Experimental relationships between Magnesium and cancer*)

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Zusammenfassung

Es wird die Rolle des Magnesiums bei Karzinogenese und Tumorwachstum behandelt. 3 experimentell belegte Fakten zeigen, daß dieses Kation bei der Ausbildung von Neoplasien involviert ist:

1. Der Einfluß von Mg auf biologische Eigenschaften von Zellmembranen,
2. der erhöhte Mg-Bedarf bei Mitose und Proliferation von Tumorzellen und
3. die Rolle von Mg bei der Regulation von Immunantworten, die je nach beteiligtem Tumortyp verschieden zu sein scheint.

Jede Mg-Therapie bei Vorliegen von Tumoren sollte diese charakteristischen Angriffspunkte berücksichtigen.

Summary

The role of Magnesium in carcinogenesis and tumor growth has been considered in this review. There are three main experimental facts showing the participation of this cation in the neoplastic phenomenon: 1. its effects on the biological properties of the cell plasma membrane, 2. its increased demand during tumor cell mitosis and proliferation, and 3. its role in the regulation of the immunosurveillance mechanisms, which seems to vary with the involved type of tumor. In order to asses its practical possibilities, any proposed Magnesium therapy of tumors should consider all these characteristics of the cation.

Résumé

Ce rapport considére le rôle du Magnésium dans la carcinogénèse et dans la croissance tumorale. D'après la bibliographie publiée sur ce sujet, trois principaux faits expérimentaux montrent la participation de cet élément dans le phénomène néoplastique: 1. ses effets sur les caractéristiques biologiques de la membrane plasmique, 2. un besoin accru de Magnésium pendant la mitose et la prolifération cellulaire, et 3. son rôle dans la régulation des mécanismes d'immunosurveillance tumorale, rôle qui semble varier selon le type de tumeur. En conclusion, tout traitemant magnésique devrait prendre en considération ces caractéristiques pour l'évaluation de ses possibilités thérapeutiques.

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Introduction

The rates of metabolism and growth of cancer cells depend on a variety of factors. The role of divalent cations is particularly important because of their involvement as critical structural and functional components of cell membranes and their requirement (as cofactors of numerous enzymes) for the functioning of the cell's biochemical machinery.

To a number of authors, the modifications at the cell membrane level are the principal factors triggering the malignant transformation of the cell [1—5]. As a consequence, the divalent cations might play an important role in the neoplastic development.

1. Magnesium and the plasma membrane

The accumulated evidence suggests that there may be a common feature underlying the diversity of tumors which is the alterations in one or more of their cell membrane systems. The plasma membrane is the site of many alterations, such as those related to invasiveness, metastasis and immunobiology of tumors, which are of fundamental importance to the process of malignancy. Magnesium, as a divalent cation, plays an important role in the cell surface phenomena controlling these cell membrane functions. The differences of permeability between cancer and normal cells, and the release of intracellular material seem to indicate that the surface of the two cells exhibit different characteristics [6, 7]. On the other hand, the fact that the divalent cations are known to change the fluidity of cell membrane lipids [8], and that the fluid state of lipids is very important in the regulation of the biological properties of the membrane, such as nutrient and passive ion transport [9, 10], suggest the possible implication of those ions in the characteristic behavior of the cancer cell membrane.

Magnesium has been found in the cell coat of Ehrlich ascites cells bound to the lipoprotein fraction [11]. The analyses of divalent cations bound to tumor phospholipids have shown a consistent low binding with respect to that of normal tissue [12—14]. In addition to this, a more recent experimental work on tumor growth inhibition by the hypocalcemic effect of calcitonin [15], has shown a significant growth inhibition only when the concentration of divalent cations bound to the phospholipid was increased with respect to the con-

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trols. This observation appears to indicate a relationship between malignancy and cell membrane characteristics (among them permeability impairment) which is in agreement with the concept that the divalent cations control the stability of the membrane by the formation of a ternary complex between the anionic groups of a protein and the phospholipid molecule.

The experimental evidence shows that a cell membrane impairment is a concomitant phenomenon of malignancy. A primary alteration of the cell membrane by interaction with the carcinogen can be inferred from the observation that amino azo dye carcinogens bind to the protein of cell membranes [16]. The interaction of chemical carcinogens with the plasma membrane seems related to their lipophilic properties determined by specific molecular characteristics [17].

During the induction by chemical carcinogens of experimental cholangiocarcinomas a relationship between ionic concentration changes in the cell and the preneoplastic and neoplastic states has been observed [18, 19]. The most striking observation in tumor has been a very significant increase of extracellular cations (calcium and sodium) while the intracellular ones (magnesium and potassium) were decreased. This modification of the ionic environment normally regulated by selective permeability and active extrusion (Calcium pump) [20], indicates drastic changes in the ionic flux from the outer and inner cell which can be explained as the result of structural and functional alterations of the plasma membrane. It is interesting to mention that during the preneoplastic state there is a decrease of magnesium bound to intracellular structures at the same time that its concentration in the cytosol increases.

The hepatotoxicity of thioacetamide constitutes a suitable model to study the role of cell membrane impairment in the changes of the intracellular ionic environment [21]. This reversible phenomenon provokes a transient change in ionic concentrations which is similar to that observed in the case of cholangiocarcinoma induced by long-lasting administration of this chemical.

This observation of magnesium decrease during chemical carcinogenesis in experimental animals appears in contradiction with some reports on increased magnesium in solid tumors. This incongruence, due in most cases to a different methodology, is also complicated by the possible influence of the tumor type, chemical characteristics of the involved tissue, nutritional and physiological conditions, way of sampling the tissue (biopsy or autopsy), and other factors which make the analysis of small ions in biological materials very difficult.

Finally, we must point out the possible influence on the ionic environment provoked in the case of transplanted tumors by the host tissues reaction to the implant.

2. Magnesium and the biochemical systems of the cell

The importance of the ionic environment in the various cell compartments is well shown by the concept of cell metabolism controlled by the intracellular ionic concentrations [22]. Together with calcium, magnesium plays a major role in the regulation of many basic cell functions. It should be emphasized that the principal regulating factor is not simply the absolute concentration of one or other divalent cation, but rather the Ca/Mg ratio in the cell compartment or in the vicinity of the ion-sensitive enzyme [23].

Since the discovery of the high aerobic glycolysis in cancer cells [24], a great deal of effort has been given to investigate the energy metabolism of these cells in an attempt to understand the reasons for the phenomenon [25]. A number of theories predict a prevalent role for Ca/Mg ratio in bioenergetic reactions regulation and in particular those of cancer cells. Recent experimental work indicates that the intracellular calcium ion level is intimately linked to that of magnesium, because a net entry of calcium results in a corresponding loss of magnesium, and that the most characteristic feature of cancer cells, the high aerobic glycolysis, is strictly dependent on the level of intracellular Ca/Mg ratio [26]. In Ehrlich ascites cells, the Ca/Mg ratio-dependent aerobic glycolysis enhancement is mediated by phosphofructokinase activation, a key enzyme in the regulation of glycolysis and with its activity modulated by a number of inhibitors and enhancers [27]. The enzyme activation could be brought about by the phosphorylating-dephosphorylating systems of the enzyme protein. Since the phosphorylation takes place in the presence of a critical Mg/ATP ratio [28], the calcium-dependent loss of magnesium could be responsible for that activation. Another possible interpretation of the Ca/Mg-dependent stimulation of glycolysis is related to the transport of glucose across the plasma membrane which also can be affected by modification of the Ca/Mg ratio [29].

Yoshida-ascites tumor cells grown in a magnesium deficient medium show a reduced synthesis of DNA, RNA and protein, accompanied by increased intracellular calcium and sodium while potassium and magnesium are decreased [30]. Depletion of magnesium in the growth medium for chicken embryo fibroblasts produces a decrease in DNA synthesis and similar changes in intracellular cations [31]. This behavior emphasizes upon the role of magnesium in plasma membrane permeability already discussed in Part I, and which also can affect the biosynthetic mechanisms which are ion-sensitive.

There are questions regarding the specific roles of calcium and magnesium in the control of cell growth. Some authors have suggested that intracellular magnesium activity plays a central role in the proliferative response [32—34] and that the effects of calcium deprivation on cell growth result from competition of calcium and magnesium for common intracellular binding sites. Contrary to this, other investigators presented experimental evidence which suggests that the effects of calcium and magnesium on cell growth are distinct [35, 36]. The extraordinary similarity observed for the biological effects of both divalent cations on cell functioning makes it difficult to assess the actual role of each cation in carcinogenesis.

3. Nutritional magnesium and cancer

Changes in calcium homeostasis are associated with altered mitotic activity within the thymus [37—39]. Magnesium effects parallel those of calcium. Its administration increases proliferation [37] while its deprivation provokes a thymic involution [39]. Prolonged magnesium deficiency leads to thymic hyperplasia [39, 40]. Thymic lymphosarcomas have been reported [41, 42]. It is interesting to note that combined calcium and magnesium deficiencies predispose to malignancy, but calcium deficiency alone does not [42, 43]. The induction of thymomas by chronic dietary insufficiency of magnesium has been reported [44].

Besides this apparent specific neoplastic action of magnesium deficiency, the probable role of this cation in tumor induction is only conjectural matter. In contrast, there is experimental evidence for the tumor growth inhibition of magnesium deficiency, especially when associated to a potassium deficiency [45]. On the other hand, the survival of mice with breast cancer is increased by administration of oral supplements of magnesium [46]. In the first case, the inhibition is likely to be of metabolic nature, not specific to malignancy but to all tissues with high growth rate. A similar phenomenon has been observed with experimental tumors under ammonium chloride-induced acidosis [47]. In the second case, magnesium as well as calcium may act promoting the function of the immune system providing the amount of cation needed for lymphocytolysis of tumor cells.

In rats under chronic magnesium deficiency, disturbances of the immunocompetence has been observed [48, 49]. However, their resistence to ordinary bacterial infections is not impaired. In contrast, mice under similar experimental conditions show a decreased production of immunoglobulin and function of antibody plaque-forming cells [50].

Experiments on chemical carcinogenesis in rats given a magnesium deficient diet seem to indicate that the deficiency might also compromise the immunosurveillance of induced tumor cells. This deficiency decreases the incidence of various spontaneous and induced solid tumors, while the non-spontaneous malignant lymphoma or myelogenous leukemia are promoted [51]. These observations together with the high incidence of lymphoreticular tumors and the low incidence of other spontaneous or induced tumors taking place in congenital or acquired immuno-deficiency conditions, including those provoked by a magnesium deficiency [52], appear incongruent with the concept of antitumor immunosurveillance based on tumor cells recognition and elimination as they arise [53].

4. Conclusion

After consideration of the experimental results concerning the role of magnesium in cancer development and inhibition, the long ago established empirical magnesium therapy must be revised on the basis of three fundamental facts: 1. Its action on the biological properties of the cell membrane, and consequently its possible value in cancer prevention; 2. the increased need of magnesium by the tumor during the period of high growth rate [54] which implicates a negative effect of its therapeutic administration, and 3. its effects on immunosurveillance systems which vary according to the type of tumor involved.

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Role of Magnesium deficiency in immunity to neoplasia in the rat *)

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Zusammenfassung

Magnesium-Mangel verursacht bei der Ratte eine zellvermittelte Immuninkompetenz, die sich durch die Häufigkeit von Enzephalitozoon-Infektionen, durch mangelnde Bereitschaft, eine allergische Enzephalitis auszubilden, und verminderte Bildung von Hämolepin gegen Schaferythrozyten zeigte, ohne daß die Bildung von Serumantikörpern oder Plasmazellen besonders beeinträchtigt war.

Weiter bestand ein deutlicher Unterschied zwischen normalen und Mg-Mangel-Ratten gegenüber der Immunisation mit lebenden Lymphomzellen. Bei Mangeltieren erfolgte keine Immunisation. Normal ernährte Tiere reagierten prompt, aber diese Immunität ging verloren, wenn den Tieren anschließend Mg entzogen wurde.

Im Mg-Mangel war die Häufigkeit verschiedener Spontantumoren und induzierter solider Tumore erniedrigt, wohingegen das Auftreten nicht spontaner lymphoretikulärer Tumore in Form von malignen Lymphomen oder myeloischen Leukämien begünstigt wurde. Hinsichtlich des Immundefektes erscheint dieser Effekt im Widerspruch zur antineoplastischen Immunüberwachung.

Aufgrund dieser Daten nehmen wir an, daß in bestimmten genetisch disponierten biologischen Systemen — ob sie nun ein nicht exprimiertes onkogenes Virus beherbergen oder nicht — Magnesium als Extrensic Factor dient, der von Intrinsic Factors benötigt wird zur normalen Bildung und Reifung von Zellen durch das leukopoetische System. Wenn dem so ist, muß eine Störung dieses Regulationssystems, die zu Leukozytose und nachfolgend zu lymphoretikulären Neoplasien führt, nicht notwendigermaßen von quantitativen Erwägungen des alimentären Mg-Mangels abhängen. Induzierte und spontane lymphoretikuläre Neoplasien müssen bezüglich ihrer Pathogenese folglich als metabolische Mangelerkrankungen aufgefaßt werden.

Summary

Magnesium deprivation caused cell-mediated immunoincompetence in rats, as indicated by the frequency of encephalitozoon infection, resistance to production of experimental allergic encephalomyelitis, and decreased formation of antisheep erythrocyte hemolysins without greatly depleted production of serum antibody or plasma cells.

Moreover, there was a conspicuous difference in the response of normal and magnesium deficient rats to anti-lymphoma immunization with live lymphoma cells. The deficient rats resisted immunization. The normal rats readily acquired immunity to lymphoma but the established immunity was lost when the immune rats were subsequently deprived of magnesium.

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