NUCLEOTIDES: SPECULATION ON LIFESTYLE-INDUCED ESSENTIALITY

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During the course of our lives, few of us have knowingly encountered scientific revelations that suggest deficiency of an entire category of micronutrients may be contributing unnecessarily to dysfunctional health or disease. We tend to assume that the science of micronutrients is well understood and relatively complete - a branch of science that's matured considerably since Albert Szent-Györgyi and a fellow researcher's discovery in 1931 of vitamin C, the molecule responsible for the long-known anti-scurvy activity of lemons and limes.

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Today, we find ourselves in an era, not where a new category of micronutrients has been discovered, but one when the importance of an already recognised micronutrient category - that until now has been considered by researchers in the field only as 'conditionally essential' (1,2) - might actually be seminally important for good health. In fact, based on its plethora of properties and activities, ranging from its role in DNA repair, gut mucosal repair and immune function, to name but a few, it may be just a matter of time before this category is generally regarded as 'essential' to human health. The micronutrient category we're referring to is of course nucleotides. In this article, we'd like to take you through some of the main landmarks in the story of discovery that leads us to this powerful speculation.

NUCLEOTIDES

Nucleotides are ubiquitous, low molecular weight, intracellular compounds that are best known as the key structural components of the 'molecule of life', deoxyribonucleic acid, or DNA. They are comprised of a nitrogenous base (= nucleobase), a pentose sugar (ribose or deoxyribose) and one to three phosphate groups. In DNA's most familiar double helix structure, two nucleobases are loosely bonded by hydrogen to form the steps in DNA's ladder, while the pentose-phosphate molecules form the backbone of the spiral.

The term ribonucleotide refers to molecules where the pentose sugar is ribose, not deoxyribose. Ribonucleotides are, in turn, categorised according to their nucleobase types; purine ribonucleotides are those where the ribose is bound to any of the purine bases adenine (A), guanine (G) or inosine (I), while pyrimidine nucleotides are those where the ribose is linked to any of the pyrimidine bases cytosine (C), uracil (U) or thymine (T).

It is clear that the requirement for nucleotides will depend on the rate of requirement of new cells. Cellular proliferation will be greatest at times of rapid growth and development, but even in adults, there are particular times where proliferation rates exceed those associated with normal metabolism. The immune system, for example, especially when reacting to infection, can ramp up output of specialist defence cells such as neutrophils dramatically (3). 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 damage to the gut mucosa is in need of repair (4).

The question is: can the body produce or salvage the necessary nucleotide building blocks to produce all these new cells, even when demand is at its highest? Extensive research has revealed that the body can both synthesise new nucleotides, as well as being able to salvage 'spare parts' to allow the production of vital DNA and RNA for each cell. These two pathways are referred to, respectively, as the de novo synthesis and salvage pathways (5).

However, it has also become apparent that there is a third and important way in which nucleotides are supplied to the cells of our bodies. This is from exogenous sources - through the diet. During periods of greatest cellular proliferation, it seems endogenous sources may not be sufficient for the body's needs. This has led to a view that dietary nucleotides are 'conditionally essential' (1,2). It is also important to note that the two endogenous pathways are costly in metabolic energy terms, making dietary intake of nucleotides particularly important when the body's resources are already under pressure (6).

WHEN DOES THE BODY DEMAND NUCLEOTIDES MOST?

Research to date reveals clear evidence for a particularly high nucleotide requirement at times of rapid growth, malnutrition, infection and injury (2,7,8). This understanding has, in turn, spawned research that has demonstrated the benefit of supplemental dietary nucleotides in particular situations:

1. in infant formulae with the aim of mimicking the nucleotide content of breast milk (2, 9);
2. to help enhance immunity and gastrointestinal health in malnourished young children (8,10,11);
3. to support adult immunity following surgery and transplant (12);
4. to help offset the effects of oxidative stress in athletes (13, 14);
5. for patients with irritable bowel syndrome (15).

What's more, recent mechanistic findings that reveal nucleotides' fundamental role in DNA repair and the maintenance of chromosomal stability (16) - two of the most important cancer protective factors - is likely to stimulate further research on the potential role of supplemental nucleotides in cancer prevention strategies.