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Correlation between dietary polyunsaturated fatty acids and plasma homocysteine concentration in vitamin B_6-deficient rats

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Summary *Background and aim:* Vitamin B_6 as cofactor of Δ6 desaturase is involved in polyunsaturated fatty acid metabolism; moreover, it is a cofactor of the trans-sulfuration pathway of homocysteine. Some studies report that low concentrations of pyridoxine, by increasing homocysteine levels, are associated with coronary artery disease, and carotid and arterial lesions. The aim of this study was to verify whether different dietary amounts of polyunsaturated fatty acids associated with low content of vitamin B_6 could modulate homocysteinemia.
Methods and results: Thirty-two rats were divided into two groups, one fed a diet with adequate vitamin B_6 content the other a diet containing low amount of the same vitamin. Within each group, rats were divided into two subgroups differing in the polyunsaturated fatty acid content of the diet (63 and 33%, respectively). The vitamin B_6-deficient diet induced an increase in homocysteine concentration compared to the vitamin B_6-normal diet. This increase was tenfold in the subgroup fed high polyunsaturated fatty acid levels and twofold in the other subgroup. The fatty acid composition of liver phospholipids showed a lower arachidonic acid relative molar content and a lower 20:4/18:2 ratio in vitamin B_6-deficient groups compared with B_6-normal groups.
Conclusions: On the basis of the different biological functions of pyridoxine and considering that some factors closely related to atherosclerosis are vitamin B_6 dependent, adequate pyridoxine availability could be necessary to assure

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a normal long chain fatty acid metabolism and to reduce the risk linked to hyperhomocysteinemia.

Introduction

High level of homocysteine in plasma has been recognized as a further marker of cardiovascular diseases among well-known risk factors. Hyperhomocysteinemia causes endothelial damage leading to a high risk for the atherosclerotic process in coronary, cerebral and peripheral vessels [1—3] and for arterial and venous thromboembolism [4].

High plasma levels of homocysteine are attributed not only to genetic, but also to dietary factors [5,6], such as high methionine content [7] or deficiencies in B vitamins, particularly folic acid, vitamin B_{12} and vitamin B_6 [8,9]. These vitamins are coenzymes or cofactors of the transmethylation or trans-sulfuration pathways of homocysteine. In pyridoxine deficiency, the increased plasma homocysteine concentration is due to the lower activity of B_6 dependent enzyme cystathionine β-synthase, with consequent slowdown of the trans-sulfuration pathway.

Since a significant proportion of the population does not meet the current RDAs for folate and pyridoxine intake, hyperhomocysteinemia could be an extensive phenomenon [10]. Many studies support the existence of an inverse correlation between plasma folate and homocysteine levels, while the relationship between pyridoxine and hyperhomocysteinemia is still controversial, although in patients with chronic renal failure, due to the vitamin B_6 deficiency caused by dialysis, pyridoxine supplementation is necessary for lowering total plasma homocysteine [11,12]. Some authors report that low concentrations of vitamin B_6, by increasing homocysteine levels, are related to coronary artery disease and carotid and arterial lesions [13—15]. On the contrary, Robinson et al. [16] suggest that the relationship between vitamin B_6 and atherosclerosis is independent of plasma homocysteine concentration. Vitamin B6 deficiency could be related to vascular damage by altering platelet function [17], cholesterol concentration and antithrombin III activity [18].

In addition to hyperhomocysteinemia, alterations in lipid metabolism and lipid peroxidation, processes in which vitamin B_6 is also involved, are other known risk factors for atherosclerosis and cardiovascular diseases.

We previously demonstrated the marginal availability of pyridoxine influenced the fatty acid composition of rat tissues, with an increase in C18:2 and a decrease in C20:4 relative molar content due to the lowest activity of vitamin B_6-dependent Δ6 desaturase [19]. Furthermore, we reported that B_6 deficiency induces an increased peroxidative risk, particularly when the dietary intake of polyunsaturated fatty acids (PUFA) is high [20,21].

Since many connections appear to exist between pyridoxine, lipid metabolism, peroxidation risk and hyperhomocysteinemia, the aim of this study was to verify whether different amounts of PUFA associated with low content of vitamin B_6 in the diet could modulate the vascular risk factor homocysteine.

Methods

Animals and diets

The trial was carried out on 32 male Wistar rats (100—110 g) randomly divided into four groups each consisting of eight animals, housed in cages in a temperature-controlled room with 12 h light/dark cycle. Animals had free access to food and water for 8 weeks. Food consumption and animal weight were measured weekly.

Each group received a diet that was different in fat quality and vitamin B_6 amount (Tables 1 and 2), as follows:

- soybean oil, normal vitamin B_6 (S-NB_6): containing 8% soybean oil and 7 mg vitamin B_6/kg diet
- soybean oil, deficient vitamin B_6 (S-DB_6): containing 8% soybean oil and 0.3 mg vitamin B_6/kg diet
- soybean oil/animal fat, normal vitamin B_6 (SAF-NB_6): containing 4% soybean oil, 4% animal fat and 7 mg vitamin B_6/kg diet
- soybean oil/animal fat, deficient vitamin B_6 (SAF-DB_6): containing 4% soybean oil, 4% animal fat and 0.3 mg vitamin B_6/kg diet

At the end of the dietary treatment, the animals were anesthetized with ether and blood was sampled by intracardiac withdrawal. The rats were then sacrificed and the liver was excised and frozen in liquid nitrogen and stored at −80°C. This study was approved by the Animal Care Committee of the University of Bologna.