Nucleotides in nutrition: The importance in infant and childhood diets.

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Introduction.

The concentration of free nucleotides in human milk is higher than in bovine milk. Because bovine milk is most often used to formulate infant milk formulas, most milk formulas are supplemented with nucleotides to increase the concentration to a level that is similar to the concentration found in human milk. This practice is justified by studies that have shown that infants who received nucleotides in their formula were less likely to have diarrhea and also had better responses to vaccination, producing more antibodies and other immune cells (Carver et al., 1991; Pickering et al., 1998). It has also been documented that term infants that had severe intrauterine growth-retardation had better catch-up growth if nucleotides were included in their milk formulas (Yu, 1998). The reason for this improved growth may be related to improved immune function, improved intestinal health, improved fatty acid metabolism, or improved cellular turn over. All of these factors have been shown to be dependent on a correct supply of nucleotides. Humans and other mammals are able to synthesize nucleotides de novo or via the salvage pathway, but it is not known if this synthesis is taking place in premature or full-term infants (Walker, 1994). Because nucleotide synthesis is an energy requiring process, it is possible that infants simply do not have enough energy to synthesize nucleotides. In addition, the tissue requirement for nucleotides is increased during periods of stress (Carver and Walker, 1995). Therefore, it is likely that the requirements for nucleotides are elevated in infants and young children compared to adults. This further indicates a need for including nucleotides in the diets for infants and children. Nucleotides are, therefore, conditional essential nutrients for infants (Uauy et al., 1994). The objective of the current contribution is to review the roles of nucleotides in diets for infants and children.

The role of nucleotides in intestinal development

Enterocytes along with brain cells and bone marrow have limited capacity for synthesizing nucleotides de novo (Yamamoto et al., 1997). These cells are, therefore, dependent on dietary nucleotides that are being absorbed from the intestinal tract or on nucleotides synthesized by other cells. Most dietary nucleotides are absorbed as nucleosides and subsequently rephosphorylated in the enterocyte. This is a relatively efficient process and more than 90% of dietary nucleotides are absorbed (Uauy et al., 1994). However, most of the purines are metabolized to uric acid in the enterocytes and only small quantities appear in the hepatic cells. Therefore, ingestion of nucleotides is followed by an increase in the expression and activity of enzymes involved in nucleotide metabolism. In contrast to the purines, relatively large quantities of dietary pyrimidines are transported from the enterocytes to the hepatic portal vein (Uauy et al., 1994). Because of the limited capacity of the enterocytes for nucleotide synthesis and because nucleotides are needed in the cell synthesis, dietary nucleotides enhance the growth and maturation of intestinal epithelial cells. It has been shown that dietary nucleotides mayl increase the formation of mucosal protein, increase the concentration of DNA, and increase the length of the villi in the small intestine (Uauy et al., 1990; Carver, 1994). Dietary nucleotides may also stimulate enterocyte differentiation (Sanderson and Youping, 1994). Parenteral supplementation of nucleic acids support mucosal cell proliferation and function as demonstrated by increased mucosal wet weight, protein and

DNA contents, villous height, and narrower tight junctions of the jejunal mucosa width (Kishibuchi et al., 1997; Tsujinaka et al., 1999).

The development of the gastrointestinal tract directly affects the degree of nutrient absorption. Because of the role of nucleotides in maintaining intestinal morphology and maturation, dietary nucleotides may be needed to maintain the structure and growth of the intestinal tract.

Nucleotides and nucleosides may regulate the intestinal microflora

Nucleotides increases the predominance of probiotic bacteria (i.e., lactobacilli and bifidobacteria) and reduces the concentration of enterobacteria in stool samples from infants fed nucleotide supplemented milk formulas compared to infants fed a non-supplemented control formula (Gil et al., 1986; Tanaka and Mutai, 1980). In a recent experiment in our laboratory, it was demonstrated that stool samples from weanling pigs had increased concentrations of lactobacilli and bifidobacteria and reduced concentrations of clostridium perfringens if the diet fed to the pigs was supplemented with dietary nucleosides compared to non-supplemented control pigs (Mateo et al., 2004; unpublished). In a subsequent in vitro experiment it was shown that supplementation with nucleosides increases the growth of both probiotic and pathogenic bacteria. From these experiments it was concluded, that the reason for the reduction in pathogenic bacteria in the in vivo experiment was competitive exclusion. It was speculated that the intestinal microflora may utilize nucleosides and nucleotides as an energy source and therefore increase the proliferation if nucleosides or nucleotides are present. However, because the probiotic bacteria are growing faster than the pathogenic bacteria, they will limit the growth of the pathogens under in vivo circumstances. These studies suggest that nucleotide supplementation may positively influence the microflora in the gastrointestinal tract, which hinders the proliferation of pathogenic bacterial species as evidenced by a lower rate of diarrhea (Yu, 1998).

Roles of nucleotides in developing and maintaining the immunsystem.

Dietary nucleotide supplementation has been associated with both humoral and cellular immunity, but the exact mechanism has not been elucidated. Nucleotide deprivation caused the arrest of T-cells in the G phase of the cell cycle, preventing a response to various immunological signals that occur by transition to the S phase (Kulkarni et al., 1994). Nucleotide deprivations also caused a decrease in phagocytic activity, lymphokine production, and/or inhibited lymphocyte maturation (Paubert-Braquet et al., 1992). Dietary nucleotides contribute to the circulating pool of nucleosides available to stimulate leukocyte production (Kulkarni et al., 1994; Carver and Walker, 1995). Therefore, there is an elevated need for nucleotides during periods of immunological challenges.

Dietary factors play a role in the antibody response to immunization of infants. Infants fed milk formula fortified with nucleotides had better responses to immunization as evidenced by an increase in humoral antibody response (Fanslow et al., 1988; Pickering et al., 1998) and increased cytokine production (Carver et al., 1991). In vivo studies in mice show similar results to nucleotide supplementation (Jyonouchi et al., 1993; Jyonouchi, 1994). Nucleotide-free diets supplemented with single nucleotides (i. e., AMP, GMP, or UMP), have been shown to increase immunoglobulin concentration (Navarro et al., 1996). Dietary supplementation of purified nucleotides to milk replacers of newborn bull calves challenged with lipopolysaccharide (LPS), resulted in calves that tended to have higher mean IgG levels compared to the unsupplemented control calves (Oliver et al., 2003). Nucleotide supplementation also increased lymphocyte stimulation to phytohaemagglutinin and concanavalin-A challenges in weanling piglets by 50 and 30%, respectively (Zomborsky-Kovacs et al., 1998). Similar results were observed to challenges by keyhole limpet hemocyanin (KLH) and non-specific T-cell mitogens in piglets fed yeast RNA (Cameron et al., 2001). In piglets, nucleotides in concentrations similar to those in human milk exert a protective effect in the intestinal lumen against an inflammatory response to ischemia-reperfusion (Bustamante et al., 1994).

The results from studies investigating the effects of dietary nucleotides on the development of the immunesystem indicate that dietary nucleotides are needed to maintain the humoral as well as the cellular immune system in infants and young children.

Effects of nucleotides in lipid metabolism and brain function

It has been demonstrated that dietary nucleotides increase the concentration of erythrocyte 2.3-diphosphoglycerate concentration in neonatal rats (Scopesi et. al., 1999). This will increase the peripheral oxygen delivery. Neonates that were deprived of nutrients prior to birth may have a reduced 2.3-diphosphorglycerate concentration. Such babies will, therefore, benefit from dietary nucleotides because this will enhance the oxygen status.

In contrast to the effects of nucleotides on 2.3 diphosphoglycerate, dietary nucleotides do not influence the concentration of phosphatidylcholine or the ratio of phosphatidylcholine to phosphatidylethanolalamine in the liver of rats. However, both the concentration of phosphatidylcholine and the ratio of phosphatidylcholine to phosphatidylethanolalamine was increased in the cerebral cortex of rats fed nucleotide supplemented diets compared to rats fed a nucleotide-free diet (Sato et al., 1995). The nucleotide-supplemented rats also had an increased concentration of docosahexaenoic acid and arachidonic acid in the cerebral phosphatidylcholine. In addition, the nucleotide supplemented rats had an increased learning ability compared to rats fed diets that were not supplemented with nucleotides (Sato et al., 1995). In a separate study, it was demonstrated that memory deficient mice, experienced improved memory if they were fed diets containing dietary nucleosides or nucleotides (Yamamoto et al., 1997). These results indicate that dietary nucleotides may be beneficial to the function of the cerebral system and the brain.

Conclusions

Supplementation of infant formulas with nucleotides to a level that is similar to that found in breast milk is widely used. This practice is well documented due to the positive responses of nucleotides on the development of the intestinal system and the proliferation of intestinal epithelial cells. Because of the inability of the enterocytes to synthesize nucleotides, these cells are dependent on a constant dietary supply of nucleotides that can be absorbed in the form of nucleosides and subsequently phosphorylated to nucleotides inside the enterocyte. In addition to the documented effect of nucleotides on the integrity of the enterocytes and the intestinal villi, recent evidence also suggest that dietary nucleosides and nucleotides have a positive effect on the intestinal microflora. The inclusion of dietary nucleotides will, therefore, result in an increased concentration of probiotic bacteria in the intestinal tract. This will in turn reduce the concentration of pathogenic bacteria due to competitive exclusion. The combined effects of nucleotides in the intestinal tract are improved intestinal integrity which will increase nutrient absorption and an improved microbial flora that will contribute to a reduction in the incidence of diarrhea in infants and children.

The beneficial effects of nucleotides on the development and maintenance of the immune system is well documented. The humoral as well as the cellular systems have been shown to be impaired in animals fed nucleotide-free diets. Infants and children that are stressed or immunocompromised may have particular benefits of receiving dietary nucleotides. The recent discoveries of the roles of nucleotides in the concentration of the cerebral decosahexaenoic acid and arachidonic acid and the subsequent influence of brain function further indicates the role of nucleotides in the nutrition of infants and young children.

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