Gut Inflammation: Effects on Animal Production and Management Approaches

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The more we learn about inflammation, the more it captures a key role in our understanding of disease mechanisms and general health in both people and livestock. The immune system (IS) is incredibly complex and highly effective at combating the universe of pathogens to which we're continually exposed. When the IS is activated, an array of specialized cells, proteins, and signaling molecules are rapidly produced and mobilized to fend off any threat, real or perceived. Providing for such vigilance and flexibility represents a high metabolic cost. Thus, avoiding excessive IS activation can free up metabolic resources (energy and nutrients) to be used elsewhere, such as for growth and reproduction. The practical outcome of this in modern agriculture is that we can boost animal production by limiting inflammation. In fact, the drastic improvements in animal performance realized in this era of advanced disease control, sanitation, and biosecurity has been attributed primarily to minimizing IS activation[1].

Many IS activities are concentrated in the gut, which has more than 70% of all the immune cells in the body[2]. Subtle changes in health status, especially gut health, can significantly impact production even in the absence of overt disease. Enteric challenges can decrease weight gain, feed intake, feed efficiency, survivability, uniformity and the ability to adapt to environmental conditions. Achieving optimal gut health should be of primary concern for producers striving for high animal performance.

Inflammation in the gut can be caused by disease, ingestion of inappropriate feedstuffs, toxins, parasites, and, especially, bacteria and viruses. Microbes can cause both overt disease and (our focus here) low-level, constitutive gut inflammation. For example, epithelial cell turnover and secretions are profoundly affected by the gut bacterial population.[3] Animals raised in germ-free environments grow much faster than their conventional counterparts.[4] This effect can be seen even if the only bacteria present are lactobacillus, so-called "good" bacteria.[5] With this in mind, it makes sense that reducing the bacterial load should increase animal growth. This is why growth-promoting antibiotics are in such widespread use. The growth-promoting effects of antibiotics in the absence of disease are traced to reducing the energetic costs of constitutive, low-level inflammation associated with intestinal bacteria.[6,7]

There are many ways for producers to minimize costly gut inflammation. Often, toxins and parasites can be readily resolved or avoided by careful management. Gut inflammation caused by inappropriate feedstuffs, on the other hand, can be a complicated issue. Fluctuating agricultural markets and cost pressures influence feed formulations

such that nutrient sources of differing quality, digestibility and palatability may be used for each batch of feed. For example, soy is often added to replace fish meal as a protein source in fish feeds, but this plant-based feed clearly causes gut inflammation in carp,[8] salmon,[9,10] and most likely other species. Thus, the economic gains from reduced feed cost must be carefully weighed against production losses arising from increased gut inflammation.

Although gut bacteria are often the primary source of inflammation, the best answer may not lie in wiping out the microbial population with broad spectrum antibiotics. A healthy population of intestinal microbiota confers resistance to pathogenic strains. Some types of bacteria even exhibit anti-inflammatory effects on the mucosa.[11] They also produce enzymes that assist in digestion.[12] The successful, broad marketing of various kinds of probiotics to improve gut health attest to the importance of maintaining a populated digestive tract.[13]

One alternative to using broad spectrum antibiotics to ameliorate gut inflammation and thus promote maximum animal productivity is to use a targeted approach to clear out only harmful microbial invaders. Theoretically, the pathogenic load can be reduced while leaving the beneficial microbes intact. This is essentially the mechanism by which probiotics work, but these effects are often weak and variable, and a targeted strong-arm method—namely, drugs— generally requires a specific diagnosis. For example, egg-derived antibodies targeted against rotavirus or parvovirus are effective for those viruses, respectively, but completely inert with regards to other organisms.[14,15] In the absence of overt disease it is extremely difficult to identify which organism—or, far more likely, group of organisms—is causing the excess inflammation. Many microbes can not be neatly classified as "pathogenic" or "benign." Each animal facility, and in fact each animal, will have a different microbial profile which shifts with age and environmental conditions. Even if they could be identified, the ability to effectively treat only pathogenic strains is severely limited. Finally, even if a lead organism could be identified and a drug designed to selectively destroy it, such a drug's effectiveness would surely be short-lived, as resistant strains rapidly develop and other pathogens move in to replace them. For these reasons, targeting any specific microbe to realize the growth and performance benefits of decreased gut inflammation in most cases is largely ineffective.

Yet there is an alternative approach to tackling the problem of excess gut inflammation. Instead of targeting transient, exogenous entities in the digestive track, one may design host-targeted mechanisms. These work on the animal's own physiology to limit the metabolic resources "wasted" on excess inflammatory responses so that growth and production are optimized. Being directed to biochemical targets in the host itself, there is no need to identify specific pathogens, and resistance does not develop.

There are many such generalized anti-inflammatory agents, such as aspirin, for oral use in humans. For animals, there is currently only one company taking this approach. Aova Technologies' BIG™ line of products employs an antibody against a host enzyme, phospholipase A_2 (PLA_2). PLA_2 is a key player in the inflammatory response of vertebrates. This enzyme enables one of the earliest metabolic steps in the inflammatory

cascade. Thus, by targeting the host animal's PLA_2, these products modulate the action of many key inflammation mediators in the gut, resulting in suppression of excess inflammation. Importantly, this does not change the immunological status of the animal, which is still fully able to mount an effective response to acute health challenges.

The BIG™ products have been featured in over 100 commercial and university trials in a wide range of species, showing significant gains in feed efficiency, growth rate, carcass yield, general health, and egg production for different animals. The success of these products confirms the broad applicability of the host-targeted approach. Growth results have been especially impressive for aquaculture. Highlights of three recent trials with BIG FISH™ are given here.

In a published university trial, rainbow trout had a positive dose response to BIG FISH™ ($aPLA_2$) supplementation, showing up to a statistically significant 27.8% increase over control for weight gain over the two month study (Figure 1).[16]

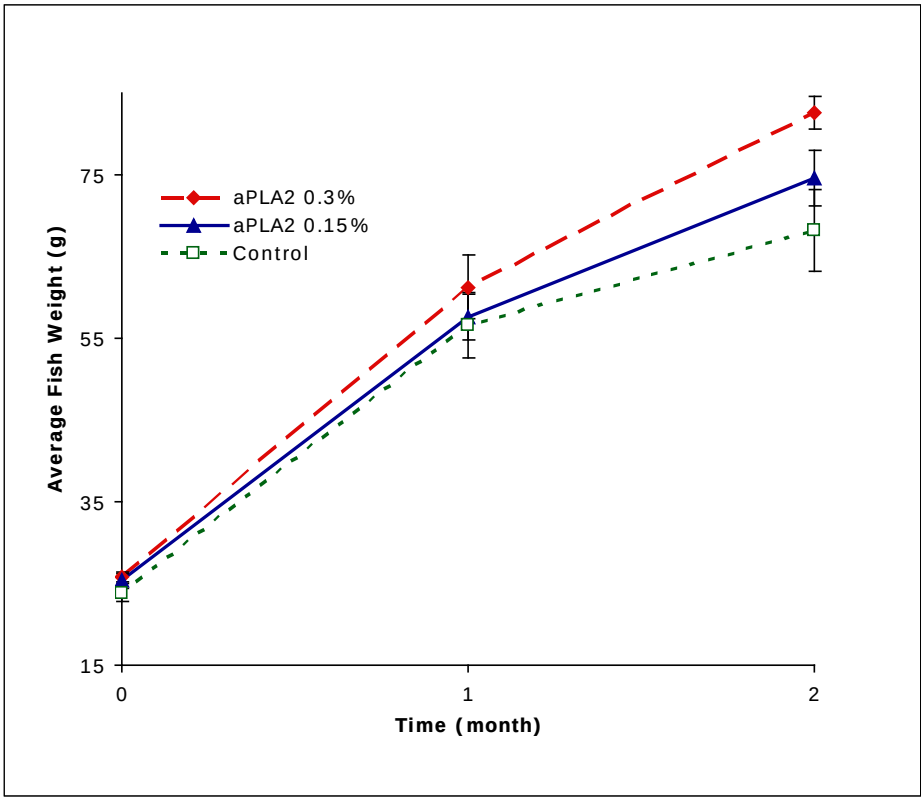

Figure 1. Effect of administering feed mixed with commercial anti-phospholipase A_2 ($aPLA_2$) on growth (±S.E.) in juvenile rainbow trout.

A commercial trial tested if BIG FISH™ confers any protection against a disease challenge. Tilapia fingerlings were raised to on 0% (control), 0.25% or 0.5% BIG FISH™, starting with triplicate tanks of 330 fish each, for each treatment. After 8 weeks, 200 median-sized fish from each treatment were distributed into ponds and challenged by feeding fish that had died from *Streptococcus agalactiae*, along with regular rations. A remarkable protective effect was seen for groups raised on BIG FISH™ (Figure 2), demonstrating that targeting host PLA_2 with this product does not compromise immune function, and in fact enabled these fish to better fight off a direct disease challenge. Additionally, the trialing party reported that feed conversion in the BIG FISH™ groups was "vastly superior" than controls.[17]

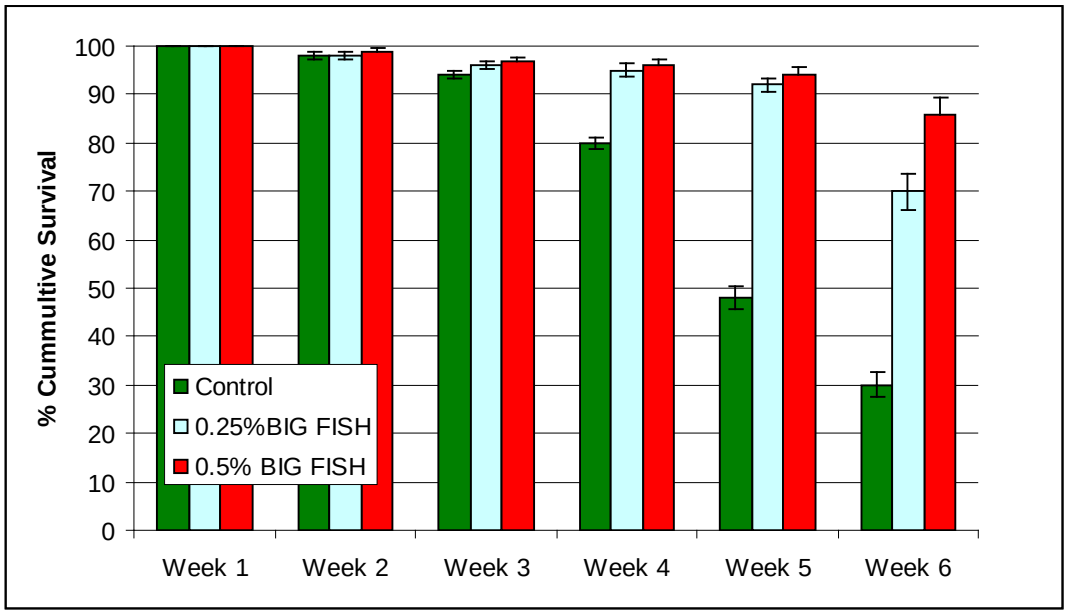

Figure 2. Enhanced survivability (±SD) of tilapia raised with $aPLA_2$ supplementation, upon ongoing *S. agalactiae* challenge in Weeks 4-6.

A positive dose response of BIG FISH™ was also seen survival, growth, and feed conversion in a commercial trial of grouper fingerlings, conducted in sea net pens off the coast of Thailand. Amount of biomass produced in $aPLA_2$-fed pens was dramatically higher than that in control pens (Figure 3). Improvement was also noted in average fish length, average weekly weight gain, and survivability.[18]

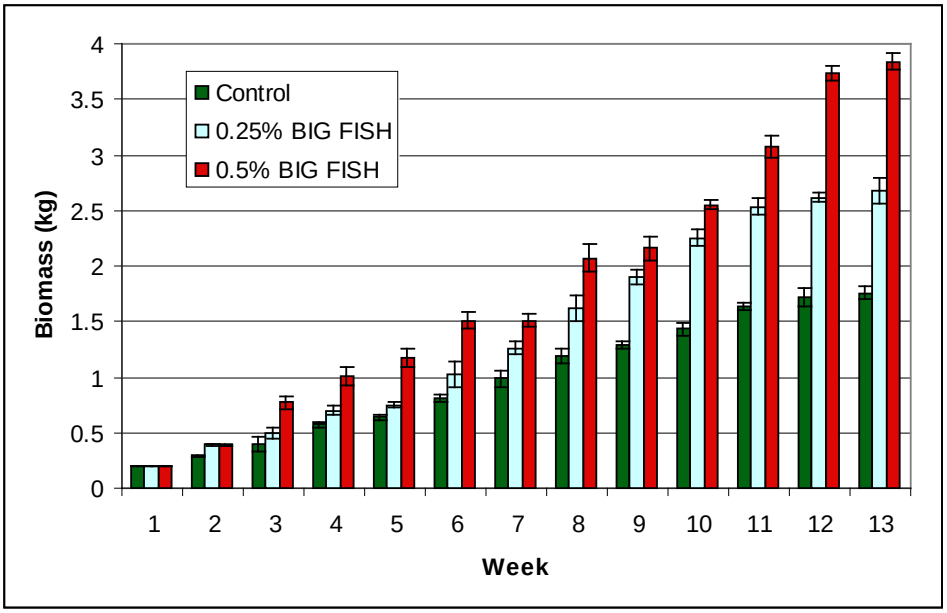

Figure 3. Enhanced biomass (±SD) of grouper upon $aPLA_2$ supplementation

Managing today's livestock for maximum productivity requires a multitude of good, informed decisions across all areas of production, such as facilities, genetics, agricultural markets, and physiology. Gut inflammation is an important piece of this puzzle. To realize the full genetic potential of his livestock—and maximum economic return—the savvy manager will be aware of how gut inflammation develops and impacts production, and be in command of the tools to best regulate it.

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