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NUCLEOTIDES

Nucleotides are the structural units of the nucleic acids RNA and DNA. They are low molecular weight compounds made of:

- a pyrimidine or purine nitrogenous base (e.g. uracil, cytosine and thymine for the pyrimidine bases, adenine, guanine and hypoxanthine for the purine bases),
- a sugar moiety (ribose or deoxyribose),
- 1 to 3 phosphate groups.

The immediate precursors of DNA and RNA are the triphosphate forms. The monophosphate forms are the most practical and common forms added to infant formulas:

- Adenosine 5'-monophosphate (AMP),
- Cytidine 5'-monophosphate (CMP),
- Guanosine 5'-monophosphate (GMP),
- Inosine 5'-monophosphate (IMP),
- Uridine 5'-monophosphate (UMP).

Nucleotides are synthesised by cells. They are found in biological tissues and fluids from animals and plants. They are also found in foods.

They can be synthesised from:

- amino acids and glucose (de novo pathway which is an expensive metabolic process in terms of energy), or
- endogenous purine and pyrimidine bases released by the degradation of RNA and DNA (salvation pathway), or
- exogenous nucleosides from the diet. [1]

The **nucleic acids RNA and DNA** can be degraded by nucleases into **nucleotides**. These nucleotides can be further broken down into **nucleosides** (adenosine, cytidine, guanosine, inosine, uridine) by cleavage of the phosphate groups by alkaline phosphatases and nucleotidases. **The nucleosides are the preferred form for absorption by the intestinal mucosa.** Once absorbed, the nucleosides can be degraded into uric acid for example or they can be reconverted into nucleotides. [1]

1. Nucleotides in human milk

Nucleotides are found in human milk and milk of other species. They are part of the non protein nitrogen fraction of milk. They were first isolated in human milk in 1960. It is not known if they result from the degradation of nucleic acids or if they are actively secreted as a response to a nutritional need of the infant.

Up to 30% of total nitrogen content in human milk is from non protein nitrogen and 2-5% of the non protein nitrogen fraction is made of nucleotides. The level decreases during lactation. After 3 months, the concentration falls to 75% of that in human colostrum. In addition to nucleotides, human milk contains nucleosides and nucleic acids. In all cells the level of RNA is higher than DNA. RNA is therefore an important potential source of nucleotides. All forms can be expressed as “Total Potential Available Nucleosides (TPAN)” (nucleosides being the preferred form of absorption). [2]

In comparison, the non protein nitrogen fraction in cow’s milk only accounts for 2 – 5% of the total nitrogen content. The content of nucleotides in cow’s milk is lower than in human milk.

With advances in analytical methods and development of TPAN approach, the nucleic acid, nucleotide and nucleoside composition of human milk is now better known.

Leach et al in 1995 identified in pooled milk from 100 European mothers:

- 48% ± 8% of the TPAN was present as RNA
- 36% ± 10% of the TPAN was present as nucleotides
- 9% ± 4% of the TPAN was present as nucleosides
- 8% ± 6% of the TPAN was present as nucleotides adducts

2. Absorption of exogenous nucleotides and possible importance

Nucleosides are the preferred form of absorption (90% of the nucleosides and bases are absorbed into the enterocyte). Once absorbed, most of the nucleosides and bases are degraded within the enterocyte. [4]

The relative contribution of dietary nucleotides to the total pool in specific organs or in the entire body is not known. Animal studies indicate that 2-5% of dietary nucleotides are incorporated into tissue pools, primarily within the small intestine, liver and skeletal muscle. Incorporation into tissues is increased at younger ages. [4]

Nucleic acids and their components are also released by the cellular turnover of the intestinal mucosa. The metabolic fate of these endogenously released nucleic acids is not known. In addition extensive salvage of purine and pyrimidine bases has been demonstrated in intestinal tissues.

Although, nucleotides are not essential nutrients as they can be synthesised by the body, it is thought that dietary nucleotides may become essentials when the endogenous supply is insufficient (e.g. rapid growth, recovery, certain disease states).

3. Nucleotide roles and functions

Nucleotides are structural elements for RNA and DNA. They encode genetic information. In addition, they are involved in a wide range of metabolic functions: energy metabolism (e.g. ATP), physiological mediators, components of coenzymes, etc.

In vitro, animal and human studies to date have essentially investigated the effects of nucleotides on gastrointestinal and immunological systems.

Intestinal growth, development and response to injury

In vitro studies have shown the exogenous effect of nucleotides on the proliferation and differentiation of intestinal cell lines. [4]

There are a number of animal studies which have shown that dietary nucleotides have an effect on gut maturation and recovery. [4]

Uauy et al (1990) observed increased mucosal protein and DNA, villus height, activities of enzymes in rats which received diet supplemented with nucleotides at a level of 0.80%.

Quan et al (1991) reported that dietary nucleotides decreased mortality and intestinal inflammation and increased disaccharides activities in rats following induced intestinal injury.

Intestinal microflora

Bifidobacteria (health promoting bacteria) are predominant in stools of breast-fed infants. The growth of bifidobacteria can be enhanced in vitro with a selective medium containing nucleic acids. [4]

A clinical study conducted by Gil et al (1986), showed differences in percentages of lactobacilli and bifidobacteria in stools of infants fed nucleotide supplemented formula compared to infants fed non supplemented formula. However the number of subject was small and children were not randomly allocated. [4]

An other study from Balmer et al (1994) did not support the hypothesis that the intestinal microflora of infants fed nucleotide supplemented formula is closer to that of breast-fed infants. [1]

Hepatic effects

The hepatic supply of nucleotides is maintained through de novo synthesis and salvage pathways. However, extra cellular nucleotides may be important to help in the growth and regeneration after injury.

Some animal studies (Ogoshi et al 1985, 1988) have shown that nucleotides and nucleosides administered parenterally improve hepatic function and promote earlier restoration of nitrogen balance following liver injury or hepactomy. [4]

Immune function and infection

There are a number of in vitro, animal and human studies which suggest an effect of nucleotides on cellular and humoral immunity.

Although mechanisms are not fully known and understood, it appears nucleotides may stimulate the immune system via different pathways: lymphocyte activation, proliferation of natural killer cells, macrophage activity, increased the production of other factors that modulate the immune system, etc.

Some animal studies have shown that nucleotide supplementation is associated with increased resistance to challenge with *Staphilococcus aureus* and *Candida albicans* (Kulkarni et al 1986). [4]

More recently, human studies have investigated the effect of nucleotide supplementation on infants.

Premature infants:
Navarro et al (1996) examined the effects of nucleotide supplementation at a level of 20mg/L in a randomised clinical study involving 32 infants. Levels in IgM and IgA were higher in infants fed nucleotides. This study was conducted on a small number of infants using a level of supplementation lower than the TPAN level measured by Leach et al in 1995. [3]

Full term infants:
Pickering et al (1998) used a supplementation level of 72 mg/L equivalent to the TPAN level identified by Leach et al. In this randomised study involving 311 infants, the antibody responses to diphteria and hemophilus influenza were higher at age 7 months for diphteria and up to age 12 months for hemophilus influenza. However, these effects may be transient. [3]

Kuo-Inn et al (2000) observed a lower risk of diarrhoea from 8 to 48 weeks in infants supplemented with nucleotides at the TPAN level. Infants also had a higher level of IgA. The number of infants for this randomised study was 336. [3]

Effects on lipids

Some studies have investigated effects and interactions between nucleotides and lipids such as LCPUFAs.

Some data suggests that nucleotides may play a role in the conversion of 18 carbon fatty acids into 20-22 carbon fatty acids. However, other studies have found no effect of dietary nucleotides upon LCPUFAs. [4]

A study reported that term infants fed nucleotide supplemented formula or breast milk had lower VLDL and higher HDL levels at 1 month of age compared with infants fed unsupplemented formula. Some authors suggest nucleotides may enhance lipoprotein synthesis. However, some studies have found no effect of nucleotide supplemented formulas on lipoprotein levels in infants. [4]

KEY POINTS

1. Nucleotides are present in human milk.
2. Nucleotides are the structural units of DNA and RNA. They are important structural and functional compounds. Based on studies, it is thought that nucleotides play a role in gastrointestinal growth, maturation and recovery. It is also thought that nucleotides play a role in cellular and humoral immunity.
3. Nucleotides from the diet may be important in supplementing endogenous levels where these may not be sufficient to meet the needs of the body in times of growth, recovery or certain diseases.

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