Symposium 2

SY2-1

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Growth is a sensitive indicator of the nutritional status of children and nutrient deficiencies are commonly reflected in impaired growth. Inadequate energy and protein intakes consistently cause growth impairment that is corrected by appropriate supplementation and often cognitive improvement can be demonstrated. This also true of micronutrient deficiencies to varying degrees. Severe iodine deficiency in pregnancy leads to cretinous dwarfism, but when less severe can still interfere with brain development in mid and late pregnancy. Essential fatty acids are also important for brain development and premature infants may not receive adequate amounts. Iron deficiency in infancy and early childhood also affects brain development at a critical time and in most studies of anemic child populations iron supplementation improves growth. There is increasing evidence that in some populations zinc deficiency is responsible for relative growth failure. Whether or not vitamin A directly affects growth, it does influence iron status. Adequate bone mass cannot be achieved without appropriate calcium and vitamin D intakes. B-vitamins have many functions essential to maintenance of cell function and their clinical deficiencies can affect any stage of development. Low birth weight at term, due primarily to maternal malnutrition, is closely associated with growth deficits at one year of age and both increase the occurrence of chronic degenerative diseases in later life.

SY2-2

Essential Fatty Acids in Early Life.

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Essential fatty acids (EFAs) are structural components of all tissues and are indispensable for cell membrane synthesis; the brain, retina and other neural tissues are particularly rich in long chain polyunsaturated fatty acids (LCPUFAs). These fatty acids serve as specific precursors for eicosanoids which regulate numerous cell and organ functions. Results from animal and recent human studies support the essential nature of n-3 in addition to the well-established role of n-6 EFAs for humans, particularly in early life. The most significant effects relate to neural development and maturation of sensory systems. Recent studies using stable isotope labeled tracers demonstrate that even preterm infants are able to form arachidonic acid (AA) and docosahexaenoic acid (DHA) but that synthesis is extremely low. Intracellular fatty acids or their metabolites regulate transcriptional activation of gene expression during adipocyte differentiation, retinal and nervous system development. Regulation of gene expression by LCPUFAs occurs at the transcriptional level and may be mediated by nuclear transcription factors activated by fatty acids. These nuclear receptors are part of the steroid hormone receptors family. DHA also has significant effects on photoreceptor membranes and neurotransmitters involved in signal transduction process, rhodopsin activation, rod and cone development, neuronal dendritic connectivity and functional maturation of the CNS. Comprehensive clinical studies have shown that dietary supplementation with marine oil or single cell oils sources of LCPUFAs results in increased blood levels of DHA and AA, as well as an associated improvement in visual function in formula-fed infants matching that of human milk-fed infants.

The main findings are that light sensitivity of retinal rod photoreceptors is significantly reduced in newborns with ω-3 fatty acid deficiency, that DHA significantly enhances visual acuity maturation and cognitive functions. To explore the possible effect of DHA on gene expression during human fetal retinal maturation we compared mRNA expression from retinal explants with and without added DHA using gene microarray methodology. Total RNA was obtained on day 14 from fetal retina (14-18 wk gestation) cultured in serum free media with and without DHA. cDNA was synthesized with labeled nucleotides and hybridized to the microarray. Fluorescent reporters were used to assess gene expression. Computer analysis of relative expression of 2400 genes was performed. Ratio of expression +DHA/Control was unchanged in 80% of genes (i.e. several ribosomal proteins and GADPH); 4% of genes displayed a ratio < 0.33 (i.e. human brain FA-BP, cytoskeletal proteins, PI kinase, Leukotriene hydrolase) and for 15 % the ratio was > 3.0 (related to fatty acid oxidation and desaturation, PAF ac-H, LDL receptor and LPL, mitochondrial oxidation processes, Protein kinases related to apoptosis and differentiation, transcription factors and mRNA, neurotransmitter receptors and IGF-BPs). We conclude that DHA is a conditionally essential nutrient for adequate neuro- development in humans. The effect is mediated not only by the known effects on membrane biophysical properties, neurotransmitter content and the corresponding electrophysiological correlates but also by a modulating gene expression of the developing retina and brain.

(Funded by Catedra Presidencial RU-96 Chilean Scientific Council)

SY2-3

Carotenoid-rich Edible Oil – Its Potential Nutritional Impact

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Red palm oil is characterized by its high content (500 ppm) of natural carotenoids (primarily alpha and beta-carotene) and Vitamin E (800 ppm), predominated as the tocotrienol isomers. These minor nutrients in red palm oil confer distinct and important physiological effects that are unlike other edible oils and fats. A large number of human clinical trials have shown that palm olein behaves as a neutral fat in its cholesterolemic response. Since the fatty acid composition of red palm oil mimics that of refined palm olein, which is rich in the monounsaturated oleic and saturated palmitic acids, similar effects on blood lipids and lipoproteins has been postulated. As a result, the fatty acids in red palm oil have a neutral effect on plasma total and LDL-cholesterol. In a rabbit atherosclerosis model study however, red palm oil resulted in a significantly lower atherogenic index) scored as total plague surface area) than refined palm olein. This has been attributed to its content of carotenoids and tocotrienols and their abilities to act as potent natural antioxidants. The beneficial effects of tocotreinols on atherogenesis was also evident in ApoE knockout mice – lesion sizes were almost 98% smaller than those of control mice receiving a similar atherogenic diet minus the tocotrienols. Tocotrienols present in both refined and red palm oil have been demonstrated to have cholesterol-lowering properties mediated through their ability to regulate HMG-CoA reductase activity, a rate-limiting enzyme in cholesterol synthesis. In addtion, tocotrienols inhibit the growth of human breast cancer cells in culture and reduce the progression of DMH induced colon carcinogenesis in rats. Similarly, the bouquet of carotenoids has been shown to have positive anti-cancer activities. Palm alpha and beta-carotene isolates were effective against the proliferation of a number of cancer cell cultures (liver, lung, skin). These beneficial health properties of red palm oil are considered an additional bonus to their currently well proven pro-vitamin A effects.

SY2-4

The expression of 25-hydroxyvitamin D-1 -hydroxylase and megalin in murine embryonic kidney.

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Aim: Vitamin D is an essential nutrient for bone and calcium homeostasis. Vitamin D must be activated by hydroxylation of two sites to exhibit its biological function. The 25-hydroxyvitamin D-1 -hydroxylase (1 -hydroxylase) is a key enzyme to activate 25-hydroxyvitamin D in kidney whose cDNA and gene have been recently cloned. The vitamin D deficiency is often encountered clinically in breast-fed premature babies unless vitamin D, calcium and phosphorus are supplemented. It is necessary to examine the expression of 1 -hydroxylase in developing kidney to understand the physiological control of vitamin D metabolism.
Methods: First, the expression of 1 -hydroxylase, 24-hydroxylase and megalin in mouse developing kidney was investigated by reverse transcription-polymerase chain reaction (RT-PCR). The kidneys from mouse embryo at 11.5 to 17.5 day of gestation were explanted and placed in DMEM supplemented with 15% FCS. Then, either forskolin or 1,25-dihydroxyvitamin D_3 was added to the culture media. 3-24 hour after the addition, total RNA was extracted from the kidney explants and used for RT-PCR. Next, the distribution of 1 -hydroxylase transcripts was examined by whole mount in situ hybridization using organ culture of metanephros taken from embryos at various stages and compared with that of 24-hydroxylase and megalin transcripts. The explants were fixed with 4% paraformaldehyde and whole mount in situ hybridization was performed using digoxigenine-labeled probe encoding entire coding region of each cDNA.
Results: The expression of 1 -hydroxylase and 24-hydroxylase was inducible in kidney explants from embryo at 13.5 to 17.5 day of gestation by the treatment with forskolin and 1,25-dihydroxyvitamin D_3, respectively, in a dose- and time-dependent manner. These results indicate that the expression of 1 -hydroxylase and 24-hydroxylase starts after the tubulogenesis. The signal for the expression of either 1 -hydroxylase and 24-hydroxylase was detected in kidney explants after the simultaneous stimulation at 15.5 day of gestation. The distribution of signals was different between the two enzymes, although which portion of renal tubules expresses the transcripts of these hydroxylases has not been identified yet. The site of expression of both enzymes was restricted to epithelium of developing renal tubules. The pattern of megalin expression was similar to that of 1 -hydroxylase expression.
Conclusions: The expression of 1 -hydroxylase is induced in a distinct epithelium of renal tubules from that of 24-hydroxylase even at the early stage of kidney development prior to glomerulogenesis.

Symposium 3

SY2-5

Clinical Studies and Animal Experiment on Vitamin B_1 Deficiency

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Aim: We investigated pathogenesis of patients with vitamin B_1 (thiamine) deficiency, i.e., beriberi, Wernicke's encephalopathy, and lactic acidosis treated with total parental nutrition (TPN). We also investigated growth, development, and neurological pathology in the B_1 deficient rats.

Methods: 1) Clinical study; Physiological findings and symptoms were investigated in 400 patients with beriberi, 25 patients with Wernicke's encephalopathy and 7 patients with TPN-induced lactic acidosis.

2) Animal experiment; Wister rats (60 g of body weight) divided into 4 groups: control group, B_1 deficient group, alcohol-administered group and alcohol-administered B_1 deficient group were fed for 35 days and their brain tissue was histlogically examined.

Results: 1) Beriberi was observed in young people who are fond of exercise. Excessive carbohydrate intake and insufficient B_1 intake induced beriberi. Observed heart failure was high out put failure, and disturbance of peripheral nerve was degeneration of axoplasma. Wernicke's encephalopathy was induced by alcohol and disturbance was mainly observed in the central nerves. TPN-induced lactic acidosis was accelerated by the infusion of large amount of carbohydrate and insufficient B_1 intake. In some patients, shoushin beriberi and Wernicke's encephalopaty were observed.

2) Abrupt weight decrease was observed in B_1 deficient rats after 14th day of feeding program and gradual weight decrease was observed after 7th day in alcohol administered rats. Alcohol administered B_1 deficient rats showed the slowest growth. Encephalopathy was first observed in B_1 deficient rats on 21st day of program. Histological changes in the brain were exclusively observed in vestibular nucleus. Histological changes were also observed in cerebella and corpus striatum of alcohol-administered rats.

Conclusions: Based on the animal experiment, growth and development were suppressed by vitamin B_1 deficiency. B_1 deficiency also caused heart failure and disturbance of nerves in human. Under marginal vitamin B_1 deficient state, lack of this vitamin may affect mental development following emergence of general physical complaints.

SY3-1

The Asia Pacific Clinical Nutrition Society Okinawan Recommendation on Nutrition and Cardiovascular Disease in the Asia Pacific Region

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The emergence of cardiovascular disease of the ischaemic type in the Asia Pacific region has been against a different food cultural background and greater rate of economic development than has occurred in Western countries. For these reasons, the assumptions about prevention and management transfer from West to East may not always be valid, and the opportunities for cardio-protection, located in the Asia-Pacific, lost to the rest of the world.

In November 2000, a working party was convened in Okinawa by the Asia Pacific Clinical Nutrition Society to address these issues. Okinawa was chosen because of its exceptionally favourable cardiovascular disease and longevity profile. The recommendations of this round-table were:

1. The prevention of macrovascular disease (MVD) in the Asia-Pacific region should be based on FBDGs (Food Based Dietary Guidelines), which take account of sustainability, culture, social settings and broad health needs.
2. Emphasise a varied, nutritious food intake as the foremost dietary guideline.
3. Greater efforts should be made to identify culturally relevant cardioprotective foods and beverages.
4. A lifelong approach to CVD prevention, from conception to old age, is required.
5. Attention should be given to the role of food, and quality of life, in ageing populations.
6. Encourage food intake decisions which are inclusive of physical fitness, mental health and social activity.
7. Develop advocacy for health food policy and programs in relation to CVD in the Asia-Pacific region through inter-sectoral partnerships and good governance.

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