have been thought of interest in order to understand the role that inorganic cations may play in the neoplastic phenomenon.

Materials and methods

In studies performed on human brain tumors as well as on experimental animal tumors, the extent of divalent cationbinding to cell membrane was determined by measuring the amount of calcium and magnesium bound to the phospholipid fraction and comparing these values with the total cation content of the tissue.

The phospholipid complexes of calcium and magnesium were extracted from the tissues by means of a mixture of chloroform, methanol and water (2:1:2, by volume) at pH 7.2. The phospholipid complexes which were present

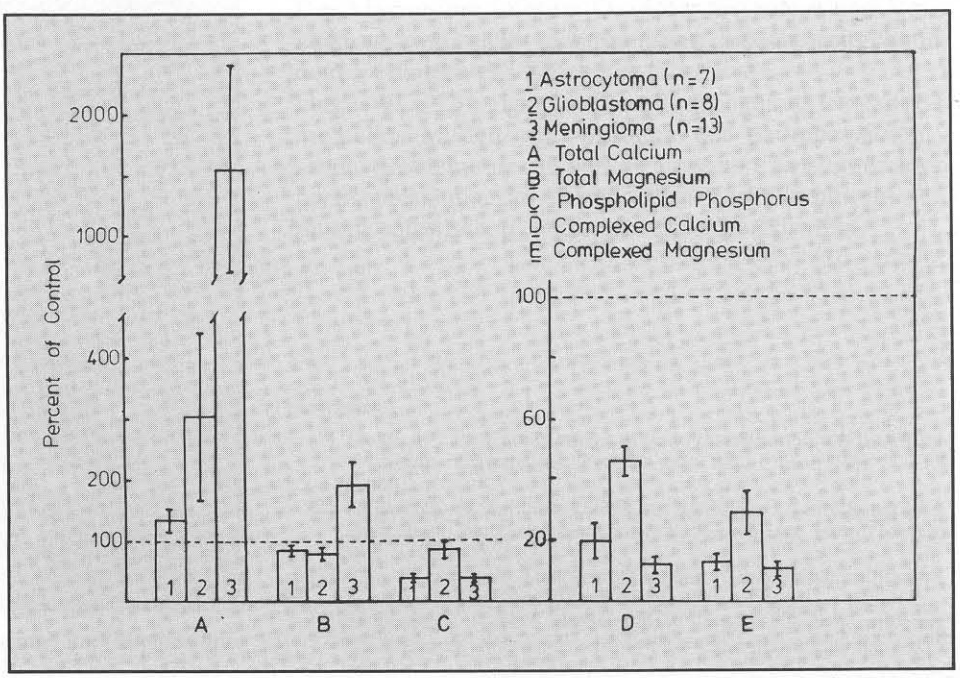

Figure 1 Distribution of calcium and magnesium in different types of human intracranial tumors

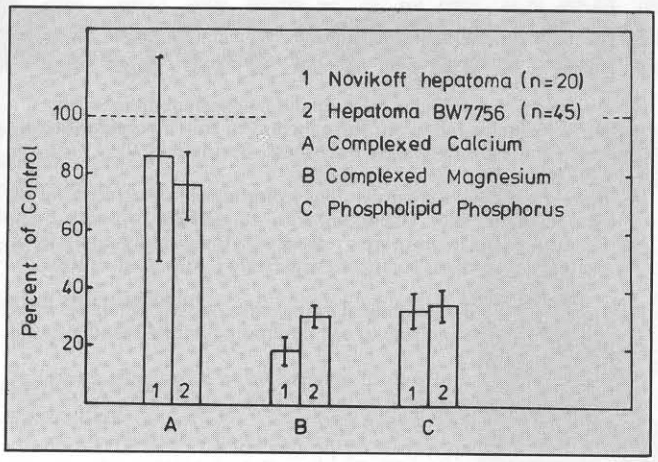

Figure 2 Calcium and magnesium complexed by phospholipid in experimental hepatoma and in normal liver tissue

in the organic phase were mineralized [2] and in the solution of the residue calcium and magnesium were determined by atomic absorption spectrometry. Phospholipid phosphorus was assayed colorimetrically using aminonaphtolsulfonic acid reagent [5].
Determinations of total calcium, magnesium, sodium, and potassium were done on mineralized samples of blood, liver tumor and normal liver tissues by means of atomic absorption spectrometry.

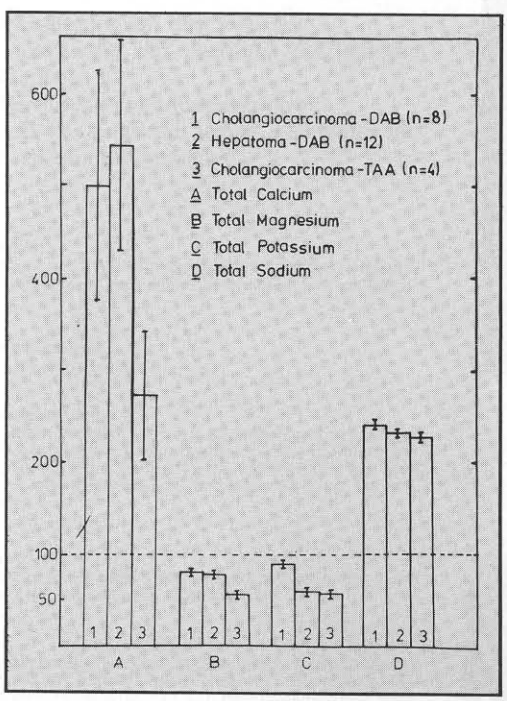

Figure 3 Comparative concentration of calcium, magnesium, sodium, and potassium in primary liver tumors produced by chemical carcinogenesis [3]. DAB = 4-dimethylaminoazobenzene, TAA = thioacetamide

Results

In comparison to normal homologous tissues, tumors present a decreased binding of divalent cations to the phospholipid fraction. This observation is more significative for magnesium than for calcium. At the same time, a considerable reduction in phospholipid concentration is observed, but in all the cases this decrease of phospholipid is not so important as the observed reduction of complexed cations. The disproportion between decreased concentration of phospholipid and concentration of complexed cation is more significative for magnesium (fig. 1 and 2).

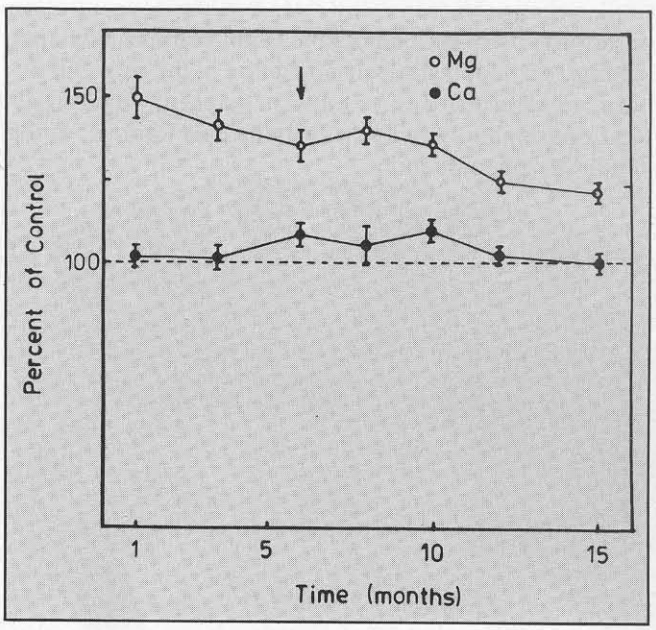

Figure 4 Calcium and magnesium in whole blood of animals undergoing chemical carcinogensis by 4-dimethylaminoazobenzene. Mean value ± SE of a 10-animal group. The arrow indicates the onset of macroscopically observable liver tumors

Primary liver tumors present an increased total concentration of normally extracellular cations (Ca^{2+} and Na^{+}) while a decreased total concentration of intracellular cations (Mg^{2+} and K^{+}) is shown by figure 3. On the other hand, blood of animals undergoing liver carcinogenesis present an increase of magnesium content (fig. 4).

Discussion

Changes in the content of phospholipid and of divalent cations bound to cell membrane have been considered of critical importance for the conservation of the normal physiological function of the membrane [1, 9]. Our experimental results showing in tumors a change of the balance of cations (increase of extracellular while a decrease of intracellular cations) appear to indicate a modification of the permeability of the cell membrane [3]. A further evidence of intracellular mobilization of magnesium from the tissue undergoing tumor development is its

increased concentration observed in blood from animals during the carcinogenesis process.

A very important effect of an uncontrolled ionic diffusion can be changes of the ratio Mg^{2+} concentration/Ca^{2+} concentration which are able to produce alterations of Mg^{2+}- and Ca^{2+}-sensitive enzymatic systems, affecting in this way the bioenergetic metabolism as well as the biosynthesis of macromolecules. In addition to these metabolic effects the changes in cation concentration also can produce modifications of the morphologic and growth pattern of the cells [7, 8, 12].

The strong reduction of magnesium-binding to cell membrane in tumors, points out that the reported effects of Mg^{2+}-sequestration on cell permeability which show a similar change in extra- and intra-cellular concentration of cations [10] may be a possible factor of ionic imbalance leading to a neoplastic transformation of the cell. Our experimental results seem to indicate that Mg^{2+}-binding alterations might play a key role in the development of the neoplastic phenomenon.

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