NEWSLETTER
Vitamin Information Center
ビタミン応報センター
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"Seminar fot Dietitian" Report

Spomsored by: The Jpan Dietetic Association, Ehime Dietetic Assocation and Vitamin Information Cente
Date: September 11, 2004 (SAT) At RIHGA ROYAL HOTEL NIIHAMA

The Japan Dietetic Association and Vitamin Information Center have held scientific lectures on dietitians in many prefectures as a part of the Nutrition Educational Program. Diverse health food products and drinks fill the current market, and there are more and more questions from patients and consumers about health foods and their functional ingredients. Therefore, this lecture intends to contribute to maintenance and improvement of national health by holding lectures for dietitians who are expected as the human power in health and nutrition instruction for more special understanding to add to future activities, so that the individual recognition on health is increased and the balance in nutrients and the role of each are understood properly. On September 11, 2004, we asked Professor Toshiaki Watanabe from University of Hyogo to talk about "Physiological Functions of Biotin and Its Effect on Health," and Professor Satoshi Moriguchi from Yamaguchi Prefectural University on "Sports and Vitamins" for approximately 120 dietitians member to Ehime Dietetic Association in Niihama City, Ehime Prefecture. The following introduces the lectures.

Physiological Functions of Biotin and Its Effect on Health

Professor Toshiaki Watanabe, School of Human Science and EnvironmentUniversity of Hyogo

Prof. Toshizki Watanabe

Vitamins are defined as organic compounds that cannot be synthesized by ourselves though they have important functions in our internal metabolism in trace volumes. Therefore, insufficient vitamin intake may lead to unique clinical symptoms depending on the type of vitamin, and such symptoms are called deficiency. In Japan, the typical vitamin deficiencies have decreased thanks to improvement in our dietary life to the level at which they are rarely seen. However, inherent deficiencies caused by imbalance in dietary life have become an issue. In addition, the existence of vitamin dependence as many hereditary disorders have been found, and new functions of vitamins are emerging.

Biotin, which is a water-soluble vitamin, is involved in carbon dioxide fixation as a coenzyme of carboxylase. Biotin is contained in a wide range of food items and is also synthesized by the intestinal flora along with vitamin B6 and pantothenic acid. Thus it is usually difficult for biotin deficiency to occur. However, it is known that dermatitis, alopecia, etc. may occur if a large volume of raw egg white is given to experimental animals. This is known as the "egg white injury." This is a state of biotin deficiency which occur when avidin, a glycoprotein in egg white, binds to biotin in digestive tract and inhibits biotin absorption.

Biotin requirement was established for the first time in the 6th Revision of Japanese Nutrient Requirements Dietary Intake Standard- (1999). Requirement is 5 micro g per day for infants of 0 months and older, and 30 micro g per day for adults. Though 5 micro g is added for nursing mothers, it is not added for pregnant women. On the other hand, biotin is not included in the 5th Revised Japanese Standard Food Product Ingredient Table. Thus biotin requirement cannot be fully utilized in nutritional instruction. The food products that contain large levels of biotin are meat such as bovine liver, beans and grains such as soybean, egg yolk and royal jelly.

Due to the reasons that there had been no deficiency before, that its safety is not fully assured, etc., biotin had not been approved as a food additive. However, biotin was allowed to be used only in food with health claims in June 2003, though it cannot be used in powdered milk. The biotin content of powdered milk commercially sold in Japan is 1.04 (0.46~1.13) micro g/100kcal on average for milk for infants, and 0.40 (0.05~1.47) micro g/100kcal on average for special milk for treatment. These levels are considerably low compared to 1.5 micro g/100kcal, the level recommended by WHO or the biotin contents in powdered milk in the U.S. Therefore, biotin deficiency symptoms such as dermatitis and eczema have been seen in infants with congenital metabolism abnormality who use special milk for treatment. As you can see, sufficient caution is required when using powdered milk.

Moreover, serum biotin levels are reduced in diabetes patients and patients of dermatitis or arthritis by pustulosis palmoris et plantaris compared to healthy people. It has also been reported that biotin administration to non-insulin-dependent diabetes mellitus patients decreases the blood sugar values. Furthermore, biotin deficiency inhibited fetal development in pregnant animals and malformations such as cleft palate and micrognathia are induced, although this has only be seen in experimental animals.

In recent years, popularization of nutritional supplements and interests in trace nutrients have increased. The system of food with health claims started in 2001, and food products are distinguished from drugs (including food

products with specific purposes). Food products with health claims are divided into food products with specific purposes and food products with nutritional claims, and food products with nutritional claims have been stipulated with specification standard and labeling standard. The upper and lower limit values are specified in specification standard, and these are based on the nutritional requirement, tolerable upper limit intake, etc. These values for biotin are 10 and 500 micro g, respectively. However, biotin has not been reported with toxicity so far. For labeling of food products with nutritional claims, that it is a nutrient that helps in maintenance of skin and mucosa health, etc. are approved for biotin.

As you can see, biotin is deeply related to health and awareness is being renewed of its advantages. While the role as coenzyme is known well as the function of biotin, it is more and more expected that the new physiological functions of biotin, such as blood sugar adjustment, growth factor, and maintenance of intestinal flora and skin health will be revealed in the future.

Sports and Vitamins

Professor Satoshi Moriguchi, Faculty of Human Life Sciences, Yamaguchi Prefectural University

Prof.Satoru Moriguchi

The researchers in Exercise and Sports Physiology and Nutrition have only studied how nutrients should be taken for the purpose of improving the competitive abilities of top athletes such as Olympics players and players of National Athletic Meet, and reality is that they study little about maintenance and improvement of health of general people. First, when considering the resultsof research for top athletes, exercise is divided into anaerobic exercise in which white muscle is mainly used and aerobic exercise in which red muscle is mainly used, and it has been shown that sufficient supplementation of vitamins is inevitable in making it smooth to supply the energy necessary for such exercises (Fig.1). While sugar, lipids, and proteins are the most well-known nutrients in energy production in our bodies, the top athletes who consume a large amount of energy by exercise require intake of a large amount of energy as well, and they also require supplementation of vitamins involved in energy metabolism at the same time. In general, sufficient intake of vitamin B1 which is the coenzyme for sugar metabolism, vitamin B2 involved in oxidation-reduction reactions, and vitamin B6 involved in amino acid metabolism is recommended. It is also necessary that niacin, which works as a coenzyme for NAD or NADP, the enzymes related to various oxidation-reduction reactions, is taken sufficiently (Fig.2).

Therefore, vitamins B1 and B2 as well as niacin are provided with nutrition requirements per energy intake of 1,000kcal in Japanese nutritional requirements (standard food intake for Japanese; DRIs). However, vitamin supplementation is not considered necessary for relatively light exercise for the purpose of health maintenance and improvement since it has been found that serum and urine concentrations of vitamins do not change considerably before and after exercising. Since production of active oxygen increases in body under aerobic exercise and hyperoxidation of lipids that construct the cell membraine advances, it is also recommended that antioxidant vitamins such as vitamin C and E and Beta-carotene be taken sufficiently in preventing it. Furthermore, considering the relationship between host immunocompetence and exercise from the viewpoint of health maintenance and improvement, it is highly likely that immunocompetence may decrease at the beginning when one starts to exercise for health maintenance or improvement while moderate exercise increases immunocompetence. It is thus important that the introductive section until exercise is a habit in daily life is proceeded smoothly, and supplementation of vitamin E, which is an antioxidant vitamin, has been found to be valid as a measure. Sufficient vitamin intake from food is important in order to maximize the effect of exercise, and vitamin supplementation by supplements may also be necessary if it is not sufficient.

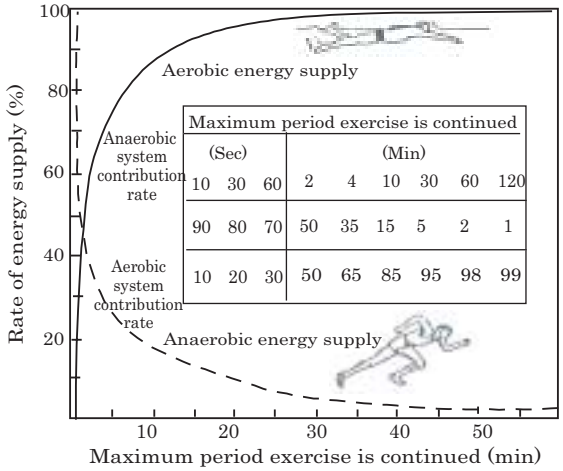

Fig.1 Relative rate of contribution by anaerobic energy and aerobic energy in maximum exercise at different periods continued (Astrand, PO and Rohahl, K: Textbook of Work Physiology, New York, McGraw-Hill Book Company, 1977)

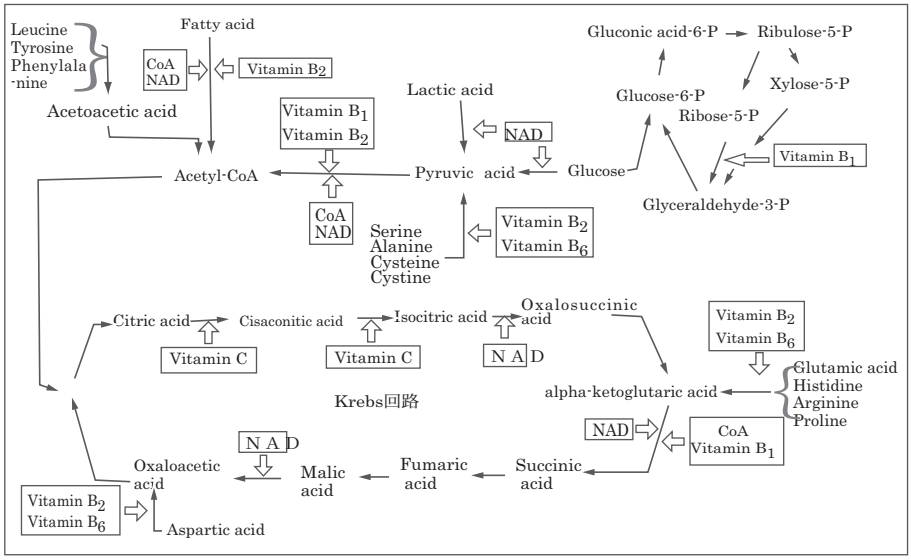

Fig.2 Energy production from glucose, fatty acids and amino acids and vitamins (Ihara H. and Hashizume N.: Clinical Sports Medicine, 13, 83 - 89, 1996)

Effect of Lutein Intake on Serum and Macular Pigments

Martha Neuringer et al, Invest Ophthalmol Vis Sci. 2004; 45: 3234-3243

Purpose

Two types of xanthophylls, lutein and zeaxanthin, are the major components of macular pigment, and are assumed to protect the macula from age-related macular degeneration (AMD). In this study, lutein or zeaxanthin was administered to rhesus monkeys reared with non-xanthophyll containing feed to record the changes in macular pigments along time.

Methods

Eighteen rhesus monkeys were reared with feed that contains no xanthophyll from birth to ages of 7 to 16 years. Then they were administered with lutein or zeaxanthin by 3.9 micro mol/kg/day (2.2mg/kg/day) for 24 to 56 weeks (6 animals for each substance). Serum carotenoid levels were measured using HPLC at the baseline, 4th week, and 12th week of administration period to determine the density of macular pigments by dual-wavelength reflectometry. Serum carotenoid level and macular pigment density were also measured for animals reared with normal feed for stock animals.

Results

<Serum carotenoid>

In the group administered with non-xanthophyll containing feed, lutein and zeaxanthin did not exist at measurable levels, and the only carotenoid detected in the serum was lycopene (<0.070 micro mol/L). When lutein or zeaxanthin is administered to this group, the xanthophyll concentration in serum increased rapidly for the first 4 weeks to reach 1.14 micro mol/L (range 0.53~1.85) lutein concentration in the lutein administration group and 0.65 micro mol/L (range 0.19~1.43) zeaxanthin concentration in the zeaxanthin administration group (Fig.1). The xanthophyll levels in serum exceeded the levels of the group fed with stock feed by 2 weeks of administration, and lutein level became approximately 10 times and zeaxanthin level 10 to 20 times higher. However, increase in xanthophyll concentration in serum ceased when 12 weeks have passed, and the total xanthophyll concentration was nearly similar for both of the administration groups after 16th week.

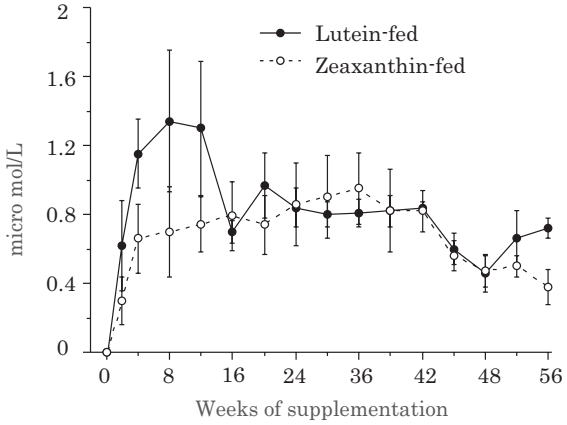

Fig.1 Changes in serum concentrations after xanthophyll intake

<Macular pigment density>

Optical density of macular pigments was extremely low after administration of non-carotenoid containing feed. However, not only serum concentration increase but also macular pigments were accumulated after administration of lutein or zeaxanthin. This result demonstrates that either lutein or zeaxanthin maintain the mechanism to accumulate macular pigments even for the retina of a primate matured without xanthophylls. Thus it is possible that lutein/zeaxanthin intake may be effective when it is desired that macular pigments be increased in elderly people with risks of macula luteal-related diseases or in people under poor dietary environment which caused continuation of low macular pigment densities.

Though optical density of macular pigments increased for the first 24 to 32 weeks, further increase was not observed with consistency for 32 to 56 weeks (Fig.2).

The color photograph of eyeground showed no formation of crystals within the retina at any point during administration period. This indicates that it is possible even for a retina which has never been exposed to macular xanthophyll to absorb xanthophylls when exposed to high administration levels. On the other hand, it may lead to generation of crystals instead of such favorable reaction if a type of carotenoid that does not exist normally in retina is administered at a high dose.

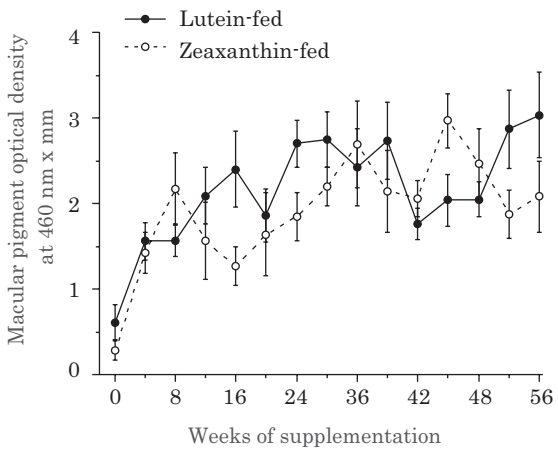

Fig.2 Changes in macular pigment density after xanthophyll intake

Conclusion

In rhesus monkey, intake of lutein or zeaxanthin lead to increase in serum xanthophyll and macular pigment levels although there had been long-term deficiency in xanthophylls for the entire period since birth. Therefore, it is surmised that this species is a potential study model for the mechanism of protection against AMD.

Anticancer Activity of EGCG

Inhibition of Vascular Tumor Growth by Epigallocatechin-3-Gallate (EGCG)

Gianfranco Fassina et al, Clin Cancer Res.10; 4865-4873, 2004

It is said that drinking green tea is related to reduction of incidence for some tumors. The current data suggests that the main intermediate for this scientific preventive effect is epigallocatechin-3-gallate (EGCG), which is the polyphenol detected in dry green tea leaves most abundantly. Thus we have investigated the effects of green tea and of EGCG both on a tumor model of highly vascularized Kaposi's sarcoma (KS) and on endothelial cells in vivo as well as in vitro. The findings of this study suggest that the green tea gallate may be used for preventive chemical treatment of vascular tumors or for the setup as a coadjuvant.

Effects of EGCG on the growth of endothelial cells and of KS-IMM cells

The effects of EGCG on cellular growth were investigated first in vitro. The growth of KS-IMM cells was significantly inhibited for EGCG concentrations of 25 micro M or higher (Fig. 1 upper panel), and the total number of cells evidently decreased for EGCG concentrations of 50 micro M or higher. Similar effects of growth inhibition by EGCG were observed on human umbilical endothelial cells (HUVEC) with a strong cytostatic effect seen 72 hours later at 25 micro M of EGCG (Fig. 1 lower panel, $p<0.001$).

Effects on apoptosis

Since it was suggested that the effects of EGCG on cellular growth were potentially either apoptotic or cytotoxic, the effects of EGCG on apoptosis were investigated. For lower doses of EGCG administration (10~25 micro M), the effect of EGCG to induce apoptosis or necrosis was not observed on the cells of either KS-IMM or HUVEC during 24 hours, whereas for doses higher than 25 micro M of EGCG, dose-dependent apoptosis was induced on both KS-IMM and HUVEC cells. The threshold concentration for inducing the apoptosis seems to be 50 micro M for both cell lines.

EGCG lowered the growth of KS tumor

The possibility for EGCG and green tea to inhibit the growth of vascular tumor cells in vivo was investigated on the assumption that EGCG inhibits the growth of KS cells and vascularization. Hypodermic injection of KS-IMM cells, which are an immortalized KS cell line, into a male nude mouse develops a highly vascularized tumor. EGCG was orally administered along with drinking water to the active-drug group every three days or every other day prior to the hypodermic injection of the KS-IMM cells. The tumor growth was significantly lowered compared with the control group to which only drinking water was administered ($p<0.05$) (See Fig. 2). Furthermore, large tumors developed in 90% of the control group, whereas only slowly developing tumors limited in size appeared in all members of the active-drug group. Since there were almost no differences in the body weights of the animals used in the study, it is suggested that the toxicity of EGCG is either only limited or absent. The size of the tumors decreased by about 50% on EGCG-administered mice.

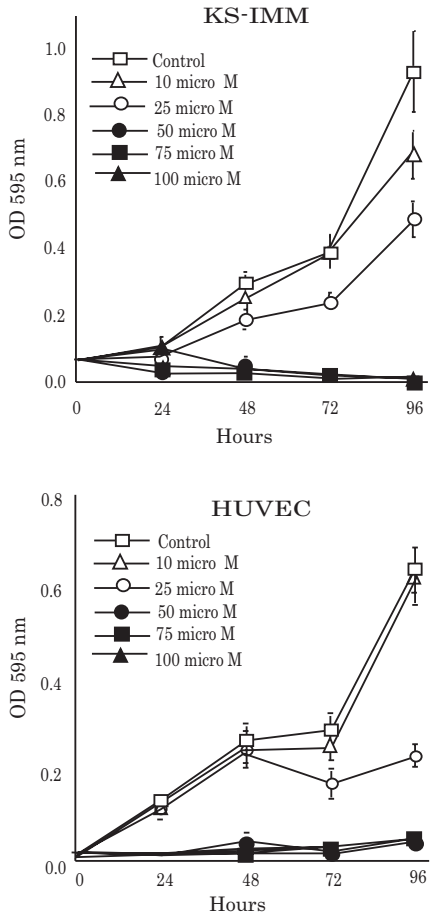

Fig. 1 Effects of EGCG on the growth of endothelial cells and of KS-IMM cells

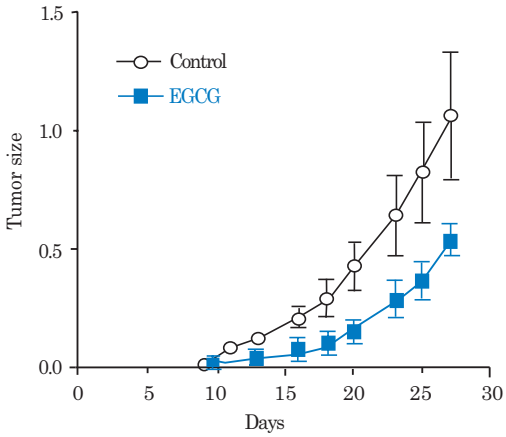

Fig. 2 Effects of EGCG on the growth of KS tumor