INTERACTION OF VITAMINS AND MINERALS

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SUMMARY

Several nutrients are known to act on the metabolism of other nutrients and also of some non-nutrient substances. The nutritional importance that may be attributed to these interrelationships depends on the levels considered to be physiological for each nutrient, and on their maintenance at acceptable levels in tissues for the defense of the organism.

Interaction of vitamins and minerals has been described in several metabolic situations and continues to be investigated by many authors. This interaction occurs in different ways, i.e. starting from the action of vitamins on mineral metabolism, from the action of both types of nutrients in the protection of the organism, and from the action of minerals on vitamin metabolism.

The most significant example of vitamin action on mineral metabolism is the role played by vitamin D in calcium and phosphorus metabolism. The interrelationship of vitamin C and some minerals is also discussed, with emphasis on its relationship with iron. With respect to the synergistic action of vitamins and minerals in the defense of the organism, we comment on the main data reported on the biochemical-physiological role of vitamin E and its interaction with selenium. Finally, in reference to the action of minerals on vitamin metabolism, we point out the inteaction existing between vitamin A and zinc. Data observed by the author at the experimental level in laboratory animals are reported on the possible interaction of niacin, vitamin B_6 and zinc.

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INTRODUCTION

Several environmental factors are known to affect the absorption, metabolism and retention of nutrients in the organism. The action of several nutrients on the metabolism of other nutrients as well as of non-nutrient substances, is also known. The nutritional importance to be attributed to such interelationships depends on what is considered the physiological level of each nutrient and on its maintenance at acceptable values in the tissues, thus guaranteeing a perfect functioning of preferential metabolic pathways.

The intestinal absorption of some minerals, for example, thus may be affected by the presence in the diet of other compounds with which some reaction may occur. In this manner the absorption of calcium, magnesium and iron may be decreased by the presence of phytates. Similarly, the utilization of vitamins may be affected by other nutrients ingested. The need for vitamin B_6 is probably modified by the ingestion of protein of animal or vegetable origin (1).

Vitamins play an important and indispensable role as catalysts in the metabolism of carbohydrates, fat and protein by acting on the supply of energy to the organism. Their biochemical function concerns coenzyme action on various metabolic pathways. This action only occurs when the enzyme and coenzyme are present in adequate amounts.

Minerals have an important function in practically every biochemical and physiological process, such as muscle contraction, transport across membranes and nervous conduction. Many minerals also participate in catalytic enzymatic processes by binding to substrates, by activating the substrate-enzyme complex, or by forming complexes strongly bound to the enzyme, but in such a manner that the two are joined as a unit but are still separate, such as, for example, the metalloenzymes.

The interaction of vitamins and minerals has been described in various metabolic situations and continues to be studied by several investigators. This interaction may take place in different ways, specifically starting from the action of vitamins on mineral metabolism, from the action of both types of nutrients on the protection of the organism, and from the action of minerals on vitamin metabolism.

1. *Action of Vitamins on Mineral Metabolism*

The most significant example is the role played by vitamin D in the control of calcium and phosphorus metabolism, described in 1967.

1.1 *Interaction of vitamin D with calcium and phosphorus*

Cholecalciferol or vitamin D_3 is the main form of vitamin D found in animal tissue, and is produced on the skin by UV irradiation of 7-dehydrocholesterol. Vitamin D_3 can also be ingested by eating food of animal origin such as butter, eggs, and fish liver and oil. Calciferol or vitamin D_2 is produced by irradiation of ergosterol, a plant sterol.

Vitamins D_2 and D_3 are absorbed in the small intestine and require chemical modifications before they can fully exert their biological activity on the organs. Vitamin D_3 is initially converted to 25-hydroxycalciferol in the

liver. The latter compound enters the blood stream circulating with a vitamin D-"binding" globulin, which is later converted to 1,25-dihydroxicholecalciferol in the kidney. The dihydroxy metabolite is several times more biologically active than the monohydroxy compound.

The active forms of vitamins D_2 and D_3 stimulate calcium and phosphorus absorption in the upper small intestine, thus helping to promote normal bone mineralization. They also promote calcium mobilization from bone and probably have a direct action on the kidney by increasing calcium and phosphate resorption. Thus, vitamins D_2 and D_3 play an important role in the homeostasis of plasma calcium. In the presence of vitamin D deficiency there is inadequate calcium absorption, plasma calcium levels tend to fall, paratohormone secretion increases and calcium is reabsorbed by the bones to maintain plasma levels (2).

1.2. *Interaction of vitamin C with minerals*

The influence of ascorbic acid on iron metabolism (and vice-versa) has been widely proposed (3). Several observations have suggested that ascorbic acid has the ability to increase intestinal iron absorption and to modify iron mobilization and transport within the organism. Recent studies have indicated that even moderate amounts of dietary supplements containing ascorbic acid can substantially increase the absorption of non-heme iron (4,5). An amount of 100 mg ascorbic acid can increase iron absorption up to four times (6). Vitamin C also acts on iron transfer from the transport protein to ferritin in the organs that participate in iron storage (bone marrow, liver, and spleen).

There is also some evidence that the concentration of iron in tissues affects blood levels, and perhaps even tissue levels, of vitamin C. Individuals with siderosis have reduced ascorbic acid concentrations in leukocytes, whereas patients with iron-deficiency anemia have higher ascorbic acid concentrations, although the mechanism of this relationship is not known (7,8).

Ascorbic acid affects copper metabolism. Several observations have demonstrated a decrease in copper levels in the liver of animals treated with ascorbic acid supplementation, suggesting that interference occurs at the intestinal absorption level or at the utilization level, or both. Other studies later demostrated that ascorbic acid depresses copper absorption at the intestinal mucosa level. According to Evans (9), ascorbic acid interferes with copper binding to metallothionein, which is the protein that mediates copper transport both in the small intestine and in the liver.

Other reports in the literature have also shown that, in man, ascorbic acid has no effect on zinc absorption (10). In contrast, Basu (11), after administering high doses of vitamin C to healthy volunteers aged more than 50 years for two consecutive days, noted up to a 50% decrease in urine zinc concentration. The author postulated that this effect may possibly be beneficial in situations of abnormal cell growth.

The participation of vitamin C in the metabolism of zinc, copper and other mineral elements has not been fully clarified. Perhaps the vitamin utilizes these elements, thus reducing their organic levels.

1.3 *Interaction of folic acid with zinc*

Zinc and pteroylglutamic acid are essential for animal organisms, especially in terms of nucleic acid synthesis. The discovery of high zinc levels in the erythrocytes of patients with megaloblastic anemia caused by folic acid deficiency and the subsequent decrease in these levels after theraphy, suggest the existence of interaction between these nutrients (12). This impression was confirmed by the reduction in hepatic folate in zinc-deficient rats (13). Later, Tamura *et al.* (14) observed that the intestinal absorption of polyglutamylfolate was reduced in zinc-depleted individuals. These results were explained on the basis of a possible suppression of the enzymatic activity of folate conjugase of the intestinal mucosa (zinc-dependent enzyme) in zinc-deficient rats (15). Milne *et al.* (16), after inducing a light zinc deficiency in adult volunteers, studied the effect of supplementation with folic acid on zinc excretion. Fecal zinc excretion was significantly higher in the group that received folic acid supplementation. Urine zinc excretion decreased by 50% during the study. These data seem to indicate once again the effect of folic acid on zinc homeostasis, perhaps through the formation of insoluble compounds with a consequent alteration in zinc absorption.

2. *Possible Synergistic Action of Vitamins and Minerals*

Vitamin E / Selenium

An interaction of vitamin E with selenium was proposed as a function of the observation that dietary alpha-tocoferol increases the concentration on the selenite form in mitochondria and microsomes (17).

The importance of selenium in nutrition was first recognized in 1957 when, as also observed with vitamin E, it was demonstrated that slenium can protect rat liver from necrosis caused by deficient diets (18). The fact that selenium was necessary in the presence of adequate amounts of vitamin E in the diet was only demonstrated in 1968 (19).

When it was discovered that selenium is a component of the enzyme glutathione-peroxidase (20), it became possible to propose a biochemical mechanism linking the metabolic role of selenium with that of vitamin E (21). The two nutrients were considered parts of an antioxidation system of body defense: vitamin E as a lipid-soluble antioxidant, and selenium as part of glutathione peroxidase (22).

The best illustration of how this interaction occurs is actually related to the occurrence of hepatic necrosis caused by deficient diets. Hepatic necrosis only occurs when there is a combined deficiency of selenium and vitamin E. In this case, vitamin E or glutathione peroxidase may be sufficient to prevent lipid peroxidation, a condition that may cause lethal liver damage (23).

It is known that the administration of large amounts of polyunsaturated fatty acids may induce abnormal membrane lipid peroxidation. A possible mechanism for lipid peroxidation in the membranes is the generation of free radicals during NADPH oxidation by liver microsomes. In the model using erythrocyte membranes, this damage caused by free radicals can be avoided by adding vitamin E to the diet for the animal that donates the erythrocytes (24).

Glutathione peroxidase activity is decreased in the tissues of selenium-deficient animals. The enzyme catalyzes the transfer of reducing equivalents of reduced glutathione to hydrogen peroxide or to the lipoperoxides. In the presence of adequate selenium levels, the nutritional level of vitamin E did not affect glutathione peroxidose activity in the liver, kidney or lung, but this activity was reduced in the muscle and adipose tissues of alpha-tocoferol-deficient animals (25). It has ben suggested that alphatocoferol prevents the membrane alterations caused by lipid peroxidation, whereas selenium, because it is a component of the enzyme glutathione peroxidase, exerts its protective action against peroxidation processes in the cell cytosol (26).

As far as the activity of glutathione peroxidase is concerned, this enzyme may act on the destruction of hydrogen peroxide and may reduce the lipoperoxides in the fatty layers of the membrane to their corresponding alcohol forms, thus preventing their oxidative degeneration. However, some questions concerning the ability of glutathione peroxidase to use lipoperoxides as substrates still await elucidation (27).

Recently, a heat-labile, glutathione-dependent factor protecting against lipid peroxidation in the membranes, which, however, is not glutathione peroxidase, was detected in the cytosol of rat liver cells (28). Some investigators have stated that certain metabolic effects of selenium cannot be explained on the basis of glutathione peroxidase activity (29). Thus, these data seem to suggest the existence of additional factors besides glutathione peroxidase in the antioxidant system. Further studies are needed to clarify the nature of these other antioxidant factors.

3. *Action of Minerals on Vitamin Metabolism*

3.1. *Interaction of vitamin A with zinc*

Vitamin A is essential for the maintenance of the normal physiologic functions of the epithelia. The vitamin is absorbed in the small intestine under the alcohol form, retinol, which is formed from retinylesters, compounds with pro-vitamin capacity and carotenes (30). The retinol produced is subsequently reesterified by long fatty acid chains inside the cells of the mucosa and then mobilized, with the chylomicrons, to the liver through the lymphatic system and stored in the hepatocytes (31). Retinol is then gradually released into plasma in order to be carried to the tissues in its alcohol form, bound to a specific compound, retinol binding protein (RBP), which has a binding site for the vitamin (32).

Inside the plasma, RBP (22,000 daltons) associates with thyroxine-binding prealbumin (PA) of 54,000 daltons, forming a 1:1 complex which is considered to have an enormous physiological value since it prevents the loss of the vitamin and of the binding protein, by decreasing the filtration rate through the kidneys (33,34). In addition, the formation of both retinol-RBP and retinol RBP-PA is of great significance in the plasma transport of vitamin A. RBP is synthetized in the hepatocytes, and its formation varies as a function of the organic levels of vitamin A and of other factors. This fact has been confirmed in several experimental studies, such as that by Smith, Brown and Smith Jr., which indicated that zinc interferes with hepatic RBP synthesis (35). Later, the same group demonstrated that plasma vitamin A levels are

decreased in zinc-deficient animals (36). It is believed, therefore, that zinc-deficient rats have low plasma levels of vitamin A. The concomitant presence of normal liver concentration of the vitamin suggests that zinc may be necessary for the mobilization of vitamin A deposits. Smith Jr., *et al.* (37) propose the use of zinc supplementation to restore normal vitamin A levels in patients with liver disease.

In addition to this participation in vitamin A transport, several experimental observations have suggested that zinc also plays an important role in the metabolic pathways related to retinol metabolization. Thus, for example, Huber and Gershoff (38) detected a decrease both in alcohol dehydrogenase and retinal reductase activity in zinc-deficient adult rats.

Zinc deficiency seems to have a marked effect on retinal reductase activity in the testicles, by significantly reducing its levels (39).

These data, therefore, seem to indicate the importance of the interaction of zinc with vitamin A metabolism in various animal tissues.

Whelan, Walker and Kelleher (40) once again showed a significant correlation between vitamin A and zinc in prostatic cancer, and these data may represent additional evidence that such nutrients are intimately involved in physiological processes in the organism and also in desease situations.

3.2. *Interaction of niacin and vitamin B_6 with zinc*

Dietary tryptophan can be utilized by the organism to produce nicotinamide via kynurenine and going through 3-hydroxyanthranylic acid which is transformed into nicotinic acid. N'-methyl-nicotinamide (N'MN) and N'-methyl-2-pyridone-5-carboxamide (2-pyridone) are its main metabolites. Some alterations occur in this metabolic pathway owing to vitamin B_6 deficiency, since the vitamin has a catalytic action on this pathway (41). Vitamin B_6 occurs under several biologically active forms such as pyridoxol, pyridoxal, pyridoxamine and their respective phosphorylated forms. Its main inactive metabolite excreted in urine is 4-pyridoxic acid, which corresponds to about 70% of the metabolites of vitamin B_6 excreted in urine (42). The different forms of vitamin B_6 are converted to coenzymes in the organism, especially pyridoxal phosphate (PLP), which act by catalyzing a variety of biochemical reactions. PLP forms the prosthetic group of several enzymes, such as kynureinase, which participates in the metabolism of niacin production from tryptophan by converting 3-hydroxykynurenic acid to 3-hydroxyanthranylic acid.

In turn, zinc is a constituent of various enzymes involved in most of the major metabolic pathways, or affects the structural configuration on nonenzymatic organic compounds (43). Zinc is known to act as an activator of pyridoxal phosphokinase, an enzyme essential for pyridoxal phosphorylation, an important reaction for the functioning of vitamin B_6 in the organism (44).

These observations show several aspects of the possible interaction of these three nutrients. It is possible that niacin deficiency manifests itself clinically at the same time as vitamin B_6 and zinc deficiency, and that each is interdependent on the others or is worsened by selective deficiency of one of these nutrients.

Animals with tryptophan, niacin, vitamin B_6 and zinc deficiency received

for two weeks diets, respectively supplemented with niacin, vitamin B or zinc, while a control group received only sucrose and another, niacin plus vitamin B_6 plus zinc (45). With the addition of zinc there was a significantly higher excretion of niacin metabolites. At least two explanations can be proposed in this case. The first has to do with the fact that the enzyme pyridoxal phosphokinase is zinc-dependent. Thus it is possible that part of these compounds may not be activated owing to lack of the mineral cofactor. When this was offered and became available, the vitamin started to be activated to a greater extent. With this, the metabolic pathway of niacin production may become more efficient. The second possibility has to do with the direct action of zinc on the metabolic pathway of tryptophan. As a consequence, the biochemical reactions may take place by utilizing the substrates still available in the organism in order to produce niacin. On the basis of these results, it is possible to suggest the existence of inteaction between niacin, vitamin B_6 and zinc in rats.

CONCLUSION

From the examples presented herein, we emphasize the importance of the interaction existing between nutrients and in particular, between vitamins and minerals. We know that investigators in the field of nutrition tend to study them separately. The possible complexity of these interrelationships often makes it difficult to determine the optimum intake to be recommended for a given nutrient. Furthermore, in situations of primary or secondary alterations of nutritional status, the function of a nutrient may not be exerted fully because of the simultaneous deficiency of the other nutrient with which the former interacts at the biochemical level. Thus, these interactions should be better studied, since they are of fundamental importance for defining the exact role of each nutrient in the metabolic process, both under normal conditions and in states of disease.

RESUMEN

INTERACCION DE VITAMINAS Y MINERALES

Se sabe que ciertos nutrientes actúan sobre el metabolismo de otros nutrientes, así como de ciertas substancias no nutrientes. La importancia nutricional que pueda ser atribuida a tales interrelaciones depende de los niveles considerados como fisiológicos para cada nutriente, y su mantenimiento en niveles aceptables en los tejidos, para la defensa del organismo.

La interacción entre las vitaminas y los minerales ha sido descrita en varias situaciones metabólicas y continúa siendo investigada por diferentes autores. Esta ocurre de tres formas por lo menos: a partir de la acción de las vitaminas sobre el metabolismo de minerales, de la acción de ambos nutrientes en la protección del organismo, y de la acción de los minerales sobre el metabolismo de las vitaminas.

En cuanto a la acción de las vitaminas sobre el metabolismo de los minerales, el ejemplo más significativo es el papel que la vitamina D ejerce sobre el metabolismo del calcio y del fósforo. También se comenta la interrelación entre la vitamina C y algunos

minerales, con énfasis a su relación con el hierro. Respecto a la acción sinérgica de vitaminas y minerales en la defensa del organismo, se discuten los principales datos en cuanto al papel bioquímico-fisiológico de la vitamina A y su interacción con el selenio. Finalmente, respecto a la acción de los minerales sobre el metabolismo de las vitaminas, se señala la interacción existente entre la vitamina A y el zinc. En lo que atañe a la posible interacción de niacina, vitamina B_6 y zinc, se informan datos observados por el autor a nivel experimental en animales de laboratorio.

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