Researchers have linked whole-body inflammation to conditions such as equine metabolic syndrome, insulin resistance, laminitis, and more.

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What researchers are learning about bodywide inflammation's effect on horses

It's ALL Connected

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When you hear the term inflammation, you might picture a localized swollen area on a limb or around a wound. But inflammation also occurs systemically, affecting the whole body. It has been a buzzword in the medical community for years in discussions on how to manage chronic diseases in humans. Equine researchers have begun studying the concept of whole-body inflammation because of its links to a variety of health problems, including equine metabolic syndrome, insulin resistance, and laminitis; "leaky gut syndrome"; and risk of musculoskeletal injury.

How does bodywide inflammation even occur? Well, if the body's normal protective responses become amplified, what started as a defense mechanism can turn into a chronic problem. The immune system normally secretes pro-inflammatory cytokines, which are chemical messenger proteins such as interleukins (IL) and tumor necrosis factor (TNFα). These substances are important for initiating a physiological response to infections or injury and seeing to a successful recovery.

While inflammation might start in one tissue, excessive inflammation releases substances into the circulation that act systemically on other tissues throughout the body. Let's look at some of the negative effects this process can have.

Obesity, Insulin, and Inflammation

Energy sources such as glucose—which horses obtain from consuming carbohydrates—can negatively affect the horse's endocrine system if not used or stored in the body's tissues properly. This can lead to bodywide inflammation.

"When an animal is sick and off feed, there is continued need to preserve glucose for tissues that require it, such as the brain," says Jessica Suagee-Bedore, PhD, assistant professor of equine science at Sam Houston State University, in Huntsville, Texas, who has a special interest in obesity and insulin resistance in horses. "TNFα is important for initiating insulin resistance that is beneficial in the face of illness. However, the body doesn't differentiate between cytokines released to initiate the sickness response or cytokines released due to diet or obesity. Therefore, insulin resistance develops when an animal consumes a diet that promotes inflammation, such as high-starch and -sugar feeds, or in an animal that already experiences high levels of inflammation due to obesity."

The association between inflammation and obesity depends on factors such as breed, exercise, diet, and aging—often referred to as inflammaging. We now know that older horses naturally have higher circulating concentrations of cytokines, namely IL-6 and TNFα.

"One chief concern of an animal's body is the prevention of hyperglycemia (elevated blood glucose levels) or hypoglycemia (low blood sugar levels), as either of these can lead to a host of physi-

ological problems," says Suagee-Bedore. For example, hyperglycemia results in inflammatory free radical production that damages tissue. Normally, the body stores any extra glucose in the appropriate tissues after eating. Skeletal muscle and the liver take up most of the glucose, converting it to glycogen the body can use for energy later on.

When this system goes awry, cells become less able to respond to the insulin hormone transporting glucose from the bloodstream into storage tissues. Suagee-Bedore compares insulin resistance development to falling dominoes, with insulin being the signal that tips off the first domino.

"For a healthy horse, the dominoes fall in a line, but in an insulin-resistant horse, one domino is slightly braced and doesn't completely fall over," she says. "More insulin has to keep hitting it to get it to tip."

Without weight loss and exercise, affected horses remain insulin-resistant for prolonged periods. "Ultimately, it seems there is a positive feedback cycle, with insulin resistance resulting from inflammation and also promoting it bodywide," she says.

She explains it like this: "Adipocytes (fat cells) secrete all sorts of cytokines, which have the same roles in initiating insulin resistance and disrupting metabolism as they would if they were secreted by the immune system during a bout of illness. In a normal healthy animal, these cytokines are synthesized and released but function to regulate metabolism. Fat cells enlarging with obesity synthesize greater amounts of cytokines to disrupt metabolism in adipose tissue (another key energy reserve) and skeletal muscle. This leads to development of insulin resistance. In response, the pancreas secretes more insulin to signal muscle cells to take up glucose for the critical task of preventing hyperglycemia. Additionally, adipose tissue harbors macrophage white blood cells, which as part of the immune system produce and secrete cytokines."

There is a great deal of "cross-talk" between macrophages and adipocytes, she adds.

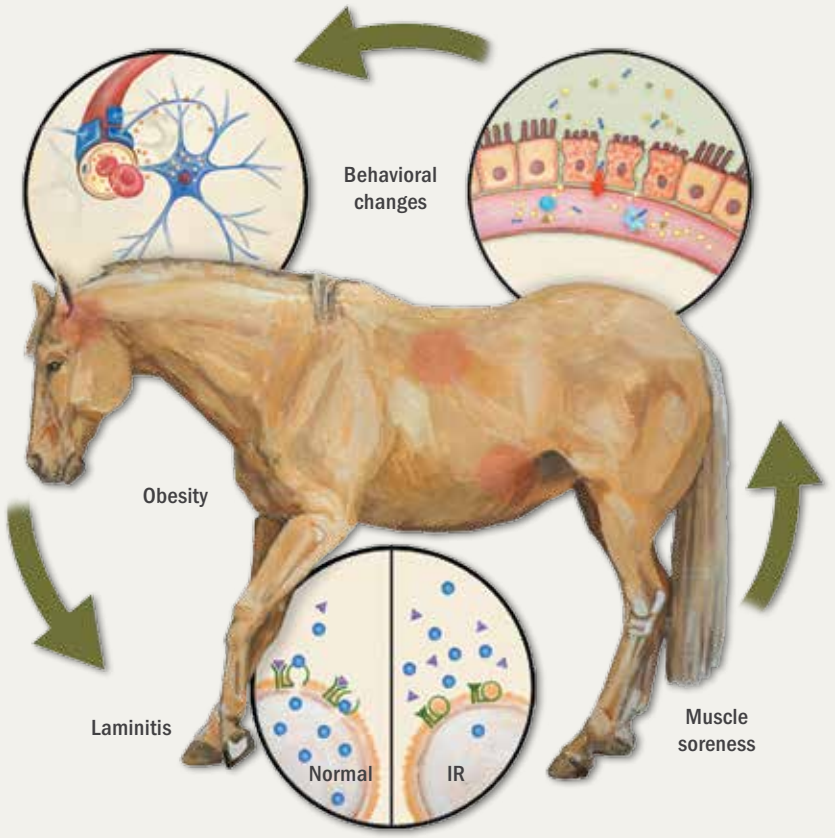
Originally, Suagee-Bedore thought glucose or insulin in the bloodstream signaled cells to synthesize inflammatory mediators. "During glucose and insulin intravenous infusion studies, we see some increase in circulating and tissue level inflammation," she says.

While this might be part of the problem, she offers an additional theory: "There may be another mechanism related to intestinal changes during feed consumption, such as fermentation of glucose to lactic acid that kills off gut bacteria. Release of lipopolysaccharide (LPS, also called endotoxin, which is a component of Gram-negative bacteria cell walls) from dying bacteria interacts with the immune system—either in the gut or systemically—to result in inflammation. Glucose and plasma LPS peak around two hours (after feeding), yet the IL-1β increase comes more quickly at one hour post-feeding, possibly from gut macrophages."

If LPS and other substances can pass out of the intestinal tract into the systemic circulation—known as leaky gut syndrome—a cascade of inflammatory events occurs bodywide.

Bodywide Inflammation

Bodywide inflammatory responses, such as those initiated by the immune system and the gut, can cause or contribute to a number of conditions, from obesity to behavioral anxiety to insulin resistance.



In insulin-resistant horses, if insulin (purple) is not attached to cell wall receptors, glucose (blue) cannot enter and circulates in abnormally high amounts in the bloodstream.

ROBIN PETERSON, DVM ILLUSTRATION

Leaky Gut Syndrome

The intestinal tract is a huge contributor—as much as 70%—to the body's immune system and tends to be the cause of many problems.

"The equine intestinal tract is lined by a single layer of barrier cells (called enterocytes) to prevent toxins and bacteria from accessing the bloodstream," says Liara Gonzalez, DVM, PhD, Dipl. ACVS, assistant professor of gastroenterology and equine surgery at North Carolina State University, in Raleigh, who studies topics related to intestinal cell integrity and

stem cell rejuvenation of the intestinal lining (the epithelium). "This protective barrier is very sensitive to small changes from stress, colic, or disease. The single layer of cells is created from intestinal stem cells (that reside within the horse). Incredibly, in a healthy horse, those cells proliferate and renew to create a new intestinal lining within a few days to a week's time."

Intestinal epithelial cells are connected via tight junctions—protein complexes that form selective permeable seals that regulate what can and cannot pass into the bloodstream. Disruption of those junctions leads to leaky gut syndrome.

"Even an intense exercise event can result in some leakiness in the GI tract," says Gonzalez. "Any stress—rigorous exercise, heat stress—that shunts blood to privileged organs (e.g., brain, kidneys) and not to the gut decreases intestinal blood flow and oxygen to the intestinal lining. Epithelial cells are very sensitive to oxygen deficits, with the resulting cell injury and loss of tight junctions causing leaky gut.

"When bacteria or inflammatory mediators cross into the bloodstream, there can be systemic signs of inflammation," she adds. "Some degree of inflammation is necessary and appropriate for the healing process. However, if a horse is unable to compensate in the face of excess inflammation, then inflammatory mediators create a vicious cycle of unchecked whole-body inflammation."

Researchers have found that leaky gut can lead to other types of systemic inflammation, such as skin allergies (hives, itching) or laminitis (inflammation of the laminae, which connect the hoof wall to the coffin bone within).

Fortunately, "the intestinal tract has an amazing capacity to repair its epithelial barrier, referred to as restitution," Gonzalez says.

When the small intestine epithelium gets injured, its villus structures (elongated projections) contract. The resulting reduced surface area limits the amount of toxins and bacteria that get transferred from the bowel lumen to the bloodstream. Then, the remaining cells elongate and stretch to cover the basement membrane that separates epithelial cells from underlying tissue. This stops unwanted substances from crossing the basement membrane.

"However, in this situation, the gut isn't as efficient in absorbing nutrients or water," says Gonzalez. "Ultimately, stem cell activation is necessary to regenerate and produce new epithelial cells," to replace damaged villus structures.

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Stresses such as intense exercise can cause inflammatory mediators to leak out of the gastrointestinal tract and into the bloodstream.

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>
> DR. LIARA GONZALEZ

She says researchers studying pigs, mice, and humans have demonstrated that early life stress—weaning, early separation, and nutritional deficiencies—correlates with a likelihood of intestinal inflammation later in life. This phenomenon might impact horses, as well. While there is no current data on the effects of early stress on aging and inflammation in horses, Gonzalez says it causes cellular changes to DNA, possibly causing tissue to injure more quickly and heal less easily.

Diet's Role

The old adage "you are what you eat" relates to many facets of equine health. "Leaky gut syndrome can occur in horses of varying body condition scores, often due to consumption of higher-starch feeds that result in acidosis and opening of tight junctions in the intestines," says Suagee-Bedore, kicking off the cycle of systemic inflammation.

Because obese horses already have slightly higher levels of inflammation, she says, if they consume high-starch and -sugar feeds, the resulting inflammation burst can tip the scales of a previously balanced teeter-totter. "A lean horse may handle the sudden burst, while the obese horse's inflammatory condition is exacerbated," she says.

Horse owners can minimize causes of inflammation, to some extent, via diet. "The companion horse population is often fed grains or sweet feed despite already being overweight," says Suagee-Bedore. "Horses should be fed more forage and fewer concentrates, particularly when excess energy sources aren't needed."

Today, commercial low-starch feeds are available and preferable for horses that need supplemental grain.

Restricted feeding practices, such as the twice-daily meals common in many barns, might injure the intestinal villi, also resulting in leaky gut. When possible, give horses free-choice access to forage. For obese horses or those suffering from equine metabolic syndrome, however, this might not be possible.

Butyric acid (butyrate, a short-chain fatty acid) is important to enterocyte

health, and intestinal epithelial cells use it as an energy source. A high-fiber diet amplifies intestinal bacteria's butyrate production during fermentation. Equine researchers are currently studying how butyric acid supplementation might help maintain tight junction integrity in the face of intestinal epithelial cell stress.

Inflammation and the Brain

Cytokines from whole-body inflammation can signal the brain to induce sickness behavior. "There are receptors for TNFα and interleukins within blood vessels in the brain," says Suagee-Bedore. "These cells respond to stimulation by activating production of cyclooxygenase (COX, an enzyme responsible for producing prostaglandins that contribute to the inflammatory process). COX then signals production of prostaglandin E2—its release into the brain side of the blood/brain barrier initiates fever and other sickness behaviors."

Signs such as fever, lack of appetite, and lethargy aren't often associated with low-grade chronic inflammation, indicating that low cytokine levels don't signal the brain's sickness behavior mechanism.

Bodywide inflammation related to leaky gut syndrome can have other behavioral effects. For example, a horse might appear calm and reliable but, if you reach to touch him, he becomes resistant and belligerent. Such "irreconcilable" behavior might have to do with a breached blood-brain barrier (normally, tight junctions between red blood cells in brain tissue carefully control what can pass through the bloodstream into the brain). Inflammatory mediators passing from the gut to the systemic circulation to the brain can alter behavioral responses to stimuli, says Suagee-Bedore.

Recent research has demonstrated that maternal obesity affects metabolism and increases inflammation in both dam and foal. For example, at 12 months of age, osteochondrosis (abnormal ossification of cartilage) was more prevalent in foals born to obese mares than foals from mares with normal body condition scores. Study results in humans and rats show that maternal obesity elicits signs of brain inflammation in offspring, leading to anxiety, behavioral abnormalities, and learning difficulties. In growing horses this has the potential to spawn behavioral problems that could carry over to their performance careers.

Effects of Exercise

Athletic horses have a reduced risk of developing insulin resistance because even minimal amounts of exercise increase insulin sensitivity, says Suagee-Bedore. Yet, inflammation affects skeletal muscle because it's a repository for glycogen storage, as well as a functional structure of locomotion.

The mechanical forces associated with exercise cause skeletal muscle to produce pro-inflammatory cytokines, says David Horohov, PhD, chair of the department of veterinary science and director of the University of Kentucky's Gluck Equine Research Center, in Lexington. While low-level inflammation associated with tissue repair is not detrimental—in fact, some inflammation post-exercise is normal, leading to muscle and bone adaptation and healing—elevated or chronic inflammation can lead to muscle tissue damage and scarring, he explains.

Transient muscle soreness can lead to temporary increases in bodywide inflammatory responses, he says, but these resolve quickly without needing intervention.

In one study Horohov and colleagues identified an increase in pro-inflammatory cytokine expression two hours following exercise. They fed half of 25 2-year old Thoroughbreds a nutritional supplement containing boswellia (Indian frankincense), curcumin (a chemical produced by turmeric and other plants), coenzyme (CoQ10, an antioxidant the body produces), glycine propionyl-L carnitine (GPLC, an amino acid the body produces), and ribose (a sugar that makes up RNA, which is important for protein synthesis). Supplemented horses had significantly lower pro-inflammatory cytokine expression following exercise and adapted to training better than nonsupplemented horses. Improved adaptation equates to less risk for injury.

"It is thought that the supplement reduces free radical production, a normal byproduct of oxidative exercise," says Horohov. "This then prevents oxidative damage to cell membranes and DNA, which in turn reduces signals for pro-inflammatory gene expression."

Consequences of Anti-Inflammatory Drugs

Horses often receive non-steroidal anti-inflammatory drugs (NSAIDs) to combat inflammation, pain, and lameness. But this is not without consequence. "By masking pain, overuse of NSAIDs allows an injured horse to continue working despite incurring more structural damage," Horohov says. "Also, mild inflammation plays an important role in the repair process; interference by NSAIDs in this process delays healing and interferes with repair mechanisms.

"NSAIDs may also interfere with normal physiologic adaptations to exercise," he continues. "When the rate of exercise-induced damage (which can occur normally post-exercise to a certain extent) exceeds the healing capacity of the tissue, the result is excessive inflammation, which undoubtedly leads to an increased risk for injury."

Long-term NSAID administration also increases intestinal permeability (that leaky gut) significantly, says Horohov. This puts the horse at risk for a systemic inflammatory response to leaked bacterial endotoxin (LPS).

NSAID administration can interfere with normal repair mechanisms

"Since NSAID administration is thought to lead to ulcer formation, omeprazole, a proton pump inhibitor (PPI) drug, is frequently given with NSAIDs," he says. "However, studies have shown the opposite effect, with PPI drugs actually exacerbating NSAID-induced intestinal damage."

Researchers believe this to be due to significant shifts in intestinal microbial populations.

Take-Home Message

The ways we feed and keep our horses have a profound effect on their overall health. Many triggers lead to bodywide inflammation, with stress, obesity, high-starch and -sugar diets, intense exercise, and NSAIDs leading the charge. Good horse-keeping and nutritional practices are instrumental in preventing many problems that could ultimately result in bodywide inflammation. Looking at the body holistically can give us a new perspective on management strategies.