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Review Article

Alterations in Intestinal Permeability: The Role of the "Leaky Gut" in Health and Disease

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ABSTRACT

All species, including horses, suffer from alterations that increase intestinal permeability. These alterations, also known as "leaky gut," may lead to severe disease as the normal intestinal barrier becomes compromised and can no longer protect against harmful luminal contents including microbial toxins and pathogens. Leaky gut results from a variety of conditions including physical stressors, decreased blood flow to the intestine, inflammatory disease, and pathogenic infections, among others. Several testing methods exist to diagnose these alterations in both a clinical and research setting. To date, most research has focused on regulation of the host immune response due to the wide variety of factors that can potentially influence the intestinal barrier. This article serves to review the normal intestinal barrier, measurement of barrier permeability, pathogenesis and main causes of altered permeability, and highlight potential alternative therapies of leaky gut in horses while relating what has been studied in other species. Conditions resulting in barrier dysfunction and leaky gut can be a major cause of decreased performance and also death in horses. A better understanding of the intestinal barrier in disease and ways to optimize the function of this barrier is vital to the long-term health and maintenance of these animals.

1. Introduction

The intestinal tract serves many vital functions that include the selective absorption of essential nutrients, ions, and other compounds while serving as a barrier against harmful, noxious substances. Dysfunction of this barrier and alterations in intestinal permeability, also known as "leaky gut" is an important topic for clinicians and researchers in all species including horses and humans. In humans, changes in intestinal permeability have been linked in the pathogenesis of debilitating inflammatory bowel diseases (IBDs) such as Crohn's disease (CD) [1] and in autoimmune diseases such as Celiac disease [2]. Currently conditions resulting in leaky gut are known to occur in equine species, yet few scientific studies have been conducted focusing on this condition. In horses, gastrointestinal issues are reported second to only old age as the leading cause of death [3]. Death or illness can result from the systemic effects of microbial toxins and pathogens that "leak" through the intestinal wall and the subsequent immune response that includes the production of inflammatory mediators. Leaky gut is therefore described in both severe, life-threatening intestinal obstructions as well as in long-term, insidious disorders that result in weight loss and decreased performance (Fig. 1). Thus, a better understanding of the intestinal barrier in disease and how to improve its function remains vital to the long-term health and the maintenance of high-level athletic performance of these animals. This paper serves to review the normal

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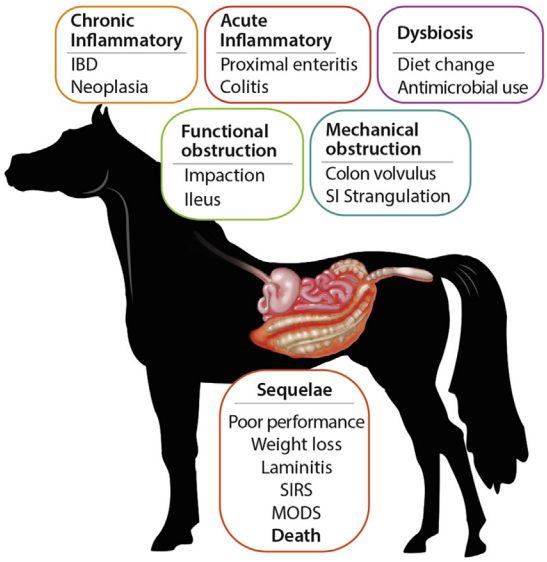

Fig. 1. Altered intestinal permeability (leaky gut) in horses. Specific causes of leaky gut in horses range from alterations in the microbiota, acute and chronic inflammatory disease, and both mechanical and functional intestinal obstructions. These conditions alter permeability in several ways including disruption of normal blood flow to the intestine, increased production of proinflammatory cytokines, and disruption of the normal cell junctions, among others. Sequelae to leaky gut may include weight loss and poor performance in mild cases and SIRS, MODS, or death in severe cases. IBD, inflammatory bowel diseases; MODS, multiple organ dysfunction syndrome; SI, small intestinal; SIRS, systemic inflammatory response syndrome.

intestinal barrier, measurement of barrier permeability, pathogenesis and main causes of altered permeability, along with highlight potential alternative therapies of leaky gut in horses while relating what is known in other species including poultry, porcine, rodent, and human.

2. Intestinal Barrier and Permeability

Intestinal permeability is determined by the interaction of several components including an unstirred water layer that forms a diffusion barrier in combination with mucus. In addition, mucus protects the villi from physical friction and bacterial adhesion [4,5]. Other barrier components include phospholipids within the mucosal surface, epithelial factors including tight junctions, the intestinal immune system including lymphocytes and the gut microbiota [4,6–8]. The gut microbiota, a complex community of microorganisms that inhabits the intestine, varies with diet, age, and environment, and influences normal physiology and susceptibility to disease through its metabolic activities and host interactions [8]. A full review of the microbiota and its interactions with intestinal barrier function is outside the scope of this article and the interested reader is directed to several recent reviews [8–12].

One of the most important and widely studied intestinal barrier components is the intestinal epithelium. The intestinal epithelium is composed of a single layer of cells and is the largest of the body's mucosal surfaces [13]. These epithelial cells are polarized, contain apical and basolateral membranes, and are responsible for creating a physical barrier, transporting nutrients, and protecting the underlying tissues [14]. The epithelial layer of the large intestine (colon) is folded into invaginated crypts of Lieberkühn that contain undifferentiated stem cells and are supported by the lamina propria (Fig. 2) [15]. The small intestinal epithelium is composed of villi that extend into the lumen and are lined by differentiated, post-mitotic cell types, and the crypts of Lieberkühn that contain Paneth cells and undifferentiated stem cells [16]. The stem cells are responsible for creating new epithelium every 5–7 days [17,18]. Enteroendocrine, goblet and Paneth cells are the specialized, secretory epithelial cells that maintain the digestive or barrier function of the epithelium via hormone, mucin, and antimicrobial peptide secretion, respectively [13]. When healthy, the epithelial barrier is impermeable to toxins, pathogens, and antigens while maintaining a selective permeability for the transport and absorption of nutrients, ions, and water (Fig. 2). Selective permeability occurs via the following two pathways: the paracellular and transcellular pathway [19]. The transcellular pathway, predominately mediated by transport channels located on the apical membrane, involves the transport of nutrients including sugars, amino acids, and fatty acids across the cell. The paracellular pathway, associated with passage of molecules in the space between adjacent cells, is regulated by an apical junctional complex (AJC) made up of adherens junctions and tight junctions (Fig. 3). Adherens junctions, along with desmosomes, provide strong connective bonds between epithelial cells. Cell to cell contact at the adherens junction is mediated by adhesion molecule complexes made up of protein families including the cadherins and catenins. Tight junctions consist of four unique families of transmembrane proteins including occludin, claudins, junctional adhesion molecules, and tricellulin, and are considered one of the principal determinants of mucosal permeability (Fig. 3) [20,21]. These transmembrane

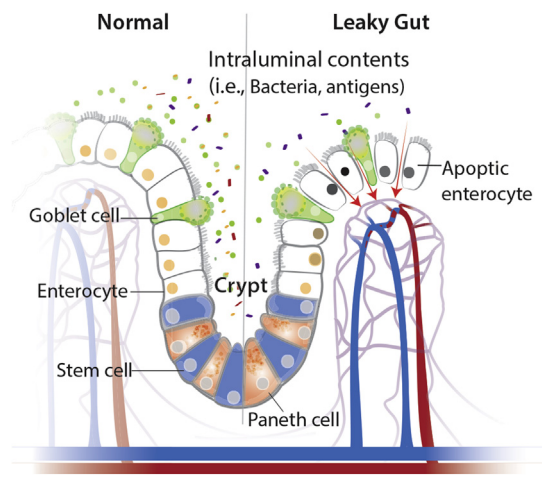

Fig. 2. Components of the mucosal barrier in health and disease. The normal intestinal barrier is made up of a single layer of epithelial cells, with normal cell death (apoptosis) and turnover every 5–7 days. Undifferentiated stem cells are located at the crypt base and interspersed between post-mitotic Paneth cells. When intestinal permeability is altered, the junctions between the cells are disrupted and luminal contents can enter the surrounding tissues as well as systemic circulation. As a result, cells may undergo increased apoptosis and decreased barrier function.