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Nucleotide supplementation may offer health benefits in cultured fish

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More study needed

Natural pond productivity may contribute to the nucleotide intake of aquatic animals.

Nucleotides consist of various nitrogenous bases, sugars, and at least one phosphate group. These compounds serve numerous essential physiological and biochemical functions, including encoding and deciphering genetic information, mediating energy metabolism, signaling information to cells, and serving as components of coenzymes.

In addition, nucleotides play important roles in immunity, such as leukocyte proliferation during disease challenge. Recently, a neutrophil extracellular trap made of DNA and certain proteins was discovered as an important defensive mechanism against bacterial infection (Buchanan et al., 2006).

Nucleotide synthesis exists for most cell types, although it is an energy-costly process. Therefore, the roles of exogenously administered nucleotides have long been debated.

Nucleotides and their metabolites have been sparingly studied in fish diets for over 25 years with regard to diet palatability, fish feeding behavior, and biosynthesis of nonessential amino acids. Worldwide attention to the nucleotide supplementation of fish diets was aroused by the reports of Burrells and coauthors in 2001, which indicated that dietary nucleotides enhanced the resistance of salmonids to viral, bacterial, and parasitic infections, and improved the efficacy of vaccination and osmoregulation capacity, as well.

To date, research on the nucleotide nutrition of fish has shown rather consistent and encouraging beneficial results in terms of growth and health management, although most of the suggested explanations remain hypothetical, and systematic research on fish is far from complete.

Chemoattraction

Certain nucleotides act as taste enhancers for many fish and some crustaceans such as lobsters, although fish such as aigo rabbitfish do not respond to any nucleotides (Ishida and Hidaka, 1987). For example, dietary supplementation with 2.5 and 4.1 percent yeast RNA extract, 1.85 percent guanine, or 2.17 percent xanthine significantly increased the cumulative feed intake of rainbow trout over a 12-week period (Rumsey et al., 1992). And dietary supplementation of inosine monophosphate (IMP) at 2,800 mg/kg was reported to enhance the feed intake of largemouth bass by 46 percent compared to a nonsupplemented soybean meal-based diet (Kubitza et al., 1997).

However, the feed intake of largemouth bass fed the soybean meal diet supplemented with either 2,800 or 5,600 mg/kg IMP was inferior to fish fed 10 percent fishmeal. This is possibly because marine organisms have relatively high concentrations of IMP, and the beneficial influence of IMP supplementation is therefore not generally noticeable when fishmeal is added to aquafeed formulations. IMP may serve as a primary candidate for feed attractant research to further explore the complete replacement of fishmeal in aquafeeds.

Growth enhancement, immunity

The growth-enhancing effects of nucleotide mixtures occasionally have been observed in freshwater fish such as tilapia larva and juvenile rainbow trout. But in most published nucleotide studies, nucleotide products did not confer benefits on growth and feed efficiency.

Research on fish also has shown that exogenous nucleotides can influence both humoral and cellular components of the innate immune systems of fish. For example, exogenous nucleotides increase serum complement and lysozyme activity, as well as phagocytosis and the superoxide anion production of head kidney phagocytes in common carp (Sakai et al., 2001). In 2004, Li and coauthors also reported that hybrid striped bass fed a diet with a commercial oligonucleotide supplement had higher blood neutrophil oxidative radical production than fish fed a basal diet. However, the effect of dietary nucleotides on the respiratory burst of head kidney cells in salmonids was not demonstrated.

Ramadan et al. (1994) first observed that dietary supplementation of nucleotides had a marked immuno-potentiating effect on antibody titers after vaccination as well as mitogenic responses of lymphocytes of tilapia after intramuscular injection or direct immersion with formalin-killed (*Aeromonas hydrophila)*. Similar effects were reported with rainbow trout and hybrid striped bass.

Stress responses

One of the most widely accepted hypotheses on the beneficial effects of dietary nucleotides in fish is that stressors such as poor water quality, crowding, and handling in aquaculture place demands on nucleotides beyond those synthesized by the fish or provided in typical feeds. Exogenous nucleotides can result in beneficial effects (Burrells et al., 2001).

The authors of the work above also found that dietary nucleotides can enhance stress tolerance through studies comparing the osmoregulatory capacity and growth performance of Atlantic salmon fed a nucleotide-supplemented diet or a control diet after acute stress by seawater transfer. Dietary nucleotides reduced the serum cortisol levels of healthy rainbow trout after 90 to 120 days of feeding in fish infected with Infectious Pancreatic Necrosis Virus (Leonardi et al., 2003). However, a study with juvenile red drum cultured in brackish water failed to confirm this result (Li et al., 2005).

Disease resistance

Enhanced resistance to various pathogenic bacteria also has been reported for several fish species including salmonids against *Vibrio anguillarum* and *Piscirickettsia salmonis*, common carp against *Aeromonas hydrophila* and hybrid striped bass against *Streptococcus iniae*.

Dietary supplementation with commercial nucleotide products can enhance the resistance of Atlantic salmon and rainbow trout against Infectious Salmon Anemia (ISA) Virus (Burrells et al., 2001) and Infectious Pancreatic Necrosis Virus (Leonardi et al., 2003). In addition, dietary supplementation of nucleotides in conjunction with cypermethrin has been reported to reduce numbers of sea lice and prevent cross-infestations to other fish.

Administration concerns

To date, most publications on nucleotide supplementation for fish have used patented or registered commercial products, so information on concentrations and ratios of various types of nucleotides is limited. Therefore, it is difficult to quantitatively estimate or compare the effects of supplemented nucleotides on the immune responses of various fish species across various published studies.

Also, estimation of optimal dosage, timing, and specific nucleotide type is very difficult. Early studies showed that overadministration of nucleic acids severely depressed the growth and feed intake of rainbow trout (Rumsey et al., 1992). Current evidence on the timing of nucleotide administration is very circumstantial, and the regimes for optimum responses are another important issue surrounding immunostimulant use in aquaculture.

To the best of the authors' knowledge, commercial nucleotide products contain less than 30 percent of pure nucleotides. It is possible that undisclosed, non-nucleotide components also influence animal performance, but complicate current knowledge on nucleotide nutrition. Recent studies by the authors used well-balanced, purified nucleotide mixtures to study nucleotide influences on red drum and Pacific white shrimp, but failed to find any immune-enhancing effect. However, they did confirm the growth-promoting effects of nucleotides on these two species when raised in indoor recirculating systems.

Future research

In all extensive, semi-intensive, and some intensive aquaculture systems, bacteria contribute significantly to the food web. They can be directly eaten by the cultured species or small animals on which the culture species feed. The high concentration of nucleic acids in microbes may partially meet the physiological requirements for nucleotides by these cultured animals. Thus, the application of nucleotide products for large-scale aquaculture in ponds or cages needs further evaluation.

Currently there are numerous gaps in existing knowledge about exogenous nucleotide application to aquatic animals, including aspects of digestion, absorption, and metabolism, as well as influences on various physiological responses, especially the expression of immunogenes and modulation of immunoglobulin production. Additional information is needed in regard to age/size-related responses, appropriate doses, and timing of administration.

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