Understanding Nucleotides and their Mode of Action (Part 1)

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The need to better understand metabolism and nutrition in livestock and aquaculture is driven by the increasing demand for high quality animal products at an affordable price and satisfying the customer's right for residue-free and flawless food. Financial losses due to diseases still strike producers severely everywhere in the world. Often the reason for an outbreak of disease is not obvious but elevated susceptibility to diseases, increased mortalities or reduced meat quality are at least partly triggered by stressful husbandry, overstocking, poorly adjusted feed levels or inferior feed, as well as unsatisfactory water conditions or malnutrition.
Lots of discussions have been launched on ways to maximise performance of animals while simultaneously minimising the use of therapeutic chemicals compromising the environment or supporting drug resistance.
An increasing number of products claiming to enhance health by supporting and enhancing immunity have appeared on the market. Probiotics, prebiotics and synbiotics have been extensively studied in terrestrial animals and the number of success stories from aquaculture is steadily increasing. The trend of both nutritionists and suppliers of additives to combine specific functionalities with food or feed is comprehensible and reasonable. The target must still be to improve feed in terms of nutritional aspects, prevention of diseases and thereby profitable animal husbandry.

Living organisms are semi-closed bio-chemical systems not sealed off from surroundings and therefore exposed to environmental changes as well as to pathogenic challenges. To operate properly organisms need to produce energy and assemble a huge variety of bioactive molecules. This so-called cellular metabolism includes the uptake of nutrients, the synthesis of cellular components, activating or converting the generated molecules and releasing unwanted by-products or waste. All vital functions of an organism occur within cells and every single cell contains the hereditary information needed for regulation of physiologic cell function and for transmitting information to the next generation of cells.
It could be expected that organisms are self-sufficient units that can produce all essential molecules autonomously. Food or feed would then be required merely to supply sufficient energy enabling biochemical reactions executed in cells. However it has been shown that this is not fully true. Although being more or less self-sustaining, there are specific nutrients that must be acquired from the diet in order to maintain physiologic functionality and performance. Essential nutrients are nutrients that are required for normal body functions but cannot be synthesized in a given organism. For most essential nutrients such as vitamins, minerals, fatty acids or amino acids a ranking in terms of nutritional importance was already compiled for different animal species. All essential nutrients must be available in the feed in a specific form and concentration required by the organism. A deficiency of one essential nutrient can not be restored by an excess of another and the nutritional bioavailability is vital for the effective utilisation in the organism.
A second class of nutrients is required from dietary sources when the internal supply can not be guaranteed. During specific circumstances similar characteristics already listed for essential nutrients likewise apply for conditionally essential nutrients. Nature in general has adjusted the supply of raw material based on average needs with temporary peaks of demand. In case the demand is persistently high systemic functions need to be adapted in order to cope with the limited supply of the compound. In most case this has adverse effects on physiology and performance.
Only feeds containing a balance of essential as well as semi-essential nutrients facilitate systemic functions to assure high performance under any circumstances allowing an appropriate handling of health challenges with reduced or no medication.

Nucleotides are chemical compounds that consist of three components: a heterocyclic base, a sugar and one or more phosphate groups. In the most common nucleotides, the base is a derivative of purine or pyrimidine, and the sugar is a five-carbon sugar (pentose). In the first place RNA and nucleotides provide basic building blocks for cell proliferation in fauna and flora. Unhindered cell proliferation is a prerequisite for growth, repair, disease resistance, healing and pre-eminent function of organs and regulatory systems (e.g. the immune system). The most important function of nucleotides is the storage of the genetic information required for identity, optimum physiology and function. Cell proliferation, imperative to the life of all organisms and fundamental to their biological functions, is wholly dependent on nucleotides. For just one single cell to divide, approximately three billion nucleotides are required. In addition, nucleotides have various molecular tasks in cell signaling, metabolism and energy management in every organism, just to mention a few.

For years, nucleic acids and nucleotides were not considered for use in any dietary program. It was assumed that all organisms are able to supply sufficient amounts of nucleotides to meet their physiological demand at any time. However scientific research has discovered remarkable and measurable benefits from supplementing diets with RNA/nucleotides. Nucleotides have universally valid, essential physiological and biochemical functions including e.g. encoding and deciphering genetic information, mediating energy metabolism and cell signalling as well as serving as coenzymes, allosteric effectors and cellular agonists. Changes in their concentrations and availability to cells may have very profound multifaceted effects on metabolism. Various trials demonstrated that RNA/nucleotides not only improve general health of organism but also trigger performance.
For healthy organisms a constant re-supply of nucleotides is very well balanced and appropriately adjusted for response to occasional stress. Any increased demand for nucleotides however, takes time and energy and stresses the body's supply of basic raw materials. During times of extraordinary stress, such as rapid growth, reproduction, environmental change, combating disease and recovery from injury, substantial amounts of additional nucleotides must be readily available for cell multiplication.

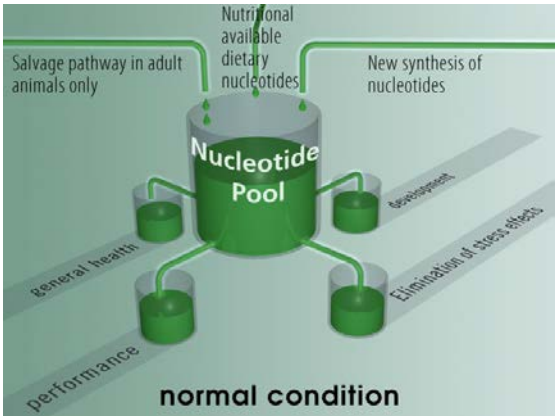

Fig. 1: Under normal conditions the supply of nucleotides is guaranteed through autogenous metabolic and catabolic processes. The "de-novo synthesis" of nucleotides, or the reuse of nucleotides from dead cells (so-called "salvage pathway") and the nutritional available dietary nucleotides allow meeting even temporary peaks in the demand for nucleotides without losses in performance.

The supply of nucleotides is controlled and maintained by the use of three metabolic or catabolic processes (Fig. 1). The limited recycling of nucleotides from dead cells in adult organisms is called "Salvage Pathway". This includes various biochemical and metabolic steps to release the nucleotides. The "de-novo synthesis" of nucleotides is a rather complicated biochemical process including 10-14 different biochemical steps. Raw materials for the synthesis of nucleotides are, among others, amino acids. The synthesis requires energy which needs to be supplied by other metabolic processes in the organism. Last but not least nucleotides may be extracted from the diet as all cellular feed ingredients contain nucleotides in form of DNA present in the nucleus of every cell. This process however is by far the most inefficient one as the DNA is protected from degradation by a specific class of proteins, the so-called Histone proteins. These proteins cover and shield the DNA and prevent it from disintegration and degradation. Nevertheless, under normal conditions these three pathways are sufficient to prevent a depletion of the internal nucleotide pool of the organism.

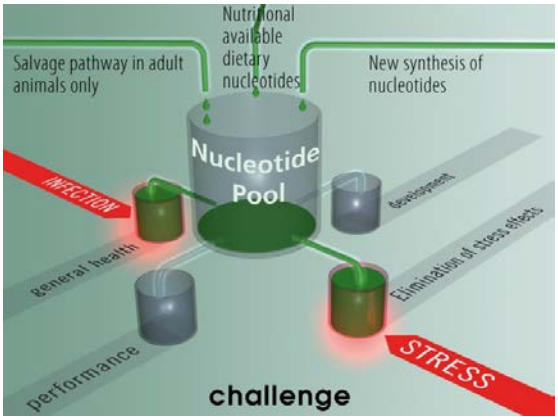

Fig. 2: Under detrimental conditions universal in modern aquaculture, the supply of nucleotides cannot be guaranteed by internal resources. An effective reaction to health challenges or regenerative activities can only be guaranteed at the expense of performance as there are not enough nucleotides available for growth, reproduction or development.

Nowadays various stressors (management, environment, transport) are present under intense farming conditions. Stress turns out to be permanent and continually poses a threat to health. Stress decreases the replication of special and crucial white blood cells and therefore negatively interferes with the body's natural immune defence. Under times of high demand, the accelerated need for nucleotides has to be met either by internal synthesis or salvage, which are insufficient in most cases or from external sources such as the diet (Fig. 2).

Health challenges or stress typically impair performance or development as the nucleotide pool is depleted and may not be refilled adequately leading to retardations in performance or recovery. One approach is to externally supply nucleotides (Fig. 3). This is of utmost importance e.g. for cells of the immune system, gastrointestinal cells or blood cells as these cells are only partially capable of producing nucleotides or lack the potential to synthesize them at all.

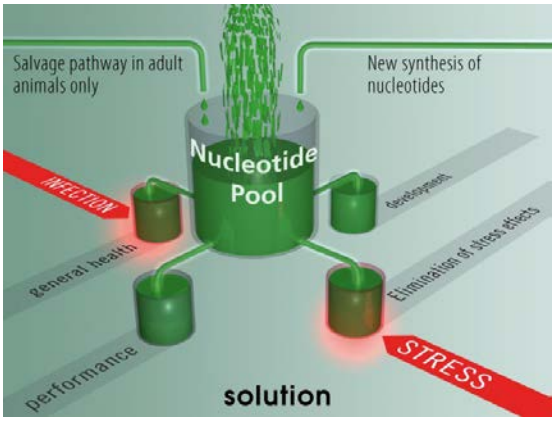

Fig. 3: Supplementing feed with adequate amounts of high-quality nucleotides replenishes the internal pool and thereby supports performance even under adverse conditions. Dietary nucleotides are a management tool to maintain general health, enhance performance and manage the harmful effects of stress.

The addition of nucleotides to the diet helps to refill the internal nucleotide pool thereby supporting processes dependent on unhindered multiplication of cells.

The benefits of RNA/nucleotide supplemented feed on performance and general health as well as on development of young animals was tested in numerous trials in agriculture and aquaculture. In the upcoming parts we will focus on specific trials and results obtained with nucleotide products to get more insight into the mode of action and potential benefits of nucleotide supplemented feeds (to be continued).