Novel sites targeted to improve efficiency

Further understanding of the gut and how it communicates with other tissues may lead to the identification of novel targets and the development of new strategies for increasing animal production efficiency.

By **EMMA WALL***

TO improve the production efficiency of agricultural animals, scientists are focusing on new potential targets of feed additives to improve animal health and nutrient absorption.

In particular, a new emphasis has been placed on the gut of the animal and how the gut communicates with other organs, which can influence animal development, health and susceptibility to disease and nutrient metabolism.

The third annual Pancosma Worldwide Scientific Exchange, held last December in Madrid, Spain, had a theme of "Languages of the Gut" and covered the topic of gut physiology as it relates to other systems of the body, immunity, nutrient metabolism and consequent production efficiency. The two-day program consisted of presentations by both basic and applied scientists, with a small group of invited attendees that included researchers and industry representatives from all over the world.

The major themes discussed were novel findings in gut physiology and how the gut communicates with other organs, as well as new insights into glucose absorption in ruminants.

Novel gut functions

The research and development team at Pancosma recently coined the term "gut effects" to describe the mechanism of action for some of its phytonutrient-based feed additives, which have been shown to act at the level of the gut. It was, therefore, not surprising that the main focus of the meeting was novel roles for the gut in regulating the function of other systems — including the endocrine, immune and nervous systems — and how these relationships might relate to changes in animal health and production efficiency.

Dr. John Furness from the University of Melbourne presented on the gut as a sensory organ. Because it is the first organ to be exposed to the ever-changing dietary environment, it is the first site of detection for materials entering the body. This includes food, pathogens and toxins, and the gut must react and adapt to incoming molecules appropriately.

In addition, the gut communicates with other systems of the body to prepare them for what's coming — to adjust ingestion, prime organs and reject toxins — and it does so using immune, endocrine and neural signals. In fact, the gut contains 70-80% of the immune cells in the body, the most extensive nervous

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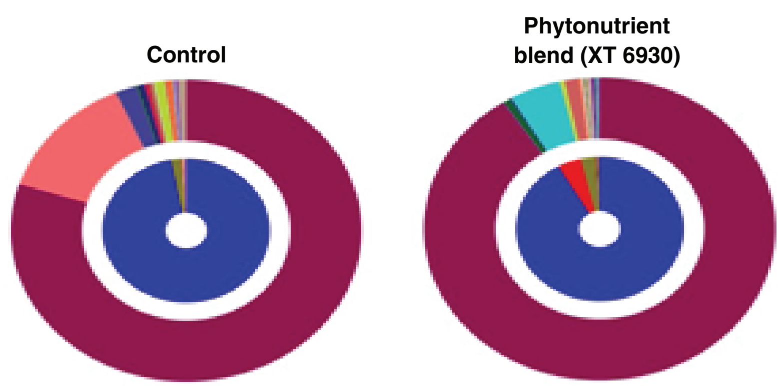
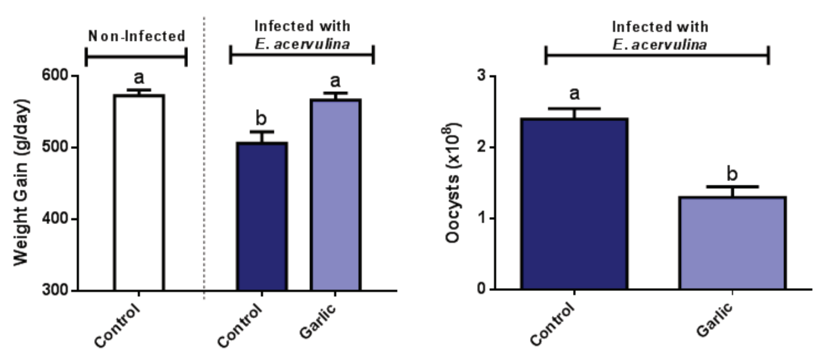
1. Phytonutrients cause a shift in gut microbial populations in broilers



Note: Inner and outer pie charts represent the composition of phyla and genera, respectively.

Source: Lillehoj et al., 2013.

2. Supplementation of broilers with garlic additive decreased bodyweight and oocyte shedding after infection with *E. acervulina*



Note: Garlic = Garlicon 40.

Source: Kim et al., 2013.

system and the largest endocrine system.

The gut expresses nutrient receptors that are known to taste sweet, umami and bitter, as well as those that are known to sense several phytonutrients. For example, members of the transient receptor potential family, all of which are expressed in the gut, are known to sense carvacrol (oregano), thymol (thyme) and eugenol (clove). Depending on the location of transient receptor potentials in the digestive tract, they are stimulated to different degrees, indicating a functional role for these receptors.

Clearly, there is an intimate connection among the endocrine, nervous and immune systems at the level of the gut: It represents a location of integrated physiology among several organ systems. If how the gut reacts to its environment and communicates with other organs can be further understood, new opportunities for manipulating the gut system and improving animal health can surely be found.

How does the gut influence immunity? Dr. Brett Finlay from the University of British Columbia presented data on the role of the gut microbiota in shaping the immune system. The gut microbiota of humans is known to have a marked impact on the incidence and severity of several diseases, including autoimmune disease.

So, what regulates the composition of the microbiota? Environmental factors — such as bacterial infection or treatment with antibiotics — can have both short- and long-term effects on the gut microbial population, and this can influence susceptibility to disease later on. For example, antibiotic treatment during the first year of life is associated with an increased incidence of asthma, whereas living on a farm is associated with a decreased risk.

Finlay found that treating neonatal mice with antibiotics for just a short period of time caused dramatic shifts in the gut microbial population and rendered otherwise resistant mice susceptible to asthma. These findings reveal that there appears to be a critical window during early development during which the gut flora is permanently determined, and this influences the immune system during adulthood.

Finlay also has an interest in exploring phytonutrient alternatives to antibiotics and found that treating mice with eugenol (from cloves) improves the gut's ability to keep pathogens out and decreases bacterial load during infections. This is an exciting area of research that will no doubt lead to novel applications in agriculture.

The interplay between the gut and the immune system was also presented by Dr. Nita Salzman from the Medical College of Wisconsin. She discussed Paneth cells, which are found in the intestine, are known to influence the composition of the microbiota and have many functions during normal development and during disease. Functional Paneth cells are critical for gut health, and disruption of their function can lead to Crohn's disease in humans (Johne's disease in ruminants).

In piglets, the gut microbiota is faced with big challenges due to drastic changes in the diet at weaning, and this disruption of the microbial population often results in increased susceptibility to diseases of the gut.

Dr. Kristian Daly from the University of Liverpool discussed some of the problems faced by swine producers in their attempt to improve piglet health. Some of Daly's work has focused on supplementing piglets with Sucram, an intense sweetener produced by Pancosma that has been shown to increase both feed intake and glucose absorption from the small intestine of piglets.

His most recent efforts have revealed that the sweetener has a marked effect on the gut microbiota and led to an increase in a specific phylotype of lactobacillus, which has probiotic properties and also inhibits pathogen growth.

How is it possible that an intense sweetener has such an effect on the gut flora? Daly's working hypothesis — the "sweet-sensing hypothesis" — is that this lactobacillus phylotype expresses a sweet sensor (receptor) that, when stimulated, initiates a signaling cascade that leads to increased glucose absorption.

Similar observations have been made in yeast, and these sensing systems are key for response and adaptation to the changing gut environment. Once it is understood how such sensing systems work in production animals, it will then be possible to target them to perturb the microbiota so gut health and animal performance can be optimized.

Phytonutrients

Dr. Hyun Lillehoj, an immunologist at the U.S. Department of Agriculture, has been collaborating with Pancosma for several years and has focused on the development of phytonutrient-based feed additives as alternatives to antibiotic growth promoters (AGPs).

Because gut health can affect egg quality and meat production, and AGPs clearly influence the gut microbiota, it is important to understand the effect phytonutrients have on gut health. Lillehoj's research has revealed that turmeric and capsicum can cause proliferation of immune cells and influence gene expression in the intestine. In addition, both molecules cause shifts in the gut microbiota (Figure 1).

Her most recent work focused on exploring the effect of garlic — known to have medicinal properties — on broiler immunity. Lillehoj explained that supplementing broilers with garlic altered the expression of inflammatory genes in the intestine and caused the proliferation of immune cells.

In addition, when broilers were infected with *Eimeria acervulina*, those supplemented with garlic exhibited no decrease in bodyweight and had decreased oocyte shedding (Figure 2) as well as increased expression of antioxidant genes relative to control animals.

Lillehoj's findings were recently published in the *British Journal of Nutrition* and have led to some exciting new opportunities for phytonutrient-based improvement of gut health and metabolic efficiency in poultry animals.

Glucose absorption

Now that more is understood about glucose absorption by the gut and how the microbiota can be targeted to influence animal health, some old questions can be revisited with a new and integrative mindset.

One relevant issue that is also an area of research at Pancosma is to explore the idea of using feed additives to improve glucose absorption in ruminants.

Dr. John Newbold, Cargill director of research and development, introduced the concept of carbohydrate digestion in ruminants and opportunities for improving starch digestibility.

How can starch digestion be improved in dairy cows at various physiological states and levels of milk production? Once improved, how can glucose absorption by the small intestine of dairy cows be increased to optimize milk yield? If the glucose is absorbed, will the mammary gland use it to make more milk? More important, is it even possible to increase the amount of absorbable glucose to a level that will translate into changes in animal health and/or milk production?

Dr. Soraya Shirazi-Beechey, a physiologist from the University of Liverpool, explored this possibility by integrating what is known about glucose absorption by the small intestine of ruminants with what she has recently observed in swine (*Feedstuffs,* March 19, 2012).

One of her main research questions is whether ruminants' digestion of starch can adapt to a changing diet, and if so, what are the mechanisms underlying the adaptation? The main transporter for glucose — SGLT1 — has been a major focus of her research program because its expression is diet inducible: It responds to changes in dietary monosaccharides but not to starch.

For example, expression of SGLT1 in the small intestine of milk-fed ruminants is quite high, whereas after weaning, it is nearly undetectable. If the animals are maintained on milk replacer, however, expression remains high.

Shirazi-Beechey explained that there are receptors in the small intestine called taste receptor type-2 and type-3 that, when combined, have the ability to "taste" sweet flavors. Upon tasting sweet, these receptors induced the expression of the glucose transporter SGLT1 in the small intestine of ruminants, and this resulted in an increase in the uptake of glucose by the gut.

These observations have now been confirmed in both milk-fed and weaned calves, as well as in non-lactating dairy cows. Therefore, ruminants appear to have all the molecular tools in place to allow for diet-inducible changes in glucose absorption.

However, the question remains: Can post-ruminal starch be hydrolyzed to glucose? If no significant amounts of glucose reach the small intestine, then the increase in SGLT1 expression will not translate into functional changes (i.e., milk yield).

Clearly, however, the integration of what is known about the mechanisms of glucose absorption in swine with that of ruminants has revealed several new and unexpected targets for developing strategies to optimize the metabolic efficiency of dairy and beef animals.

Adaptive metabolism of ruminants was also discussed by Dr. David Harmon from the University of Kentucky. One of Harmon's main research interests is to understand what limits starch digestion in ruminants. Possibilities include pancreatic amylase, pH, intestinal retention time and glucose transport.

Early research pointed to pancreatic amylase, which is often regulated by changes in the diet. In addition, as starch digestion shifts from the rumen to the small intestine, energy availability increases. However, even when the abundance and activity of pancreatic amylase was increased in the small intestine, starch digestion was not always affected. This indicates that other factors are limiting starch digestion, and Harmon continues to work on understanding what the factors are and how they work.

In a related topic, Dr. Chris Reynolds from the University of Reading discussed the potential benefits of shifting the site of starch digestion. The location of starch digestion has clear effects on milk production, energy and protein partitioning and the efficiency of nutrient utilization; these effects vary with the stage of lactation.

Some research has shown that when grain is flaked, more starch is digested in the rumen, and milk yield increases. However, research also supports the small intestine as a desirable location of starch digestion because although no microbial protein is produced, there is an increase in glucose supply with low energy losses, and there is often a positive effect on milk composition and marbling.

Because of the effect of diet and stage of lactation on starch digestion as it relates to the efficiency of nutrient utilization, it is very difficult to paint a clear picture that leads to obvious targets to optimize glucose availability and absorption. Further understanding in this area and integration of knowledge from other fields should lead to the identification of novel targets and the development of new strategies for increasing the efficiency of starch digestion. ■