# Gut Integrity During Periods of Stress and its Implications on Performance

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## Introduction

Livestock production relies heavily on nutrition and feeding programs that are designed to promote maximal or optimal production. Quality of feedstuffs included in animal diets influence nutrient supply, digestibility, and absorption, and will ultimately have a great impact on animal performance. In addition to feed quality, intrinsic animal factors also determine how animals respond to dietary manipulations. Of these factors, the gastrointestinal tract (**GIT**) is of critical importance for efficient animal production because of its obvious role in digestion and absorption; however, the GIT also plays a substantial role in immune status of the animal. Therefore, the objective of this article is to highlight the interaction of the GIT and nutritional management of livestock and the impacts of this interaction on animal performance.

## The Roles of the Gut

In ruminants, the sum of reticulorumen, omasum, abomasum, and intestines accounts for as much as 71% of body weight (Holstein cows, Beecher et al., 2014). The large mass of the GIT, relative to total body mass, involves physiological processes that demand a great deal of nutrients for maintenance and turnover of tissue. The GIT has a clear and obvious role in digestion of feed and absorption of nutrients. The gut presents a diversity of large anatomical features such as a multi-chamber stomach in ruminants as wells as microscopic differences in arrangement and number of cell layers in the different segments of the GIT. Morphological features such as villi and microvilli magnify the surface area of the intestines by several orders of magnitude which increase digestion and absorption potential.

In addition to the role in digestion and absorption processes, the gut serves a physical and chemical barrier to prevent intrusion of foreign substances or organisms into the body. In fact, the gut is the first line of defense against pathogens and toxins and represents the largest organ of the immune system. The gut has a mucus layer composed of threonine-rich glycoproteins called mucins (Perez-Vilar and Hill, 1999). This layer is a physical barrier that impedes direct contact between the enterocyte and the contents in the lumen of the intestine which include digestive secretions, toxins, and microorganisms (Forstner, 1995). In addition to these glycoproteins, the integrity of the gut is reinforced by tight junction proteins between enterocytes. This barrier protects against the infiltration of ions, toxins, and other molecules through the paracellular pathway (González-Mariscal et al. 2003).

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Overall, the gut has a paramount role in protecting the body through various mechanisms including chemical signaling pathways, physical mucosal barrier, and tight junction proteins. Alteration of any of these mechanisms can lead to reduced integrity of the gut barrier, reduced thickness of the mucosal layer, or altered synthesis and function of tight junction proteins.

## Stress Factors and Gut and Immune System Responses

Livestock species experience stressful events at various points in their productive cycles. Some of the events are weather-related, heat being the most common factor associated with stress. Other stressful events include weaning and shipping or transportation. Each one of these factors may elicit a variety of ethological and physiological alterations, but they all share reduced feed intake as a commonality. Thus, it is important to highlight that other situations in which feed intake is compromised can also elicit a response similar to that of major stressful events. High stocking density in pasture or pens, drought, prolonged periods away from pen due to milking or extended times in a palpation rail, or animals running out of feed for a few hours per day are common farm scenarios that can lead to restricted feed intake.

Recent work by Kvidera et al. (2017a) has shown that feed restriction in dairy cows compromises gut integrity. The response to increasing feed restriction resulted in altered morphology of the intestinal epithelium so that animals that were feed-restricted had decreased villus height and width as well as reduced crypt depth. These alterations in gut histology not only imply altered digestion and absorption processes but can also lead to loss of effective barrier function. In the same study, the authors also reported increased concentration of circulating biomarkers of inflammation which may be a direct result of increased permeability due to loss of architectural integrity in the gut.

Heat is a common stress factor that can alter integrity of different tissues, Weng et al. (2017) reported that heat-stressed dairy cows had reduced expression of proteins involved in barrier function in the mammary gland. Similarly, Pearce et al. (2013) demonstrated deleterious effects on epithelial architecture due to heat stress and increased gut permeability in as little as 1 day of heat stress in pigs. A reduction in feed intake during periods of heat stress may be a response to reduce metabolic heat production (Baumgard and Rhoads, 2012) and commonly associated with subpar animal performance. However, there is evidence that feed restriction alone accounts for only 35 to 50% of reduction in milk yield during experimental hyperthermia (Rhoads et al., 2009; Wheelock et al., 2010; Baumgard et al., 2011) which indicates that there are other mechanisms responsible for reduced productivity in dairy cows. During heat stress, blood flow is preferentially diverted toward the peripheral circulation as a strategy to dissipate heat (Lambert et al., 2002). This shift causes less irrigation to the splanchnic area (Hall et al., 1999) resulting in hypoxia of the gut, reduced nutrient supply, and depletion of ATP accompanied by increased oxidative and nitrosative stress (Hall et al., 2001).

## Impacts of Gut Health on Animal Production

There is no clear diagnosis for gut barrier dysfunction, therefore, it is important to highlight that the animal industry would benefit from a generalized definition of gut health so that dysfunctional gut barrier can be subsequently defined. Animals that suffer from dysfunctional gut barrier can present a myriad of signs that can affect animal performance. More importantly, there is a cascade of physiological changes that are brought on upon disruption of gut barrier and translocation of bacteria or toxins from the lumen of the GIT into the general circulation. As a result, the body mounts an immune response which is known to divert energy and nutrients away from production towards the immune system. Namely, there is a hypoglycemic response which is thought to be a way to spare glucose from other tissues towards the immune system; however, it was unknown how much glucose was utilized during an immune challenge. It was only until recent discoveries that it was possible to obtain an estimate of the energy diverted towards the immune system upon activation. Kvidera et al. (2017b) conducted a study in which a euglycemic clamp was used to determine the energy requirements of an activated immune system. The authors estimated that the immune system can use slightly more than 1 kg of glucose in a 12 h period. In terms of milk production, that amount of glucose would be enough to synthesize close to 15 kg of milk since 72 g are required for every kg of milk produced (Kronfeld, 1982). Furthermore, the energy contained in that amount of glucose is approximately 4,100 kcal, considering a rate of 10 kcal for each gram of protein synthesis; the glucose diverted toward the immune system would have been enough to synthesize 410 g of protein. This amount of protein would be found in ~1,366 g of lean tissue.

In addition to energy being diverted away upon reduced gut integrity, it is reasonable to expect an increase in the requirements for certain amino acids. Tight junctions and mucins are proteins, therefore when alterations occur so that gut permeability is increased, the animal may respond by mobilizing amino acids or diverting dietary amino acids towards re-establishment of gut permeability. Maintaining mucin synthesis seems to be a primary function of the GIT. Rémond et al. (2009) induced inflammation of the ileum in minipigs and reported increased intestinal mucin synthesis with a concomitant increased requirement for threonine. Interestingly, the increased demand for threonine was ameliorated from mobilization of endogenous proteins rather than luminal supply of this amino acid. Furthermore, recent discoveries in minipigs confirm that intestinal tissues retain a disproportionate amount of threonine to maintain mucin synthesis even during periods of deficiency (Munasinghe et al., 2017). This indicates that protein synthesis in non-mucin producing organs or tissues would have a lower metabolic priority; from a livestock producing perspective, this would translate in lower production of animal protein. The discoveries in energetic and amino acid trafficking indicate that animals may redirect glucose to supply energy to the immune system while breaking down endogenous proteins to supply threonine for mucin synthesis. Both of these metabolic adaptations would translate into subpar animal performance and inefficient use of nutrients.

Even though most of the studied responses involving induced gut barrier dysfunction involve an acute stimulus, it is reasonable to think that less intense situations are more commonly present in farm scenarios (animals running out of feed, long distance transport, heat stress) with less severe but similar partitioning of nutrients away from production for a few days or even a few hours throughout the day. These non-acute but frequent situations may represent cumulative inefficiencies in production similar to sub-clinical diseases or disorders.

## Summary

The GIT serves a major role in digestion and absorption of nutrients and it also has a substantial barrier function to protect the animals from pathogen intrusion. Integrity of the gut may be negatively affected when animals undergo stressful events; because of its large mass and its close interaction with the immune system, gut health should be considered paramount for efficient animal production. Because an activated immune system utilizes substantial amounts of glucose and alters amino acid utilization, it is important to highlight that management and feeding practices should not only consider nutrient supply for the animal but also promote and support gut health and integrity. Doing so can lead to partitioning energy and other nutrients more efficiently towards animal production.

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# <u>SESSION NOTES</u>