Nucleotides- An Overview

Nucleotides are organic molecules which make up the building blocks of DNA and RNA.

Nucleotides are composed of three basic units; a nitrogenous base, a 5-carbon sugar, and a phosphate group. These units are held together by bonds which involve the sharing of electrons between each of the units. This type of chemical bond is known as a covalent bond.

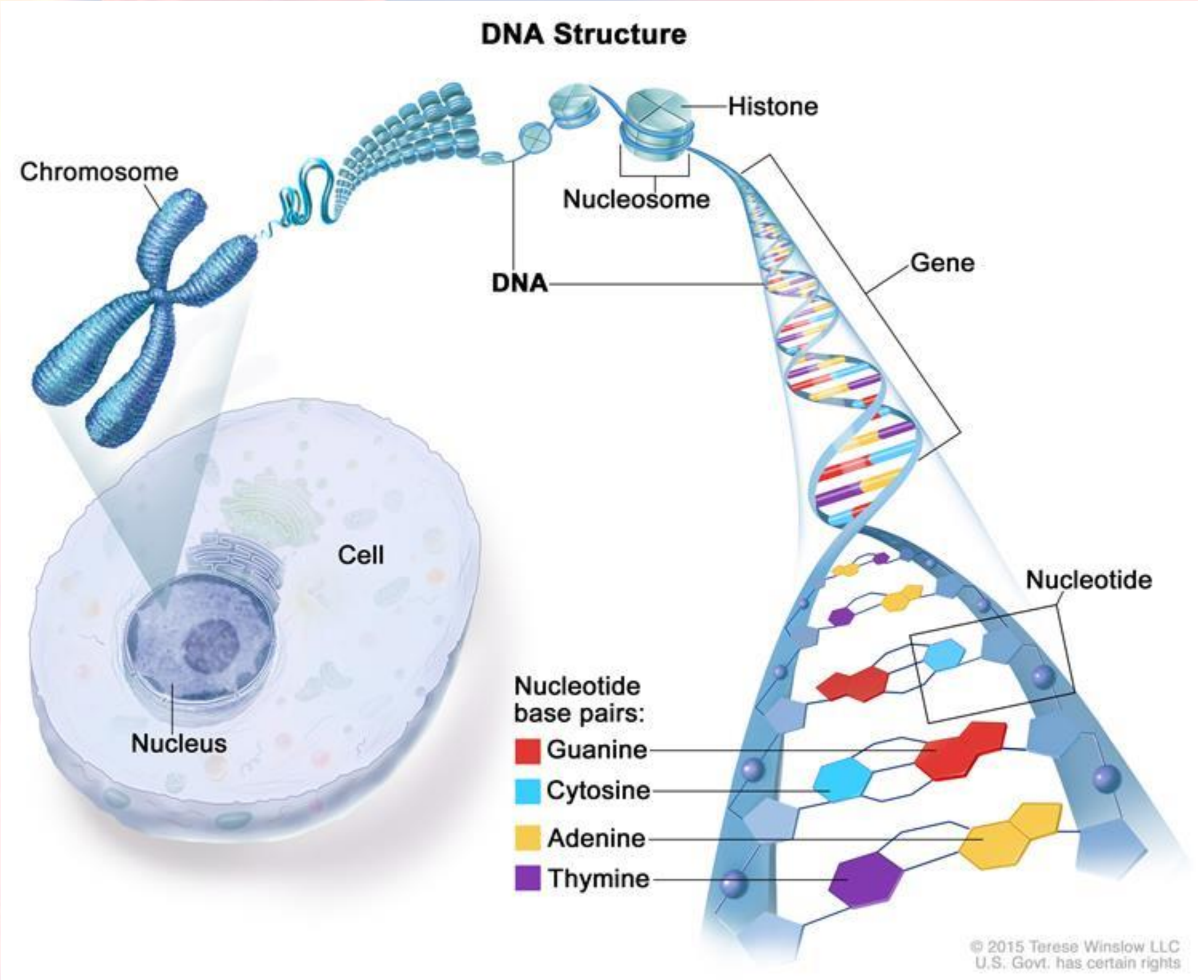
Nucleotides differ according to the type of nitrogenous base and sugar units that exist in their structure. For example, there are in total five different nitrogenous bases that can be used to complete the structure of a nucleotide, these include Uracil, Thymine, Cytosine Adenine and Guanosine. The names of individual nucleotides depend largely on the types of molecular units of which they're formed. For example, a nucleotide that includes Adenosine, the 5-carbon sugar ribose, and a single phosphate is called Adenosine-5-Monophosphate (AMP). A nucleotide that includes Guanosine instead of Adenosine is simply called Guanosine-5-Monophosphate (GMP). A nucleotide that includes Guanosine, phosphate but includes deoxyribose instead of ribose, is simply called a Deoxy-Guanosine-5-Monophosphate (dGMP).

There are a number of different nucleotides in total; AMP, CMP TMP, GMP, UMP with ribose as the sugar unit, and dAMP, dCMP, dTMP, dGMP. dUMP with deoxyribose as the sugar unit. Ribose and deoxyribose are the only two sugar units which form nucleotides and these five-carbon long monosaccharides are also used to form RNA and DNA, respectively. A phosphate group is simply a molecule containing a phosphorus atom bonded to four oxygen one of which involves a double bond, phosphate is also the conjugate base of phosphoric acid.

Nucleotides are not to be confused with nucleosides which are similar, except a nucleosides molecular composition excludes the phosphate group and are only composed of the nitrogenous base and the sugar unit.

Therefore, a nucleotide is also a phosphate ester of a nucleoside.

Nucleotides are more broadly classified into two groups based on the type of nitrogenous base it has in its structure. Pyrimidines are nucleotides which include Uracil, Thymine, and Cytosine as nitrogenous bases in their structure whilst Purines include Adenine and Guanosine.



Nucleotides can be synthesised de novo mostly in the cytosol using amino acids substrates but they can also be synthesised via the salvage pathway using free bases (Berg, Tymoczko and Stryer, 2002). However, much of the substrates for nucleotide synthesis comes from the diet. Some foods contain higher concentrations of nucleotides than others, however, nucleotide metabolism can easily exceed daily dietary intake especially during times of rapid growth and development, stress or illness. Absorption of dietary nucleotides is likely to occur in the small intestines via facilitated diffusion and Na+ dependent transporters (Schwenk et al., 1984; Jakobs and Paterson, 1986; Bronk et al., 1987; Bronk and Hastewell, 1987; Jarvis 1989).

Historically, nucleotides have been termed "conditionally essential" because of their known biological importance. To date, there is a substantial amount of animal and human evidence to suggest that nucleotides are essential for achieving optimal immune function and are important for the maintenance of gut health. Findings from several trials also suggest nucleotide supplementation may also have ergogenic effects.

Animal studies

In a study involving mice, the mortality rate for mice that were given a nucleotide-free diet for a period of several weeks prior to Staphylococcus *Aureus* infection was 100%, whereas the mortality rate was only 56% for mice whose diets were supplemented with nucleotides. The authors concluded that the restriction of dietary nucleotides increased the risk of mortality from Staphylococcus sepsis whereas supplementation decreased this risk (Kulkarni et al., 1986). A similar study was later conducted whereby mice on a nucleotide-free diet that had been exposed to Candida *Albicans* had a significantly decreased mean survival-time compared to mice who were fed diets containing sources of nucleotides. The recovery of viable Candida *Albicans* in the spleen was also much higher in the mice on nucleotide restricted diets implicating dietary nucleotides as playing a role in the phagocytosis and clearance of the pathogen (Fanslow et al., 1988). Research on fish showed the addition of nucleotides to the diet increased immune response and increased resistance to Streptococcus *Iniae* infection. Additionally, nucleotides also promoted better growth of fish and increased the feed conversion ratio compared to the control fish. These effects were greatest in the fish who had the highest intake of nucleotides (Tahmasebi-Kohyani et al., 2011). This evidence suggests nucleotide offer resistance against pathogenic infections by acting as immunomodulators and nucleotides may also enhance growth by increasing utilisation of food energy.

It has been previously shown that extended fasting and malnutrition can negatively affect intestinal health and that nucleotides may play an important role in the growth, maintenance and repair of intestinal tissue. In a study of weanling rats with lactose induced diarrhoea and malnutrition, rats supplemented with nucleotides had improved recovery compared to non-supplemented controls (Nunez et al., 1990). A separate study on weanling rats with lactose induced diarrhoea found histological abnormalities from a lactose enriched diet including loss of microvilli, decreased number of goblet cells and enlarged mitochondria with lower cristae density. After supplementation with nucleotides, histological examination showed greater improvements in intestinal health and restoration of cellular structures compared to the non-supplemented control group (Bueno et al., 1994).

In a study involving older rats that have a naturally lower capacity for intestinal repair, the rats were deprived of food for five days and then were fed a nucleotide-free diet or a nucleotide supplemented diet for either three or six days. Deprivation of food significantly decreased growth markers of the intestinal mucosa, markers of cell differentiation in parts of the small intestine, as well as the ATP levels. Refeeding led to some restoration, however, rats on a nucleotide-free diet had a much slower and incomplete recovery compared to those on a nucleotide supplemented diet (Ortega et al., 1995). The authors of this study suggest nucleotides play a role in accelerating normal growth and recovery of intestinal tissue after food deprivation related stress, which may be of relevance to the elderly where malnutrition is prevalent.

Other work supports the importance of nucleotides in the normal growth and maintenance of intestinal health by showing a deprivation of dietary nucleotides decreases protein synthesis in the small intestine and in the liver (Lopez-Navarro et al., 1996). Whilst others have shown in vitro, nucleotides encourage the maturation of enterocytes, whilst in vivo, nucleotides increase digestive enzyme activity of rat intestinal mucosa as well (Sato et al., 1999). Later research showed again nucleotides play a role in the physiological restoration of intestinal abnormalities resulting from lactose induced diarrhea including the restoration of mitochondrial function (Arnaud et al., 2003).

Intra-uterine growth-restricted piglets have shown to exhibit decreased villous height, crypt depth and key markers of immune function compared to normal birth weight piglets. When growth-restricted piglets were given nucleotides increased villous height and activity of leukocytes, IgA, IL-1β, as well as an increased feed conversion ratio, were observed (Che et al., 2016). This research suggests nucleotides may be able to reverse under-feeding associated intestinal abnormalities whilst improving markers of immune function.

Some animal studies have even suggested supplementation with nucleotides may decrease stress responses. This was evidenced in one study by fish having lower plasma cortisol levels when handled and crowded (Tahmasebi-Kohyani et al., 2011) and in another where fish showed again lower blood glucose and cortisol levels in response to acute stress event when their diets were supplemented with nucleotides (Palermo et al., 2013).

Research using animal models offers the theoretical basis that intestinal repair, restoration of immune function, increased utilisation of nutrients and psychophysiological changes result from nucleotide supplementation which could be translatable to humans.

So what evidence is there that nucleotide supplementation is beneficial for humans? Are there any studies on humans that support the findings in animal models?

In short, yes, and then some…

Human studies

A clinical trial investigated differences in immune cell activity between breast-fed infants, infants fed nucleotide-supplemented formula and infants fed only standard formula. The results of this trial showed infants fed with nucleotide-supplemented formula had a higher natural killer cell (NK-cell) activity than infants fed standard formula. The NK-cell activity of the nucleotide group was also comparable to the breast milk group, with breast milk being a naturally rich source of nucleotides. Interleukin-2 production was also higher in the nucleotide group compared to the standard formula groups indicating an immunostimulatory effect as a result of nucleotide-supplemented formula feeding (Carver et al., 1991).

In a separate clinical study involving supplementation of infant formula with nucleotides, supplementation lowered the incidence of diarrhoea and enhanced catch-up growth in low birth weight infants. Furthermore, infants who were supplemented with nucleotides had greater weight gains than infants fed a standard formula (Cosgrove, Davies and Jenkins, 1996) which is supported by previous animal research. In another trial, infants randomly assigned to receive nucleotide supplemented formula had increased gut microbiota ratios of bifidobacterium as a result of nucleotide supplementation which was greater than the standard formula-fed controls and comparable to breastfed infants (Singhal et al., 2008). Later research showed infants supplemented with nucleotides had improved growth rates compared to controls with greater head circumference recorded at eight, sixteen and twenty weeks and greater body weights at eight weeks (Singhal et al., 2010).

In a placebo-controlled trial, the immune and stress responses were measured in exercise-trained adult males before and after endurance exercise, at baseline and after sixty days of Nucleotide supplementation. Following exercise, cortisol was raised and salivary IgA levels were lower in all groups. However, in the nucleotide group, cortisol and salivary IgA levels were significantly lower and higher in the nucleotide group, respectively, compared to the placebo group (Mc Naughton, Bentley and Koeppel, 2006).

Another placebo-controlled trial involving intense exercise showed similar findings with post-exercise cortisol response and IgA response being the lowest and highest, respectively, in the group taking nucleotides compared to the control and placebo groups (Mc Naughton, Bentley and Koeppel, 2007). A similar double-blinded, placebo-controlled trial measured immune markers in males after a progressive running protocol which was undertaken before and at fourteen days after sublingual nucleotide supplementation. Immune markers were depressed following exercise in all groups. However, after fourteen days of supplementation, significant increases in serum IgA and NK-cell count were seen in the nucleotide group as well a significant attenuation of post-exercise suppression of salivary IgA compared to the placebo group and compared to before supplementation began (Ostojic and Obrenovic, 2012).

Sublingual nucleotides were shown again in to improve markers of immune function including increases in Nk-cells, serum immunoglobulins A, M and G, at a 50mg dose. Furthermore, this study also showed nucleotides were able to significantly increase run time to exhaustion after fourteen days of supplementation compared to the placebo group (Ostojic, Idrizovic and Stojanovic, 2013).

Nucleotides have also shown to alleviate exercise-induced immunosuppression and some findings so far suggest they may also have ergogenic effects. In a trial of elite martial arts athletes, 480mg of nucleotides were given daily for four weeks to assess the benefits of nucleotides on the immunosuppressant effects of exercise. After intense cycling to exhaustion, both groups had suppressed immune function. However, the nucleotide supplemented group recovered levels of blood lymphocytes significantly faster than the placebo group (Riera et al., 2013).

In a double-blinded cross-over style study involving trained men and women, a nucleotide-vitamin complex was pre-loaded for two weeks during which participants maintained their exercise regime. At the beginning of the third-week participants undertook an acute and heavy resistance training protocol after which findings were recorded. Nucleotide supplementation was able to offset some of the exercise-induced physiological changes which resulted in lowers levels of cortisol and myeloperoxidase both which were uninhibited in the placebo group. Additionally, a significantly greater increase in isometric force from baseline was seen in the nucleotide group compared to the placebo group (Sterczala et al., 2016).

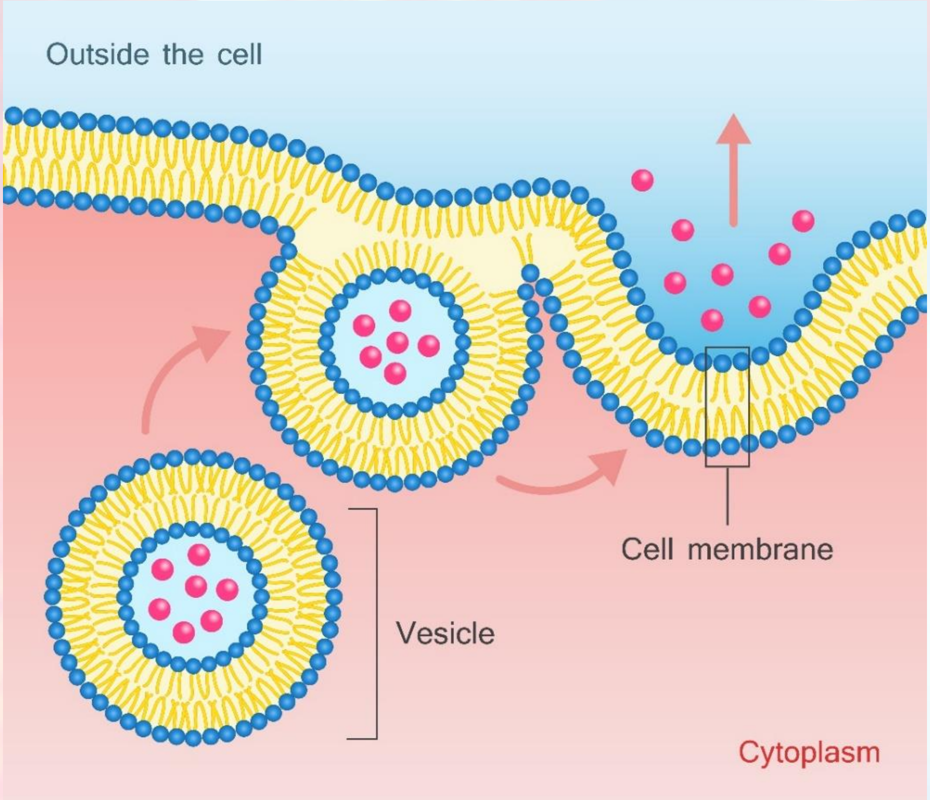
Conclusion

Taken together, evidence from humans coupled with support from animal studies, nucleotides modulate immune function at all stages of life, play a key role in the renewal and proliferation of intestinal cells, reduces exercise-induced stress responses and may also have ergogenic effects. Therefore nucleotides should form a fundamental part of any therapy seeking to optimise immune function and gut health. Furthermore, nucleotides may also be useful for athletes or those involved in exercise for maintaining a healthy immune system and for improving parameters of exercise performance.

There may also be many more unexplored benefits from nucleotide supplementation which further research should investigate.

Nucleotides in Liposomal Formulas

By their very nature, liposomes have the extraordinary advantage of being able to carry a wide range of compounds making them the ideal and far superior method for effectively delivering nutrients. What makes liposomes extra special is that they can deliver their contents directly into the cells of the body, protecting the contents from digestion or oxidation before the final delivery and without the consumption of mitochondrial energy.



The huge potential offered by Nucleotides combined with the targeted delivery of liposomes makes the possibility of a truly "super supplement" very real indeed.

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