Veterinary Bioscience: Digestive System

LECTURE 27
THE GASTROINTESTINAL BARRIER

LECTURER

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INTENDED LEARNING OUTCOMES

At the end of this lecture, you should be able to:

- Describe the histological structures of the gastrointestinal tract that contribute to its functional integrity and explain the structures and mechanisms that provide protection from damage caused by gut contents including parasites and microbes.
- Explain the functional significance of the crypt-villus unit in the replenishment of intestinal epithelial cells, and the kinetics of gastrointestinal turnover.
- Explain the importance of mucosal blood flow in maintaining the integrity of the mucosal barrier and describe the important factors that regulate mucosal blood flow.
- Describe the processes that govern drug absorption from the gastrointestinal tract, and the physiological and pathological factors that may limit drug absorption.

KEY WORDS

Villus, crypt-villus unit, microvillus, brush border, goblet cell, tight junction, prostaglandin, stem cell, mucosal barrier, mucus, bicarbonate, gastric ulcer, villus atrophy, drug absorption.

LECTURE OVERVIEW

How is it that the gastric mucosa can secrete acid at a pH of less than 2, and proteolytic enzymes that digest ingested meat and other proteins, yet the single celled mucosal lining of the stomach is not digested by its own secretions? What determines why a nutrient is absorbed, yet a potentially harmful molecule is not? How can drugs be designed to enhance or to limit their absorption from the gastrointestinal tract? How are bacteria and other microorganisms prevented from entering the mucosa? Understanding the answers to these questions involves understanding the biological principles that underpin the concept of the gastrointestinal barrier.

Disruption of the gastrointestinal barrier is a significant contributor to disease processes. It allows intestinal microorganisms to cause systemic disease, and in other situations, systemic disease can result in disruption of the mucosal barrier, that further compromises the patient.

Structural aspects of the mucosal barrier

The intrinsic mucosal barrier is composed of the epithelial cells and the tight junctions that hold them together. Once toxins or microorganisms cross this epithelial surface, they have relatively unimpeded access to the circulation. The integrity of tight junctions is therefore critical and understanding factors that modulate their permeability is important.

Epithelial cells themselves differ in their permeability to ions and hence their resistance to damage from luminal content. Parietal cells in the stomach for example, are less permeable to protons than intestinal epithelial cells and hence less prone to acid damage than intestinal cells.

Secretions and the mucosal barrier

The surface of the gastrointestinal tract is coated with mucus that contributes to the barrier in a number of ways. Mucus reduces shearing forces on the epithelial surface, helps bind and aggregate bacteria, preventing their colonisation, and impairs absorption of some water-soluble molecules. A range of mucins are produced in different parts of the digestive tract. Some are membrane bound and recognise and repel bacteria, others exert their protective effects by creating a physical barrier. Some are involved in cell signalling, leading to secretion of bactericidal compounds by surface epithelial cells.

Epithelial cells in both the stomach and intestines also secrete bicarbonate ions, that help to create a neutral pH at the apical cell surface, despite widely fluctuating pH in the gastrointestinal lumen.

Cell turnover and the mucosal barrier

An important functional component of the intrinsic mucosal barrier is provided by the constant turnover and replenishment of epithelial cells in the stomach and intestines. Integrity of the mucosal barrier relies on a balance between stem cell proliferation, differentiation and epithelial cell death.

In the intestine, this dynamic cell population is described as the crypt-villus unit. Epithelial cells migrate from the base of a crypt to the tip of a villus where they are extruded, over a period of three to five days. As they do so, they differentiate from a stem cell to a secretory cell and finally to an absorptive epithelial cell. A number of disease states are characterised by changes in the balance of cell types in the crypt-villus unit as a result of changes to proliferation, differentiation or the rate of cell death. Villus atrophy is one outcome of such a perturbation.

In the stomach, stem cells that give rise to the various cell types are located in the mid gland region and migrate as they differentiate in both directions in the gland.

Mucosal blood flow

Another important component of the mucosal barrier is provided by the mucosal blood supply. The submucosa is richly supplied with blood vessels, that in addition to providing nutrients and oxygen to mucosal cells, allow for rapid removal of hydrogen ions that diffuse from the lumen. Any disease state that causes significant reduction in mucosal blood flow will result in damage to the mucosal barrier. Gastric ulceration associated with haemorhagic shock occurs by this mechanism.

Control mechanisms and the mucosal barrier

Each of the functional aspects of the mucosal barrier that have been described above is subject to regulation- some that are better understood than others. Important and well described regulators of a number of these functions are the prostaglandins (PGs)- particularly PGE and prostacyclin, that are synthesized and released locally in the gastrointestinal mucosa. PGs increase mucus and bicarbonate secretion, stimulate cell proliferation and increase mucosal blood flow. Nonsteroidal anti-inflammatory

Drugs (NSAID's) such as aspirin increase the risk of gastric ulceration because they impair prostaglandin synthesis.

Other chemicals known to be involved in maintenance of the mucosal barrier are epidermal growth factor (EGF) secreted in saliva and by duodenal glands and transforming growth factor alpha (TGF- alpha), that is secreted by gastric epithelial cells. Both bind to a common receptor to increase epithelial cell proliferation, and also increase gastric mucus secretion and decrease acid secretion.

How do drugs cross the mucosal barrier?

There are a number of potential routes for drugs to cross the mucosal barrier. How they cross and the rate of absorption depends on characteristics of the drug and also the functional state of the mucosa. A reduction in mucosal surface area (for example as a result of villus atrophy,) will reduce absorption of drugs as well as nutrients, and this needs to be taken into account if drugs are administered orally. Equally, disease states that increase permeability of the mucosal barrier can result in absorption of drugs not normally absorbed, or in increased rate of absorption of a drug, beyond what is expected.

Many drugs are absorbed in a concentration dependent manner; (the greater the concentration the greater the absorption of drug). For these drugs diluting the drug in food may result in reduced absorption of drug. The concentration gradient of the drug across the mucosal surface also depends on mucosal blood flow. Local variations in blood flow as a result of exercise or feeding can change the concentration gradient for absorption of drugs- so can be important when determining timing of drug administration.

Solubility of the drug is also important. For amphoteric drugs, that are weak acids or bases, their solubility varies depending on the pH of the luminal content- which of course may vary along the gut length and also with feeding status.

To be absorbed drugs must cross both the apical and basal epithelial cell surface. Lipid soluble drugs cross these membranes readily and so can establish a large concentration gradient between the lipid membrane and the cytosol. Some water-soluble drugs move readily across the membrane by bulk flow, with water absorbed in active co-transport mechanisms. Some very small drugs may also move by diffusion through tight junctions.

FURTHER READING

Blikslager AT, Roberts MC: *Mechanisms of intestinal mucosal repair*. J Am Vet Med Assoc 211:1437-1441, 1997.

Cunningham's *Textbook of Veterinary Physiology* 6th Ed Elsevier 2020 Ch 27 & 28