Know your NUCLEOTIDES

Dr Peter Köppel and **Rachel Hoyle** investigate the importance of nucleotide nutrition in relation to the gut.

In Japan, infant formula has been supplemented with nucleotides since 1965, but it took the rest of the world another 20 to 30 years to catch onto the concept.

Supplementation of infant formula is reported to have beneficial effects on faecal microbiota, by increasing the count of 'friendly' *bifidobacteria*[1], decreasing the count of enterobacteria, reducing the incidence of diarrhoea[2] and modulating immune function[3].

Yet, the proportion of the population which understands the importance of dietary nucleotides – and that includes those in healthcare professions as well – is miniscule; nearly everyone with an interest in health understands the importance of macronutrients, including proteins and their composite amino acids, fats (along with healthy essential fatty acids) and carbohydrates (especially complex ones from plant-source foods). In terms of micronutrients, we're all familiar with vitamins and minerals and more are becoming aware of the vital role played by plant compounds (phytonutrients) that act as anti-inflammatory agents, antioxidants (free radical scavengers) and also help modulate a wide range of key metabolic processes in all our body systems (for example, endocrine, immune, cardiovascular, musculo-skeletal, brain/nervous system, dermis [skin, hair, nails]).

But who's ready to accept another, whole category of nutrient, namely nucleotides? We believe any person who's spent time digesting (pun intended) the science around these nutrients will be convinced. And it's why we feel it's so important to get the word out far and wide.

This has triggered research by us into whether nucleotides are important in adult health and if supplemental nucleotides can enhance health or prevent or treat clinical conditions.

WHAT ARE NUCLEOTIDES?

DNA is the blueprint of life and nucleotides are the building blocks of the double helix. Nucleotides consist of a nitrogen-containing base (mostly adenine, thymine, cytosine, guanine and uracil), a five-carbon sugar (ribose or deoxyribose) and one to three phosphate groups.

FUNCTIONS

Obviously, nucleotides are an integral part of the structure of DNA and RNA and are essential compounds in the energy transfer system (i.e. in ATP, NADP, NADH)[4, 5], thus it has been assumed that they play an important role in carbohydrate, lipid, protein and

nucleic acid metabolism[3,6].

It is anticipated that cells of tissues which are growing rapidly or have a high turnover rate will have a higher requirement for nucleotides, for DNA/RNA synthesis, than cells of tissues growing more slowly. Such cells include enterocytes in the gastrointestinal tract and cells of the immune system[4].

THE SOURCE OF NUCLEOTIDES

Nucleotides can be synthesised by the body *de novo* from some amino acids, for example, glutamine, aspartate, glycine and formate[6]. Nucleotides, nucleosides, nucleic acids, bases and deoxyribose can also be salvaged from DNA and RNA degradation or from the diet and be recycled[6].

It appears that the intestinal mucosa, bone marrow haematopoietic cells and lymphoid tissue have a limited capacity for *de novo* synthesis and probably depend more heavily on the salvage pathways that supply nucleotides from the diet or from the degradation of DNA and RNA[3,7]. Thus, if the exogenous supply of nucleotides is low, these tissues may struggle to fulfil their need for nucleotides.

DIETARY NUCLEOTIDE METABOLISM

Nucleotides are a normal component of the adult human diet and are ingested in the form of nucleoproteins[5]. Proteases and nucleases degrade nucleoproteins and nucleic acids into nucleotides; phosphatases and nucleotidases cleave the phosphate group(s) to yield nucleosides.

Dietary nucleotides are not considered essential in the traditional sense because they can be synthesised by the body[7]. However, a number of investigators have described dietary nucleotides as conditionally essential in a variety of clinical situations and during development[7,8].

But it's the intestinal tract that has the highest rate of cellular turnover in the body, this rate being greater during periods of infection or when the gut mucosa has been damaged and is in need of repair. Additionally, the 100 trillion or so microbes that make up the gut's microbiome turn over even more rapidly, and have an insatiable requirement for nucleotides to build RNA and DNA within the nucleus of every new cell. There is approximately 1,000 times more RNA in a typical cell than DNA, most of it present as messenger (mRNA), transfer (tRNA) and ribosomal (rRNA) RNA, with the all-important mRNA comprising usually around just one to five per cent of total cellular RNA.

The slides below show the cross-section of the gut, and how under 'stress' the villi development of an animal becomes stunted and lesions start to form. Just three weeks of nucleotide supplementation enabled the villi to grow to optimal levels (25 per cent higher), and there was improved morphology and surface area available for nutrient absorption[9].

Histological slides from Burrells et al.

ARE DIETARY NUCLEOTIDES ESSENTIAL?

Dietary nucleotides could theoretically become conditionally essential under three circumstances[10]:

- During periods of insufficient intake.
- Where there is a high demand/high rate of growth, and
- In the presence of disease[3].

It has been demonstrated that enterocytes, whilst having a high demand for nucleotides, have a low capacity for *de novo* synthesis[8]. Thus, it could be postulated that enterocytes rely more heavily on an exogenous supply of nucleotides from the diet. Further, if the dietary intake of nucleotides is low, due to a restrictive diet, these compounds could be considered conditionally essential.

In a study examining the effect of a nucleotide supplement on symptoms in Irritable Bowel Syndrome, it was felt that dietary nucleotides were probably not essential in healthy people but under conditions of stress, illness or a poor diet nucleotides may well become semi-essential[11].

THE EVIDENCE FOR ESSENTIALITY – DO DIETS DEVOID OF NUCLEOTIDES CAUSE PROBLEMS?

The supplementation of infant formula with nucleotides is considered beneficial since it has been found to influence lipid metabolism, immunity and tissue growth, development and repair[12]. The majority of standard infant formulas are now supplemented with nucleotides.

Studies have demonstrated that babies fed nucleotide-supplemented infant formula have increased 'friendly' *bifidobacteria* counts in faeces compared to infants fed standard formula milk, but counts were still lower than found in breastfed babies[13].

Nucleotide supplemented formulas have also decreased the prevalence and duration of diarrhoeal disease in infants but this was not associated with changes in faecal microflora[14]. Thus, mechanisms other than the modification of faecal microflora, for example, effects on the immune system, might be responsible for the reduction in diarrhoeal disease.

Infant studies also suggest those receiving nucleotide supplemented formula have an improved antibody response following immunisation[15,16].

Feeding a nucleotide supplemented diet to rats has also demonstrated gastrointestinal benefits. Rats with experimentally induced ulcerative ileitis fed nucleotide-supplemented enteral and parenteral feeds show accelerated healing of small-bowel ulcers compared with rats fed a standard formula[14]. In another study, weanling rats fed a nucleoside-supplemented diet saw increased villus height and enhanced gut maturation compared to rats fed a standard diet[17].

DIETARY NUCLEOTIDES AND DEFICIENCIES: WHERE DO DIETARY NUCLEOTIDES COME FROM?

The short answer is, from a lot of foods that most of us eat very little of these days. The richest sources are offal meats, yeast extracts and fermented foods, such as traditionally fermented tofu, tempeh and natto (Fig. 2, overleaf). Most plant foods contain very low levels of nucleotides (Fig. 2), with broccoli being an exception.

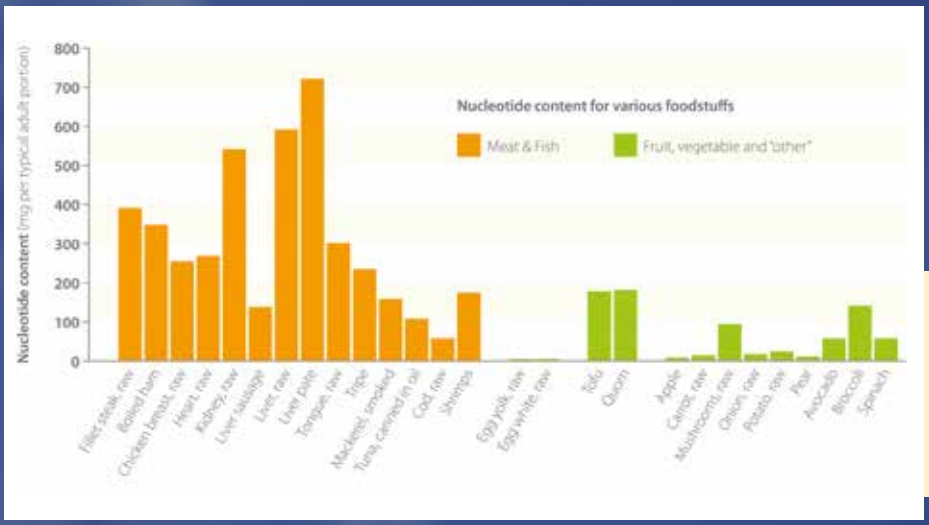


Fig 2. Nucleotide content (mg) of standard portions of various foods (analysis by Pro Bio AG, Switzerland). *IHCAN* magazine Sept 2011 (Verkerk & Koeppel). Lifestyle induced essentiality: Science takes another look at nucleotide supplementation.

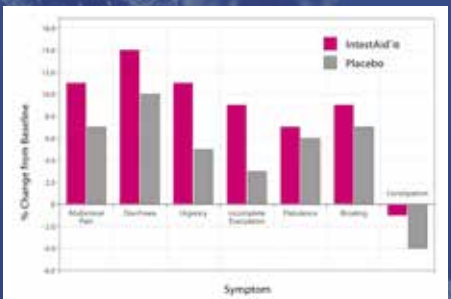
NUCLEOTIDE SUPPLEMENTATION

A number of studies examining the effects of supplemental nucleotides have also been carried out in differing populations and for different beneficial effects.

Treatment by dietary nucleotides* has been shown to be beneficial for people with IBS. *Using a nucleotide supplement containing a balanced formula of pyrimidine and purine nucleotides[11].

A total of 37 people with IBS found that taking a nucleotide-based supplement (one 500mg capsule three times daily) resulted in a statistically significant improvement in three of seven symptom scores of IBS compared to placebo[11]. Namely, abdominal pain, urgency and a feeling of incomplete evacuation. Severity of diarrhoea was also improved. The improvements were modest, as would be expected in a community sample (i.e. not drawn from a clinical trial population), but no adverse side effects were reported.

The authors speculate that improved gut function could be via similar mechanisms found in animal studies, namely increased mucosal protein, DNA and villus height.



GRAPH SHOWING SYMPTOM IMPROVEMENTS

CONCLUSION

It is clear that nucleotides are involved in many aspects of cellular metabolism, growth and immune function. Their precise mechanism of action remains to be fully understood.

The addition of nucleotides to infant formula milk and more recently to enteral food clearly demonstrates a consensus in the scientific community that nucleotides are essential for normal functioning of the body.

It is accepted that dietary nucleotides are conditionally essential under conditions of immunological stress, during periods of rapid growth or insufficient intake and for disease or injury to the gastrointestinal tract. Much of this research has been carried out in animals, but there are encouraging results from human trials of enteral food, and the independent clinical studies with IBS[11], URTI (colds) infections[18], stress (intensive[19], moderate endurance[20] and resistance[21]).

The more we understand about the roles nucleotides play – particularly in areas of the body with rapid cellular turnover rates, most notably the gut mucosa, the gut microbiome and the immune system – the more we realise that nucleotides may not just be 'conditionally essential', but essential for most of us, most of the time. Our high stress levels, including exercise-induced stress, along with our ever-decreasing nucleotide intake from food sources in the Western diet, and even trauma and injury, will all contribute to dramatically increasing our dietary requirement for these nutrients. ***in Focus***

For references, please visit www.ihcan-mag.com/References

ABOUT THE AUTHORS

■ Dr Peter Köppel has a PhD in Biochemistry and Immunology. He was trained in Biochemistry, with a special interest in clinical immunology, at the Institute of Virology at the University of Zürich. He then worked as a researcher in osteoarthritis and osteoporosis in a pharmaceutical company in Basel. As Managing Director of Chemoforma and Pro Bio, in Switzerland, Dr Köppel has, for over 20 years, led research and production of special nucleotide ingredients for both animal and human nutrition. This has led him to being seen as one of the world's foremost experts on nucleotides for health and performance.

■ Rachel Hoyle, BSc, a science graduate, has been involved in the development of special nucleotide-based products, in collaboration with Dr Peter Köppel, since the 1990s. Her initial responsibility was to develop natural products that reduce the dependency on antibiotics in animal nutrition. More recently, Rachel has devoted her time to the research and development of nucleotide supplements for human health. Her company, Nucleotide Nutrition, now markets these products, which are all based on the Nutri-tide formula.