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## COMPARATIVE GUT PHYSIOLOGY SYMPOSIUM: Comparative physiology of digestion<sup>1</sup>

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**ABSTRACT:** The digestive systems of all species have been shaped by environmental pressures over long evolutionary time spans. Nevertheless, all digestive systems must achieve the same end points, the ingestion of biological material and its conversion to molecules that serve as energy substrates and structural components of tissues. A range of strategies to extract nutrients, including for animals reliant primarily on foregut fermentation, hindgut fermentation, and enzymatic degradation, have evolved. Moreover, animals have adapted to different foodstuffs as herbivores (including frugivores, folivores, granivores, etc.), carnivores, and omnivores. We present evidence that humans have diverged from other omnivores because of the long history of consumption of cooked or otherwise prepared food. We consider them to be cucinivores. We present examples to illustrate that the range of foodstuffs that can be efficiently assimilated

by each group or species is limited and is different from that of other groups or species. Differences are reflected in alimentary tract morphology. The digestive systems of each group and of species within the groups are adaptable, with constraints determined by individual digestive physiology. Although overall digestive strategies and systems differ, the building blocks for digestion are remarkably similar. All vertebrates have muscular tubular tracts lined with a single layer of epithelial cells for most of the length, use closely related digestive enzymes and transporters, and control the digestive process through similar hormones and similarly organized nerve pathways. Extrapolations among species that are widely separated in their digestive physiologies are possible when the basis for extrapolation is carefully considered. Divergence is greatest at organ or organismal levels, and similarities are greatest at the cell and molecular level.

**Key words:** comparative physiology, digestive enzymes, digestive physiology, fermentation, hormones, microbiota

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### INTRODUCTION

All vertebrates need to achieve the same end point, which is to convert food into constituent molecules (i.e., free fatty acids, monosaccharides, amino acids, etc.) that can be absorbed to be used as structural molecules and energy substrates and to absorb

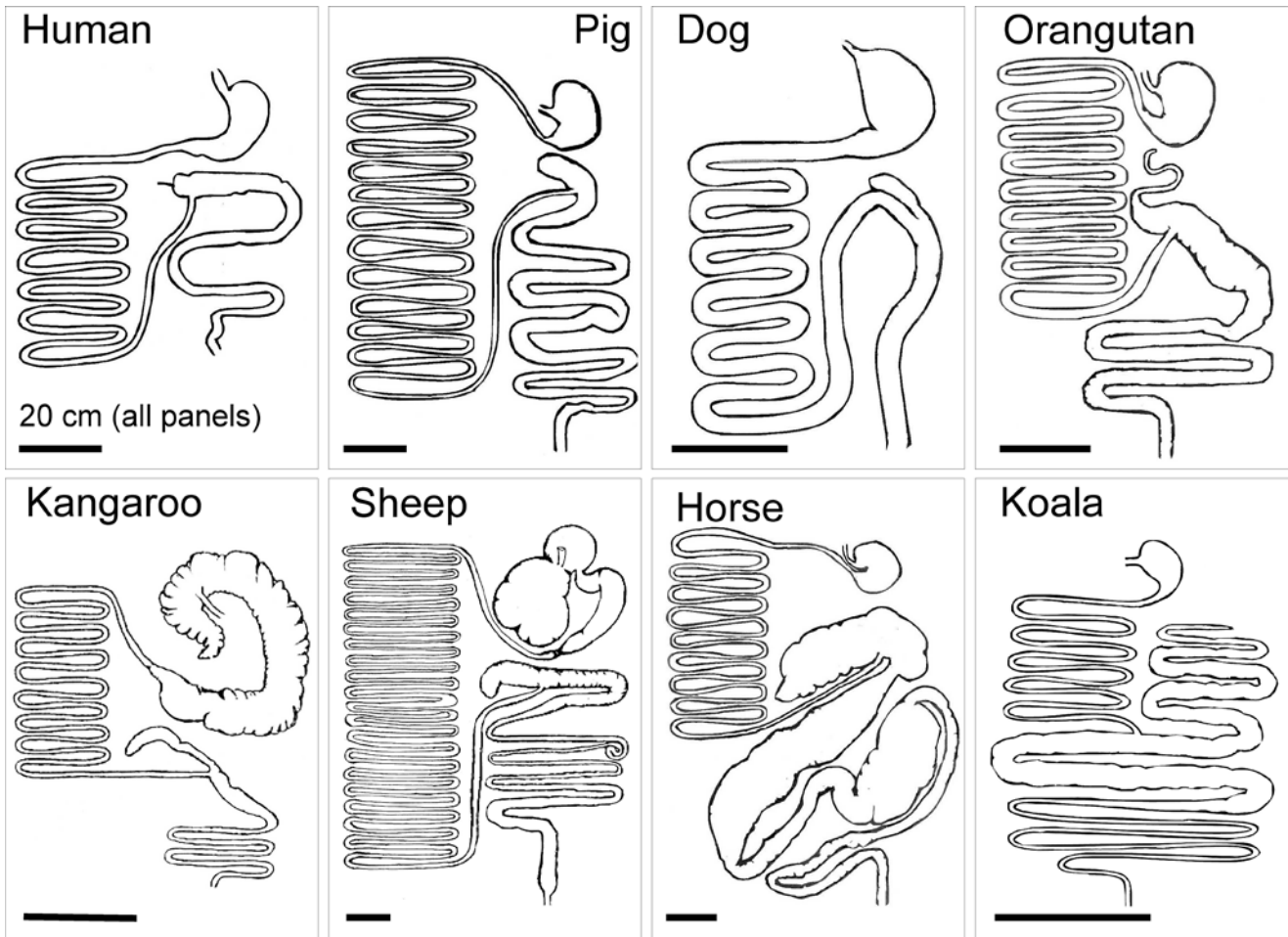
other essential components, such as vitamins and ions. How each species reaches this end point and the ways in which they enlist microbiota to aid the tasks differ. Differences in digestive physiology are important in determining, inter alia, the diet appropriate to a particular species, how broad a range of foods an animal can eat, the efficiency of conversion, and food tolerances. Even within a species, the appropriate diet depends on life stage and animal condition (e.g., differing between preparturition and lactation in dairy cattle). Conversion efficiency is an important consideration for agriculture, in which animal feed is an input cost. In the development of nutritional strategies to improve conversion efficiency, most attention has been paid to the metabolism of farm animals and

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**Figure 1.** Comparisons of digestive tract anatomy. It can be seen that the human digestive tract is relatively small. Compared with that in the pig, an omnivore that is often regarded as a model for humans, the human large intestine is much reduced. The dog intestine is capacious but relatively short. The human large intestine is also small compared with anthropoid apes, here illustrated by the orangutan. The kangaroo, a nonruminant foregut fermenter, has a large sacculated stomach, whereas the hindgut fermenter, the horse, has a capacious, multicompartiment large bowel. The koala, which consumes only leaves that are rich in tannins and volatile oils, has an extensive large bowel and reduced small intestine. Reproduced with permission from Stevens and Hume (1998).

to processes happening within the lumen of the digestive tract. The primary interest was to optimize the purely digestive process without considering the gut as a target organ per se. With recent progress of technologies and subsequent new knowledge generated by biological sciences, there is an increased interest in physiological processes that occur in the digestive tract. The gut is now considered to be an intelligent sensory organ controlling physiological functions of zootechnical importance. Undoubtedly, knowledge and progress are quicker in other fields of biology compared with animal nutrition. The relatively slow progress reinvigorates the quest for better knowledge of digestion and absorption in animals and also for improved understanding of comparative aspects among species.

### COMPARATIVE ASPECTS OF DIGESTION: DIFFERENT STRATEGIES

Despite the diversity of solutions to the problems of nutrient assimilation, no mammal has evolved to be a universal digester. A human could not exist on the diet of a sheep, koala, or panda and neither could a cat. Further, a koala probably could not exist on the diet of any of these other species. These differences are reflected in substantial variations in digestive tract anatomy (Fig. 1). To simplify discussion, we divide species into ruminant foregut fermenters (such as cattle and sheep), nonruminant foregut fermenters (e.g., kangaroos and colobus monkeys), hindgut fermenters (such as the horse), and (predominately) autoenzyme-dependent digesters (pigs and humans). Species such as the pig that rely primarily on nonbacterial enzymatic breakdown of food in the foregut also gain nutrition from hindgut fermentation. Harnessing bacteria for fermentation is only a partial bargain because the bacteria themselves utilize components of the food. Protozoa and fungi in the gut

lumen can also contribute nutrients to host species. In general, animals have evolved so that they have limited spare digestive capacity while having significant plasticity of the digestive system that allows individual animals to adapt to different types and amounts of food (Karasov et al., 2011).

### RUMINANT FOREGUT FERMENTERS

Ruminants are efficient digesters because the ruminal movements are able to stratify food into gas, fluid, and particle components; ruminants retain food to be digested in the forestomach and pass more fully digested material into the abomasum and duodenum and are also able to return food from the forestomach to the mouth for mastication and enzyme exposure (Clauss et al., 2010). Ruminants lose efficiency in that most carbohydrate is fermented by rumen bacteria, and on a natural diet little glucose reaches the small intestine. Most glucose is synthesized from propionic acid produced by bacteria, whereas species such as the pig and human convert carbohydrate to glucose by enzymatic breakdown. Ruminants also derive some glucose from the conversion of amino acids (Aschenbach et al., 2010). Thus, ruminants are more prone than other groups to enter into negative glucose balance, for example, during postpartum lactation (Gordon et al., 2013). Foregut fermenters are also advantaged by being able to readily utilize vitamins produced by bacteria, particularly B vitamins (Stevens and Hume, 1998). For this reason, ruminants do not require B vitamins in the diet. Coprophagy by hindgut fermenters, such as rabbits, provides access to such vitamins. Foregut fermentation also contributes to detoxification, for which hindgut fermenters and primarily enzymatic digesters rely mainly on the liver. Humans have a long history of detoxification by cooking food, as discussed below.

The rumen holds large populations of cellulolytic and xylanolytic bacteria, as well as pectinolytic bacteria, which are adapted to the breakdown of plant cells. It is notable that all mammals lack cellulases and that in animals with only hindgut fermentation and short hindguts, such as cats, plant cell walls are essentially indigestible, except through limited microbial fermentation. By contrast, cellulases are present in some invertebrates (Watanabe and Tokuda, 2001). Ruminal bacteria are almost entirely anaerobes that utilize glucose and produce short-chain fatty acids, notably acetate, propionate, and butyrate, plus ethanol, hydrogen, methane, and CO<sub>2</sub>. Protein ingested by ruminants is broken down by bacteria into peptides, amino acids, and ammonia, with the ammonia being the major source of nitrogen for bacterial protein production (Stevens and Hume, 1998). The bacteria also recycle urea from protein breakdown elsewhere in the body. Thus, the

majority of protein entering the small intestine is of bacterial origin (Bach et al., 2005). Ruminal bacteria also incorporate nitrogen into nucleic acids that are digested by RNases in the small intestine, with the RNases coming primarily from the pancreas, which in ruminants contains considerably greater concentrations of RNases than in nonruminant species (McAllen, 1982).

In addition to ruminal handling of nutrients, the small and large intestines have important roles. In particular, in cattle fed high-concentrate diets, large amounts of dietary starch reach the small intestine, where some is digested by pancreatic amylases and brush border disaccharidases. However, the carbohydrate digestive capacity of the small intestine is limited, and with high-starch intakes excess passes on to the large intestine, where it is a substrate for fermentation (Huntington et al., 2006). The ruminant small intestine also has an important role in the digestion of bacterially derived protein.

### AUTOENZYME DIGESTERS: CARNIVORES, OMNIVORES, AND HUMANS (CUCINIVORES)

Autoenzyme digesters refers to those species that have considerable reliance on foregut and midgut digestion, utilizing enzymes that they themselves produce, rather than relying on bacterial enzymes. Examples are humans, pigs, practically all carnivores, and rodents. These species commence the digestive process by mastication in the presence of salivary enzymes, primarily amylases. They have simple stomachs that subject the masticated food to acid hydrolysis and exposure to enzymes, mainly proteases. Gastric acidity and proteases also kill the majority of bacteria (with an exception being *Helicobacter pylori*) in the food. As in ruminants, the stomach has a reservoir function and, perhaps with less efficiency than in ruminants, sorts digested from nondigested foods by trituration. In humans, antral contractions massage and push the contents toward the pyloric sphincter, and triturated aspirates containing only small particles, less than about 1 mm in diam., are propelled into the duodenum (Kelly, 1980).

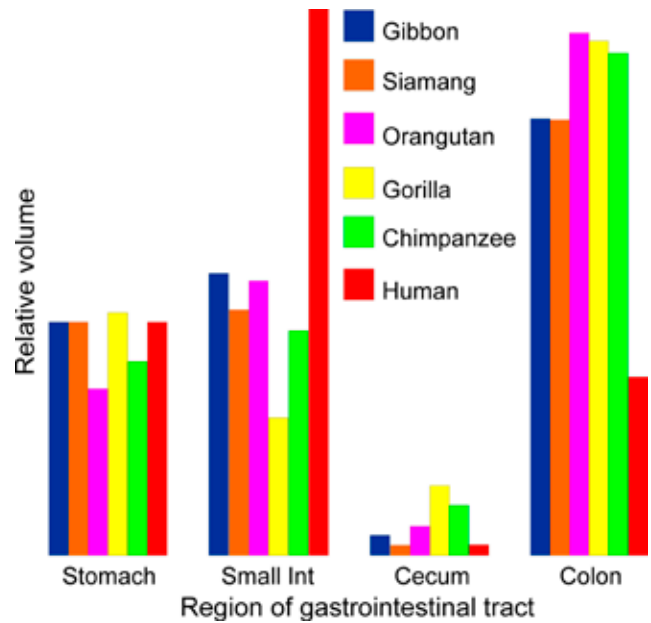
Further autoenzymatic digestion occurs in the small intestine, utilizing enzymes released from the exocrine pancreas and those in the gut wall, especially in the glycocalyx of enterocytes. The pancreatointestinal enzymes include a range of proteases (trypsins, chymotrypsins, carboxypeptidases), carbohydrases (amylases, disaccharidases), and lipases. The effectiveness of lipases is enhanced by emulsification of fats by bile salts. None of these enzymes is able to digest plant walls or plant wall components, such as pectin and cellulose, because pectinases and cellulases are absent. On the other hand, indigestible plant carbohydrate can influence the digestion of other dietary

components. Pectin binds cholesterol, tends to reduce plasma cholesterol, and may slow glucose absorption by trapping carbohydrates (Brouns et al., 2012).

The large intestines of autoenzyme digesters differ considerably among omnivores, in which the large intestine can be capacious, as in the pig, and can include a significant cecum, as in the rat and guinea pig. It is not until the substantially digested food reaches the cecum and colon that significant populations of bacteria are encountered in omnivores. The populations of hindgut bacterial colonies express digestive enzymes similar to those found in the rumen. Carnivores have relatively short hindguts (Fig. 1), which are often continuous with the small intestine and in external features and diam. are similar to the midgut (Stevens and Hume, 1998). Most carnivores have little need and reduced ability to digest carbohydrate.

### CUCINIVORY

Humans have consumed cooked foods for some 300,000 to 400,000 yr, perhaps 12,000 generations, and no groups of humans who lived without cooking have been recorded (Wrangham and Conklin-Brittain, 2003; Weaver, 2012). So a human can be classified as a cucinivore, rather than an omnivore. Humans also initiate food breakdown through storage, such as by hanging meat, drying, or prolonged marination (e.g., civet de lièvre), and by pounding and grinding. Cooking changes the palatability, digestibility, and texture of food and removes toxins. This history may have influenced humans to have alimentary tracts that are quite different from that expected in an anthropoid primate. In humans, the colon represents only 20% of the total volume of the digestive tract, whereas in apes it is about 50% (Fig. 2; Milton and Demment, 1988; Milton, 2003). The sizeable colons of most large-bodied primates permit fermentation of low-quality plant fibers, allowing for extraction of energy in the form of short-chain fatty acids (Leonard et al., 2007). Thus, humans are relatively poor among autoenzyme-dependent omnivores in digesting uncooked plant fiber. The human large intestine lies somewhere between that of the pig, a similar omnivore, and the dog, a carnivore capable of consuming an omnivore diet that has a reduced cecum and short colon. Evidence for this trend is that hindgut absorption of short-chain fatty acids accounts for 2% of maintenance energy for dogs, 6% to 9% for humans, and 10% to 31% for pigs (Stevens and Hume, 1998). In horses, it provides 46% of maintenance energy requirements. A further adaptation to softer foods is the smaller molars and reduced bite strength in humans compared with other primates (Eng et al., 2013). The smaller gastrointestinal tract of humans requires smaller abdominal and



**Figure 2.** Relative volumes of the stomach, small intestine, cecum, and colon in modern humans and extant apes. Note that for the apes, the colon represents about 50% of gut volume, whereas the volume in humans is less than 20% of the total. This difference is reflected in the greater reliance on processed foods for humans. Reproduced with permission from Milton (2003).

pelvic cavities (Aiello and Wheeler, 1995), which may be an advantage to a mammal that stands erect.

### AN EXTREME EXAMPLE OF DIVERSITY

The koala, an arboreal mammal that eats exclusively a diet of eucalyptus leaves, has a number of anatomical, physiological, and microbial hosting adaptations (Barker et al., 2013). Its primary digestive organ is the hindgut (Fig. 1). The koala cecum is the largest of any mammal in relation to body size, and its mean gastrointestinal retention time is the longest known among mammals. Eucalyptus leaves contain high levels of tannins, and the pure eucalyptus leaf diet would be toxic for other mammals. However, the koala's large intestine is colonized by tannin-digesting bacteria, including *Lonepinella koalarum*, which was discovered in the koala and is perhaps unique to this species (Barker et al., 2013). Mother koalas are observed to feed their young a fecal paste that is presumably a mechanism to ensure colonization with appropriate bacteria.

### COMPARATIVE ASPECTS OF DIGESTION: SIMILAR BUILDING BLOCKS AND PROCESSES

Up to this point, this review has illustrated how general aspects of digestion and absorption differ among animals. The optimal utilization of nutrients requires an integrated response of the gastrointestinal tract to ingested food. All mammals sense food com-

**Table 1.** Levels of pancreatic amylase in the cat compared with those of the dog, a carnivore that adapts to a mixed diet; the pig, an omnivore; the horse, a hindgut fermenter whose major carbohydrate source is bacterially generated short-chain fatty acid; and the sheep, a ruminating foregut fermenter<sup>1</sup>

| Species | Pancreatic amylase, units/g wet wt |
|---------|------------------------------------|
| Cat     | 70                                 |
| Dog     | 3,000                              |
| Pig     | 3,500                              |
| Horse   | 350                                |
| Sheep   | 1,100                              |

<sup>1</sup>Data are from Kienzle (1993).

ponents through olfaction and taste and also using specialized receptors within the stomach and intestines. The sensing of food components leads to release of gut hormones and activation of nerves, which in turn modify digestive functions and absorptive capacity.

Despite the differences in the processes by which foods are broken down into absorbable molecules, the cellular and molecular organization of the sensing system and reactions to the presence of food are very similar among animals. For example, regarding the digestive function itself, digestive enzymes, such as amylases, are highly conserved, from insects to mammals (Payan, 2004). Likewise, nutrient transporters, such as the sodium-glucose linked transporter (**SGLT1**) and **Glut1** (glucose transporter 1), are highly conserved, even between vertebrates and invertebrates (Caccia et al., 2007). The sensing of food components by the stomach and intestine involves a triad: 1) receptors in contact with the gut lumen, 2) specific gut cells called enteroendocrine cells that express these receptors in their apical domain, and 3) gut hormones secreted by these endocrine cells into the lamina propria. Interestingly, the individual hormones and receptors and the triad itself are present in all vertebrate species. Initially described in rodents and humans, similar classes of enteroendocrine cells have been observed in a variety of other animals, for example, in fish (Latorre et al., 2013), birds (Rawdon, 1984; Nishimura et al., 2013), horses (Daly et al., 2012), and ruminants (Moran et al., 2014). They behave as specialized transducers of luminal signals and partner with neurons to magnify the signal, leading to a range of effects on digestive processes (Dockray, 2013; Furness et al., 2013). The receptors used by these cells to detect luminal signals have been observed in many species. One well-illustrated example is the taste receptors initially found in the lingual epithelium and later described in enteroendocrine cells of a number of species, including rodents and humans (Wu et al., 2002; Rozengurt and Sternini, 2007), fish (Latorre et al., 2013), horses (Daly et al., 2012), pigs

(Moran et al., 2010), and ruminants (Moran et al., 2014). Finally, the hormones secreted by the endocrine cells when they are stimulated (gut hormones) arose early in evolution and have been well conserved across species (Rehfeld, 2004). For example, peptide YY is present in all vertebrates (Larhammar, 1996; Conlon, 2002). The glucagon-like peptides have also been described in very different animals, including chickens, pigs, sheep, and ruminants (Moran et al., 2010; Nishimura et al., 2013; Moran et al., 2014). Finally, the innervation of the gastrointestinal tracts of all vertebrates is similar, and primary neurotransmitters are well conserved (Olsson and Holmgren, 2011; Uyttbroeck et al., 2010). In all species, an integrated neural control involving the enteric nervous system, the central nervous system, and reflex pathways that pass through sympathetic ganglia regulates aspects of digestive system function (Furness, 2012).

Interestingly, when their gut is stimulated, different species sharing the same molecular and cellular machineries also share physiological responses. For example, even if its effect in chickens and quails is equivocal, ghrelin is present in birds, fish, reptiles, and amphibians, as well as in mammals (Kaiya et al., 2008); in most fish species, ghrelin treatment appears to promote food intake and a more positive energy balance (Jönsson, 2013) like it does in mammals (Kojima and Kangawa, 2005). The enhanced glucose uptake following upregulation of the glucose transporter **SGLT1** in response to glucose or artificial sweeteners appears to share the same molecular series of events in rodents and humans (Margolskee, 2002; Margolskee et al., 2007) and also horses, piglets, dairy cows, calves, and sheep (Moran et al., 2010, 2014; Daly et al., 2012; Nishimura et al., 2013). Conversely, animals lacking specific molecular machinery do not respond to certain stimuli. This is the case of a specialty feeder, the cat; **Felidae** have little need to handle carbohydrate, and it is interesting that they have lost functional expression of the carbohydrate-detecting sweet taste receptor (Li et al., 2005). Moreover, the induction of carbohydrases and monosaccharide transporters that occurs with carbohydrate feeding in omnivores does not occur in cats (Buddington et al., 1991; Kienzle, 1993). Also, cats have very low levels of amylase (Table 1). Thus, cats have the digestive physiology of obligate carnivores.

An example of a difference coupled to eating habit is the control of intestinal transit by the migrating myoelectric complex (**MMC**). The MMC is a cyclical pattern of electrical and mechanical activity that moves slowly along the small intestine, sweeping the contents before it. It has been investigated in most detail in dogs, in which it occurs during fasting and is interrupted, to be replaced by irregular contractile (i.e., mixing) activity, when the dog is fed (Code and Marlett, 1975). Human small intestinal MMC occur in the fasted state at about

90-min intervals and are also interrupted by a meal (Rees et al., 1982; Husebye et al., 1990). In herbivores, which tend to be continuous eaters, the MMC occurs during the fed state, as demonstrated for sheep (Ruckebusch and Bueno, 1975), rabbits (Grivel and Ruckebusch, 1972), and guinea pigs (Galligan et al., 1985). In sheep, the MMC occurs about every 90 min and travels slowly along the small intestine, a traverse taking 90 to 120 min. The MMC also occurs in poultry, in both the fed and fasted states (Jimenez et al., 1994). It is unclear what initiates the MMC in different species. Administration of the gut peptide hormone, motilin, initiates the MMC in humans (Vantrappen et al., 1979) and in dogs (Lee et al., 1983) but not in pigs (Buéno et al., 1982) or rabbits (Guerrero Lindner et al., 1996). Rats and mice have MMC but lack motilin. In herbivores, the MMC, which is persistent throughout digestion, appears to have a role in ensuring the passage of digesta, whereas in carnivores it is thought to sweep away food residue and sloughed enterocytes between meals (Wingate, 1981). An improved knowledge of the factors that determine the occurrence of the MMC and its rate of passage in different species may lead to strategies to modify digestive efficiency, for example, by restricting the MMC and increasing the duration of the digestive phase.

## SUMMARY AND CONCLUSIONS

Mammals have evolved to occupy a broad range of environmental niches. This evolution has favored the divergence of digestive strategies, a divergence that is reflected in a range of digestive tract gross morphologies and in food specialization. Nevertheless, fundamental cellular and molecular features of the digestive tracts of mammals are shared and are found in nonmammalian vertebrates and, to a significant extent, in invertebrates. Many of the building blocks of the digestive systems are similar. This similarity includes carbohydrases and other digestive enzymes, the transporters, the neural control systems, and gastroenteropancreatic hormones. Divergence is greatest at organ or organismal levels, and similarities are greatest at a the cell and molecular level. Extrapolations between species that are widely separated in their digestive physiologies are possible when the basis for extrapolation is carefully considered. More insights into molecular and cellular events governing the response of the gut to its environment may be a basis for fruitful extrapolations to production animals.

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