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Review: Nutritional regulation of intestinal starch and protein assimilation in ruminants

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Pregastric fermentation along with production practices that are dependent on high-energy diets means ruminants rely heavily on starch and protein assimilation for a substantial portion of their nutrient needs. While the majority of dietary starch may be fermented in the rumen, significant portions can flow to the small intestine. The initial phase of small intestinal digestion requires pancreatic α-amylase. Numerous nutritional factors have been shown to influence pancreatic α-amylase secretion with starch producing negative effects and casein, certain amino acids and dietary energy having positive effects. To date, manipulation of α-amylase secretion has not resulted in substantial changes in digestibility. The second phase of digestion involves the actions of the brush border enzymes sucrase-isomaltase and maltase-glucoamylase. Genetically, ruminants appear to possess these enzymes; however, the absence of measurable sucrase activity and limited adaptation with changes in diet suggests a reduced capacity for this phase of digestion. The final phase of carbohydrate assimilation is glucose transport. Ruminants possess Na^+-dependent glucose transport that has been shown to be inducible. Because of the nature of pregastric fermentation, ruminants see a near constant flow of microbial protein to the small intestine. This results in a nutrient supply, which places a high priority on protein digestion and utilization. Comparatively, little research has been conducted describing protein assimilation. Enzymes and processes appear consistent with non-ruminants and are likely not limiting for efficient digestion of most feedstuffs. The mechanisms regulating the nutritional modulation of digestive function in the small intestine are complex and coordinated via the substrate, neural and hormonal effects in the small intestine, pancreas, peripheral tissues and the pituitary—hypothalamic axis. More research is needed in ruminants to help unravel the complexities by which small intestinal digestion is regulated with the aim of developing approaches to enhance and improve the efficiency of small intestinal digestion.

Keywords: carbohydrate, amino acid, intestinal, digestion, absorption, cattle

Implications

Feed digestion represents a critical process of the utilization of nutrients for productive purposes such as meat or milk production. In high-producing ruminants, starch represents the major component of dietary energy, whereas protein represents a high cost and dietary, environmental concern; thus, it is critical that the utilization of both be optimal. Evolution has dictated that ruminants use protein derived from microbial fermentation, and this tends to be a critical driver for nutrient assimilation. In contrast, starch does not result in signalling to increase starch assimilation, and evolutionary constraints may exist for maximal use in the small intestine of ruminants.

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Introduction

In ruminants, the composition of digesta flowing to the small intestine differs substantially from what is consumed in the diet because ruminants have a complex stomach with four compartments allowing for pregastric fermentation (Merchen, 1988; Swanson, 2019). This differing digesta composition is because of fermentation in portions of the stomach (rumen, reticulum and omasum) resulting in the production of volatile fatty acids (**VFAs**) and microbial biomass. The VFA provides a large proportion (approximately 50% to 85%) of the total metabolizable energy to the animal. A portion of the feed carbohydrates and proteins are degraded in the forestomachs, and a portion escapes fermentation in the forestomachs and flows to the small intestine along with microbial biomass containing microbial protein and is utilized by the animal. Microbial protein supplies a

substantial portion (approximately 50% or more) of the protein digested and utilized by the animal.

The small intestine is the primary site of digestion and absorption of the macronutrients, escape starch, protein (microbial and escape) and lipids, aside from VFA absorption in the forestomachs. Because of the microbial influence on the nutrient profile, a complete description of these processes remains elusive. The objectives of this review are to describe: (1) the processes and potential limitations of small intestinal starch and protein assimilation and (2) the mechanisms regulating the nutritional modulation of digestive function in the small intestine in ruminants.

Small intestinal starch digestion

The feeding of large amounts of grain to ruminants is still a relatively new practice encompassing approximately the past 70 years. The continued availability of comparatively inexpensive cereal grains has insured that the practice will continue for the foreseeable future as modern production practices continually expand in scale with ever-decreasing profit margins. Research into these practices is also relatively recent with the earliest work characterizing the adaptive responses in ruminants fed high-starch ingredients (Clary *et al.*, 1969).

In forage-based diets, fibre and microbial polysaccharides are the primary carbohydrates flowing to the small intestine (Swanson, 2019). Limited fibre is digested in the small intestine because there are no fibre-digesting enzymes produced by the animal and there is a much smaller population of microbes in the small intestine than in the forestomach. When forage-based diets are fed, limited amounts of soluble carbohydrates such as starches flow to the small intestine as the small amounts in forages are fermented by the microbes in the forestomach, and any α-glucosides present may arise from microbial sources (Branco *et al.*, 1999). However, from 4% to 60% of dietary starch passes to the small intestine, depending on grain source and processing methods, when high-concentrate diets based on cereal grains are fed (Theurer, 1986). A recent summary for dairy cows (Moharrery *et al.*, 2014) reported that ruminal digestion averaged 68% with a range of 22% to 94%.

Pancreatic α-amylase

Most species readily adapt their complement of digestive enzymes to match their diet (Brannon, 1990), ensuring maximum digestion of major dietary components. Early work suggested that ruminants fed high-grain diets had increased pancreatic concentrations of α-amylase (Clary *et al.*, 1969; Russell *et al.*, 1981; Janes *et al.*, 1985). Kreikemeier *et al.* (1990) were the first to demonstrate that pancreatic α-amylase was linked to dietary energy intake and that earlier studies suggesting that pancreatic α-amylase was up-regulated with increased starch intake were confounded by dietary energy. This study (Kreikemeier *et al.*, 1990) demonstrated that cattle do respond to increased dietary energy, whether it is from forage or concentrate, by increasing pancreatic α-amylase content. When starch intake was increased while controlling energy, the content of pancreatic α-amylase decreased.

This adaptive response is unique and unexpected. Follow-up experiments using steers with pancreatic cannula confirmed that starch infused directly into the abomasum would decrease pancreatic α-amylase secretion compared with water or starch infused into the rumen (Walker and Harmon, 1995).

The nature of ruminant digestion insures that increased dietary energy increases the intestinal supply of microbial protein. Thus, the interpretation of experiments reporting that increased dietary energy intake increases pancreatic α-amylase is inherently confounded with energy and protein. Experiments have shown that increasing the small intestinal protein supply by infusing casein abomasally increases small intestinal starch disappearance (Richards *et al.*, 2002) and abomasal casein infusion increases pancreatic α-amylase secretion (Richards *et al.*, 2003). These results could indicate that the increased pancreatic α-amylase responses to increased dietary energy resulted from the increased supply of small intestinal protein.

To directly examine the relationship between the small intestinal supply of protein and energy, calves were infused abomasally for 10 days with casein and starch in a 2×2 factorial arrangement (Swanson *et al.*, 2002a). Compared with control (water infusion), calves receiving starch had reduced pancreatic α-amylase, whereas calves receiving casein had increased pancreatic α-amylase. However, calves receiving both starch and casein had reduced pancreatic α-amylase, similar to starch alone. These results suggest that the positive effects of casein to increase pancreatic α-amylase are suppressed by increased small intestinal starch.

The regulation of pancreatic α-amylase is obviously complex and involves translational events. In the casein and starch infusion study (Swanson *et al.*, 2002a), casein infusion increased both pancreatic α-amylase mRNA expression and α-amylase protein, whereas starch + casein decreased both.

The ability of starch, or a partially hydrolysed starch solution (Walker and Harmon, 1995; Swanson *et al.*, 2002a), to down-regulate pancreatic α-amylase questions the capacity of the ruminant to hydrolyse starch and how starch influences the regulation of pancreatic α-amylase. However, a comparison of glucose infused abomasally compared with starch demonstrated that glucose also down-regulates pancreatic α-amylase (Swanson *et al.*, 2002b) indicating that the hydrolysis of α-glucosides is not limiting the adaptive response.

The downregulation of pancreatic α-amylase in cattle remains an intriguing and unexplained adaptive response. The concept has been studied and repeated across multiple experiments and experimental models. Several experiments have sought to characterize factors that affect pancreatic α-amylase, particularly factors that appear to stimulate increases in pancreatic α-amylase. The most notable of these is increasing casein supply to the small intestine. Research infusing starch and casein either ruminally or abomasally into steers (Taniguchi *et al.*, 1995) reported that starch and casein infused abomasally increased the net portal

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and total splanchnic fluxes of glucose suggesting greater small intestinal starch hydrolysis and glucose absorption. Casein infused into the abomasum of lambs has been reported to increased glucose transporter activity in the small intestine (Mabjeesh *et al.*, 2003).

The observation that casein could enhance small intestinal starch assimilation was followed by experiments showing that small intestinal starch disappearance (Richards *et al.*, 2002; Brake *et al.*, 2014b) and pancreatic α-amylase secretion (Richards *et al.*, 2003) increased with casein infusion. Subsequent work comparing the feeding of intact and acid-hydrolysed casein demonstrated that intact casein stimulated pancreatic α-amylase secretion in steers as well as increasing cholecystokinin (**CCK**) secretion (Lee *et al.*, 2013).

The exact mechanism for stimulation of pancreatic α-amylase and increasing starch digestion remains unclear but attempts to refine the response to individual amino acids have been made. Brake *et al.* (2014a) infused duodenally and ileally cannulated steers with starch and compared additions of casein, crystalline amino acids similar to casein and essential or non-essential amino acids similar to casein. The small intestinal starch digestion was highest for the casein and crystalline amino acids similar to casein treatments. These authors then followed with a second experiment comparing casein, glutamate equivalent to casein, phenylalanine plus tryptophan plus methionine equivalent to casein or both. Small intestinal starch digestibility was highest in the casein and glutamate treatments, and based on differences in the ileal flows of small-chain α-glycosides the authors suggested that casein and non-essential amino acids may increase starch digestion by different mechanisms with casein favouring increased pancreatic α-amylase. The differential response suggesting a greater pancreatic α-amylase response was not present in a follow-up study where glutamate infusion from 30 to 120 g/day linearly increased small intestinal starch digestibility (Blom *et al.*, 2016).

Numerous mechanisms may contribute to what is measured as increased small intestinal disappearance. Research on milk-fed calves reported that 89% of starch intake might have been fermented prior to the terminal ileum (Gilbert *et al.*, 2015) suggesting that microbial activity may contribute substantially to the small intestinal carbohydrate disappearance. The infusion of casein into the small intestine causes dramatic increases in large intestinal digestion suggesting that stimulation of microbial activity in the small intestine is undoubtedly a contributor to the increased disappearances observed with casein and may explain some of the differential responses attributed to casein and amino acids (Brake *et al.*, 2014a and 2014b; Blom *et al.*, 2016), albeit 89% disappearance from fermentation may be unique to the milk-fed calf. However, the increases in intestinal starch disappearance observed with individual amino acids are less attributable to increased microbial activity and have been associated with increased pancreatic α-amylase.

Other amino acids have been evaluated for their effect on small intestinal starch digestion. Goats were infused duodenally with phenylalanine at 0, 2, 4 and 8 g/day for 2 weeks and pancreatic secretion was measured (Yu *et al.*, 2013). Pancreatic α-amylase secretion responded quadratically with a small increase at 2 g/day. A follow-up experiment using short-term, 10 h infusions showed that pancreatic α-amylase secretion responded cubically with increases in secretion at 2 and 10 g/day of phenylalanine. A similar experiment using goats reported that both short- and long-term infusions of leucine at 0, 3, 6 or 9 g/day increased pancreatic α-amylase secretion (Yu *et al.*, 2014a).

The inconsistent responses may result from the difficulty in assessing pancreatic α-amylase secretion with few animals and because of the pulsatile and variable secretion from the pancreas. However, these studies (Yu *et al.*, 2013 and 2014a) indicate that phenylalanine and leucine have the ability to up-regulate pancreatic α-amylase secretion, whereas the combination of phenylalanine plus tryptophan plus methionine did not increase small intestinal starch digestion in steers (Brake *et al.*, 2014a). These observations were confirmed in goats receiving duodenal infusions of leucine (3 and 9 g/day) and phenylalanine (2 g/day) that were slaughtered and enzyme activity in the small intestine measured (Yu *et al.*, 2014b). The infusion of leucine and phenylalanine caused large increases in pancreatic α-amylase activity in the proximal small intestine and tended to increase small intestinal starch digestibilty.

The effects of leucine on pancreatic secretion have also been studied in cattle. Heifers fitted with pancreatic cannula also received duodenal infusions of 10, 20 and 30 g/day of leucine (Liu *et al.*, 2015). They reported that leucine infused at 10 g/day increased pancreatic α-amylase secretion. However, supplementing additional phenylalanine and leucine in milk-fed calves did not increase pancreatic α-amylase (Cao *et al.*, 2018).

The milk-fed calf may have differing mechanisms of regulation compared with the previous studies in mature ruminants. However, leucine has been shown to up-regulate pancreatic α-amylase in pancreatic acinar cells isolated from new-born calves and maintained in culture (Guo *et al.*, 2018a). They demonstrated an upregulation of the m-TOR signalling pathway that may have resulted in increased α-amylase synthesis. This response contrasted with the influence of phenylalanine that was studied using pancreatic acinar cells and tissue segments isolated from 2-month-old calves (Guo *et al.*, 2018b). Phenylalanine stimulates α-amylase secretion and mRNA expression as well as the phosphorylation of S6K1 and 4EBP1 indicating that phenylalanine could regulate the synthesis of α-amylase through the mRNA translation initiation factors, S6K1 and 4EBP1. Thus, these studies report that phenylalanine and leucine both stimulate pancreatic enzyme synthesis but through different mechanisms.

Mucosal carbohydrases

Research on the deficiencies of mucosal carbohydrases in infants has dramatically increased our understanding of the processes involved in mucosal carbohydrase function (Nichols *et al.*, 2018). The major starch hydrolysis activities within the small intestine function through two proteins that

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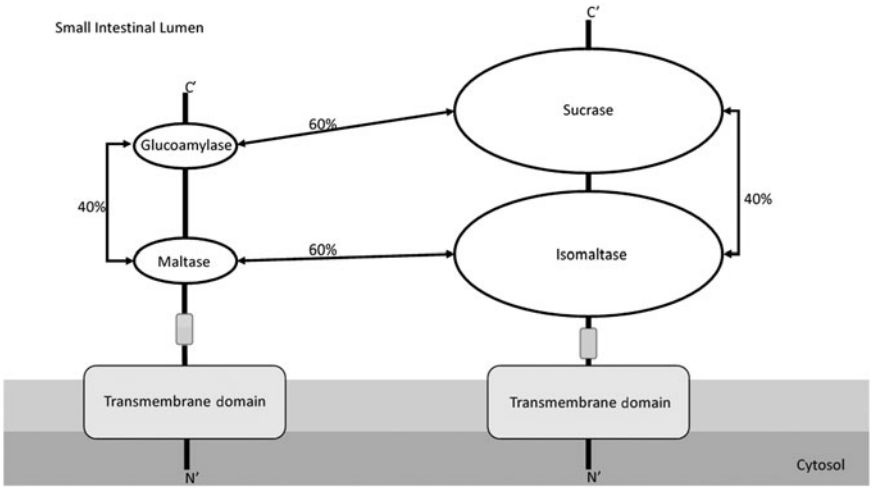

Figure 1 Maltase-glucoamylase and sucrose-isomaltase protein structures. Percentages represent sequence identity. Size differences represent greater relative protein abundances for sucrose-isomaltase. Adapted with permission from Lee *et al.* (2016) Copyright ©2016 American Chemical Society.

contribute four hydrolytic activities, sucrase-isomaltase and maltase-glucoamylase (Galand, 1989). These proteins have a high degree of homology (Figure 1), and sucrase-isomaltase is generally present in much higher quantities. These four activities are better described as α-glucosidases because they digest multiple linear starch oligosaccharides to glucose, not just maltose. An excellent chronology of the study of intestinal disaccharidases is available (Lentze, 2018).

The process of starch assimilation in humans has been described in detail by numerous authors. The process involves six carbohydrase activities: salivary and pancreatic α-amylase, n-terminal and c-terminal activities of sucrase-isomaltase and maltase-glucoamylase (Lin *et al.*, 2012b). Ruminants lack salivary α-amylase, and they possess no sucrase activity (Huber *et al.*, 1961). Thus, of the six required enzyme activities ruminants possess perhaps four, pancreatic α-amylase, mucosal isomaltase activity and mucosal maltase(s) activities (Coombe and Siddons, 1973). The enzyme profile of ruminants resembles humans exhibiting congenital sucrase-isomaltase deficiency where patients have genetic mutations resulting in the absense of one or both subunits of sucrase-isomaltase resulting in limitations in carbohydrate digestion.

A complete understanding of starch assimilation may also be limited by terminology. The textbook description has been that pancreatic α-amylase α-1,4 endoglucosidase hydrolysis in the intestinal lumen produces maltose and a collection of limit dextrins, so named because of the presence of α-1,6-bonds 'limits' the activity of α-amylase in these regions. These products of pancreatic α-amylase are then exposed to mucosal carbohydrases that hydrolyse this collection of starch fragments at the brush border membrane prior to glucose transport. While this description is not inaccurate, it is simplistic. For example, studies characterizing the substrate preferences of the n- and c-terminal subunits of recombinant mammalian maltase-glucoamylase and sucrase-isomaltase reported that the c-terminal subunit of maltase-glucoamylase provided rapid and high digestion of cooked starch, nearly 80%, while other subunits showed 20% to 30% digestion (Lin *et al.*, 2012b). Thus, multiple proteins may contribute to the hydrolysis of starch molecules.

Referring to maltase as a specific enzyme is also misleading, but rather there are multiple proteins possessing maltase activity, or more specifically, each subunit possessing carbohydrase activity has activity on multiple substrates (Lin *et al.*, 2012a). Characterization of the substrate preferences of the intestinal carbohydrases for various α-linked substrates demonstrated that c-terminal and n-terminal maltase-glucoamylase and c-terminal and n-terminal sucrase-isomaltase all possessed some hydrolytic capacity for isomaltose, whereas both c-terminal sucrase-isomaltase and c-terminal maltase-glucoamylase hydrolysed sucrose (Table 1). This would suggest that since ruminants possess no measurable sucrase activity there are differences in the structure and function of the mucosal carbohydrases.

The process of multiple entities acting on multiple substrates increases the complexity of carbohydrate assimilation exponentially. However, strides have been made in understanding this process. The roles of maltase-glucoamylase and sucrase-isomaltase have been characterized using a maltodextrin substrate chosen to emulate a pancreatic α-amylase

Table 1 *Hydrolysis of different substrates by c-terminal (ct) and n-terminal (nt) mouse recombinant α-glucosidases*

		Substrate	
Protein	Major activity	Sucrose	Isomaltose
ct-maltase-glucoamylase	Glucoamylase	14.8 ± 0.6	8.8 ± 0.2
nt-maltase-glucoamylase	Maltase	0.6 ± 0.1	28.4 ± 1.0
ct-sucrase-isomaltase	Sucrase	73.1 ± 0.1	18.1 ± 0.1
nt-sucrase-isomaltase	Isomaltase	0.9 ± 0.0	98.4 ± 3.6

One unit of enzyme activity was arbitrarily defined as the amount of enzyme that released 1 μg of glucose from 1% maltose per 10 min at 37°C.; Mean value ± SD of measurement of experiments performed in triplicate. Adapted from Lee *et al.* (2016).

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end-product (Quezada-Calvillo *et al.*, 2007). They reported that at low-substrate concentrations maltase-glucoamylase was more active than sucrase-isomaltase; however, at higher substrate concentrations, maltase-glucoamylase was inhibited, whereas sucrase-isomaltase was not. Thus, maltase-glucoamylase contributed only 20% of the hydrolytic activity, and pancreatic α-amylase was stimulatory to both the hydrolytic activities of sucrase-isomaltase and maltase-glucoamylase. This inhibitory activity was later localized to the C-terminal 'glucoamylase' subunit (Quezada-Calvillo *et al.*, 2008). It has been proposed that maltase-glucoamylase is responsible for the rapid hydrolysis at low-starch intakes, whereas sucrase-isomaltase provides sustained hydrolysis at high-starch intakes (Diaz-Sotomayor *et al.*, 2013). This greater overall activity of sucrase-isomaltase is consistent with the relative abundances of the proteins in that sucrase-isomaltase is approximately 3-fold greater than maltase-glucoamylase (Amiri and Naim, 2017).

While our knowledge of the brush border carbohydrases has increased dramatically for non-ruminants, much less is known in regard to their function in ruminants. The expression of sucrase-isomaltase and maltase-glucoamylase has been shown to be highly responsive to diet changes in mice, increasing in response to increased digestible starch and regressing when fed resistant starch (Goda and Honma, 2018). This response is thought to be elicited by available hexose as corresponding increases in glucose transporter (SGLT1) accompany increases in sucrase-isomaltase with both glucose and fructose feeding, with the reponse being more significant for fructose (Kishi *et al.*, 1999).

The structural similarities of sucrase-isomaltase and maltase-glucoamylase (59% homologous) suggest a common route for post-translational processing in that both are type II membrane glycoproteins (Nichols *et al.*, 1998; Amiri and Naim, 2017). A similar path of post-translational processing could result in a common alteration in c-terminal processing affecting both proteins. However, differences in processing do exist (Amiri and Naim, 2018). Particularly, sucrase-isomaltase is cleaved at the luminal membrane by trypsin into the two subunits (Naim *et al.*, 1988) whereas maltase-glucoamylase is not.

Generally, ruminant mucosal carbohydrase activities are non-responsive to changes in diet (Siddons, 1968; Russell *et al.*, 1981; Janes *et al.*, 1985; Kreikemeier *et al.*, 1990; Bauer *et al.*, 1995; Gorka *et al.*, 2017). Ruminants possess measurable activities for maltase (Siddons, 1968), isomaltase (Coombe and Siddons, 1973), trehalase (Coombe and Siddons, 1973; Kreikemeier *et al.*, 1990) and lactase (Siddons, 1968).

Heat inactivation suggested that activities of trehalase, isomaltase and lactase were single entities, whereas maltase represented multiple activities (Coombe and Siddons, 1973). Based on the Lee *et al.* (2016) study (Table 1), the n-terminal activities of both proteins would represent multiple enzymes with no sucrase activity. Whether both proteins differ in ruminants remains to be determined.

The apparent absence of changes in mucosal carbohydrase activities in ruminants suggests that ruminants do not adapt to increased intake of carbohydrate. However, increased intestinal length (Kreikemeier *et al.*, 1990) and increased mucosal mass (Kreikemeier *et al.*, 1990; Gorka *et al.*, 2017) led to increases in total hydrolytic capacity of the intestine and in the jejunum with increases in energy intake (Kreikemeier *et al.*, 1990; Gorka *et al.*, 2017).

These studies suggest that, as ruminants consume increased amounts of high-concentrate diets, there is a greater ability to assimilate the starch in the small intestine. However, that capacity when compared with the ability of the non-ruminant to adapt, and perhaps with a more efficient complement of enzymes, may explain the inefficiencies of ruminant small intestinal digestion. We have calculated that starch digestibility in the small intestine must be maintained to at least 70% (Huntington *et al.*, 2006) to maintain the energetic efficiency advantages of small intestinal digestion. These limitations may explain some of the challenges of meeting that requirement.

Glucose transport

Early research suggested limited amounts of glucose are absorbed into the portal blood of functioning ruminants (Schambye, 1951). However, studies directly evaluating glucose transport by measuring disappearance of sugars from isolated loops of the small intestine filled with sugar solutions determined that absorptive capacity decreased along the length of the small intestine as measurements proceeded distally and that the capacity decreased following weaning (White *et al.*, 1971). These workers also suggested that the capacity for glucose absorption was less than the rat, mainly as a function of intestinal length per kg BW.

The presence of active transport of sugars was reported (Scharrer, 1976) and a decrease in transport capacity associated with weaning was described (Scharrer *et al.*, 1979). These authors (Scharrer *et al.*, 1979) also demonstrated that the declining transport of glucose associated with weaning could be delayed by prolonged milk feeding.

These early studies, which contributed significantly to our understanding of sugar transport in ruminants, were all conducted using anaesthetized sheep, with measurements made using intestinal perfusions and measurement of glucose disappearance. These observations were later confirmed using brush border membrane vesicles prepared from sheep small intestine (Shirazi-Beechey *et al.*, 1989). These authors reported that Na^+-dependent glucose transport (SGLT1) was present throughout the small intestine of pre-ruminant lambs but absent in ruminants. These observations were later extended (Shirazi-Beechey *et al.*, 1991a) to show that SGLT1 was maximum 2 weeks following birth then declined to negligible amounts following weaning and that increased transport activity could be maintained by maintaining lambs on milk replacer. This study was also the first to report SGLT1 could be induced in the small intestine of 2- to 3-year-old sheep infused for 4 days with 30 mM glucose or α-methyl-D-glucopyranoside (a non-metabolizable analogue).

Subsequent work (Lescale-Matys *et al.*, 1993) showed that maintaining lambs on milk maintained tissue SGLT1 mRNA levels, whereas infusion of glucose into functional

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ruminant sheep increased mRNA only 2-fold compared with a 60- to 90-fold increase in transporter activity. Changes in SGLT1 activity in sheep were associated with changes in SGLT1 protein abundance (Shirazi-Beechey *et al.*, 1996) whereas the regulation of SGLT1 synthesis was thought to occur post-translationally.

The presence of SGLT1 in cattle jejunum has been established (Kaunitz and Wright, 1984) and one of the first to address SGLT1 expression throughout the gastrointestinal tract was conducted in lactating cows (Zhao *et al.*, 1998). They reported that SGLT1 was expressed throughout the gastrointestinal tract of cattle and that SGLT1 was active in the small intestine, being greater in the proximal small intestine. Bauer *et al.* (2001b) infused both cattle and sheep abomasally or ruminally with a partially hydrolysed starch solution for 7 days before slaughtering and measuring transport activity in small intestinal tissues. They reported that SGLT1 increased 2.1-fold in the proximal jejunum of animals receiving the abomasal compared with the ruminal infusion. However, a subsequent study (Bauer *et al.*, 2001a) was unable to demonstrate changes in SGLT1 activity throughout the small intestine in response to abomasal *v.* ruminal infusion of partially hydrolysed starch. Obviously, a limitation of this model could be the conversion of starch hydrolysate to glucose or that mechanisms other than SGLT1 contribute to small intestinal glucose disappearance in cattle.

To determine if increased glucose in the small intestine upregulates glucose transport, glucose was abomassaly infused into steers and compared with steers receiving either ruminal or abomasal partially hydrolysed starch (Rodriguez *et al.*, 2004). Sodium-dependent glucose uptake was not affected by treatment, but uptake decreased distally along the intestine. This work is supported by results from dairy cows (Lohrenz *et al.*, 2011) fed high- (24%) and low-starch diets (12%). These workers reported no differences in expression of SGLT1 or GLUT2 mRNA or protein in brush border membrane vesicles prepared from mid-duodenum and mid-jejunum. Thus, it appears SGLT1 is functional in cattle, activities are highest in the proximal intestine, but activity does not appear to respond to higher intakes of starch-based diets.

The contribution of diffusion was assessed in cattle (Krehbiel *et al.*, 1996) by infusing glucose along with 2-deoxyglucose, a non-metabolizable, non-SGLT1 transportable analogue, into the proximal and mid-intestine of steers. They reported that glucose disappearance was much higher in the proximal small intestine and that passive diffusion was a minor contributor to portal glucose appearance. These results would suggest that SGLT1 is the major pathway for glucose transport from the intestinal lumen.

Dyer *et al.* (2003) using glucose molecules bound to polyethylene glycol to make them non-absorbable showed that glucose stimulates increased SGLT1 protein by interacting luminally with a glucose sensor. An alternative mechanism for enhancing luminal sugar removal was proposed using mice (Gouyon *et al.*, 2003) where the presence of sugars stimulated the recruitment of basolateral GLUT2 into the brush border membrane and the presence of this facilitated transporter contributed to the upregulation of glucose removal. This mechanism, however, remains controversial (Daniel and Zietek, 2015) or may be species dependent (Moran *et al.*, 2010). The latter work using piglets (Moran *et al.*, 2010) demonstrated that GLUT2 was expressed only in the basolateral membrane and that there was no uptake of substrate specific for SGLT1. Similarly, work using SGLT1 and GLUT2 knockout mice (Roder *et al.*, 2014) reported that SGLT1 was the major intestinal apical glucose transporter. At this writing, there is no information on whether GLUT2 plays a role in apical glucose transport in ruminants.

Sheep v. *cattle*

Evidence would suggest that perhaps sheep are more able to adapt to increasing small intestinal starch. When starch is infused into the abomasum, pancreatic α-amylase secretion decreases as it does in cattle (Wang and Taniguchi, 1998); however, when casein is infused with the starch pancreatic α-amylase secretion is restored, unlike cattle (Swanson *et al.*, 2002a). While the early work was confounded by dietary energy (Janes *et al.*, 1985) there were increases in carbohydrases with increased intake and when dietary energy was balanced using moderate starch diets (Swanson *et al.*, 2000), pancreatic α-amylase protein and activity tended to increase despite the trend for reduced pancreatic α-amylase mRNA.

Adaptive responses in glucose transport to carbohydrate in the small intestine have been demonstrated in sheep (Shirazi-Beechey *et al.*, 1989; Shirazi-Beechey *et al.*, 1991a and 1991b; Mabjeesh *et al.*, 2003) but changes have been more difficult to demonstrate in cattle (Bauer *et al.*, 2001a; Klinger *et al.*, 2013). Collectively, these data suggest that sheep may be better able to adapt to high-starch diets, but at present, there is no definitive comparison of starch utilization in sheep and cattle.

Limitations to post-ruminal starch digestion

Many researchers have suggested that the ruminant small intestine has a limited capacity for starch digestion (Orskov, 1986; Owens *et al.*, 1986; Swanson and Harmon, 2002; Swanson, 2019). Owens *et al.* (1986) summarized several studies and reported that only 55% of starch entering the small intestine disappears in the small intestine of cattle fed high-concentrate diets. A recent summary for dairy cows reported that small intestinal disappearance ranged from 11% to 90% with a mean of 60% (Moharrery *et al.*, 2014). Similar conclusions have been drawn from studies with dairy cattle (Nocek and Tamminga, 1991) and studies with both beef and dairy cattle (Harmon *et al.*, 2004). Aside from inefficiencies of undigested starch exiting the small intestine, large quantities of starch flowing to the large intestine can result in excess fermentation which can result in diarrhoea and acidosis.

Specific factors limiting starch digestion, proposed by Owens *et al.* (1986), include limited carbohydrase activity, insufficient time for complete starch hydrolysis, inadequate

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access of enzymes to starch granules and limited glucose absorption.

Pancreatic α-amylase has been suggested as a possibility by numerous authors; however, attempts to increase small intestinal α-amylase have not enhanced starch assimilation (Remillard *et al.*, 1990; Westreicher-Kristen *et al.*, 2018).

The downregulation of pancreatic α-amylase by starch has been overcome by casein infusion (Richards *et al.*, 2003; Brake *et al.*, 2014a) and this has been associated with increased small intestinal starch disappearance (Richards *et al.*, 2002) and similar responses have been shown with amino acids mimicking casein (Brake *et al.*, 2014a; Blom *et al.*, 2016). Whether these treatments achieve this increased intestinal disappearance through increased pancreatic α-amylase or some other means is unknown. It has been suggested that luminal pH in the proximal small intestine limits pancreatic α-amylase resulting in a shift in carbohydrate hydrolysis to the distal intestine where glucose transport is more limiting (Mills *et al.*, 2017); however, attempts to increase intestinal pH have not been shown to increase starch assimilation (Remillard *et al.*, 1990).

The apparently striking differences in mucosal carbohydrases in ruminants may pose another limitation. Knockout mice without maltase-glucoamylase had a 40% reduction in their ability to generate blood glucose from starch (Nichols *et al.*, 2009). This essential role plus the recent demonstration of the role of mucosal enzymes in hydrolysing starch (Quezada-Calvillo *et al.*, 2007) suggests that the ruminants evolutionary limits to starch hydrolysis may be greater than previously thought.

While glucose transport has been shown to be inducible in the small intestine of ruminants (Moran *et al.*, 2014) benefits of this increase for increased small intestinal starch assimilation are lacking.

Combined data suggest that ruminants are limited users of small intestinal starch and that the low digestibilities in the small intestinal are likely the outcome of multiple factors that are only overcome by supplying small amounts of highly digestible substrate.

Limitations in post-ruminal protein assimilation

Compared with carbohydrates, research on the processes of protein assimilation has received little attention. Excellent reviews covering many of the processes are available (Beck, 1973; Snook, 1973; Hooton *et al.*, 2015). However, scant information is available describing the processes in ruminants. The fact that ruminant digestion produces a relatively continual flow of microbial protein to the small intestine places a high priority on protein assimilation suggesting a highly efficient system is in place. Estimates used for small intestinal assimilation of protein are usually 80% (NASEM, 2016) based on N measurements; however, this is an apparent measure and values for true digestibility in the small intestine may be substantially higher. Estimates of small intestinal digestibility of feedstuffs made using the mobile nylon bag technique (Hvelplund *et al.*, 1992) suggest that a single value for small intestinal digestion is inadequate or more importantly, the digestibility of protein sources does vary in the small intestine. Previous research in ruminats showing that protein assimilation has not been exceeded when protein was infused at very high levels suggests that the small intestine has a high digestive and absorptive capacity for protein (Owens *et al.*, 1986). Apparent small intestinal digestion of N compounds in ruminants has been reported to be between 65% and 75% of duodenal N flow (Santos *et al.*, 1984).

Pancreatic proteases

The major endopeptidases, trypsin, chymotrypsin and elastase are all present in the ruminant pancreas, and bovine sources have been well characterized (Walsh *et al.*, 1964). The exopeptidases, carboxypeptidases A and B are also present, but there are limited data on their nutritional characterization.

The adaptation of protease activity in the small intestine of rats has been known for many years (Snook, 1965 and 1973). These adaptations to changes in diet involved increases in the synthesis and content of proteases in the pancreas and increased secretion of enzymes (Brannon, 1990). The complexity of ruminant digestion, that is, the pregastric fermentation necessitates that the majority of these studies infused proteins or amino acids into the abomasum or small intestine. Most of these studies reported steady amounts of trypsin or chymotrypsin activities in concert with the steady flows of microbial protein in the ruminant small intestine. However, adaptation did occur with changes in activity up to 1.5-fold common with the highest being 2.0- (Swanson *et al.*, 2004) to 2.85-fold increases (Yu *et al.*, 2014b). Contrast this with changes up to 6-fold reported in rats (Brannon, 1990) and it appears ruminant pancreatic protease activity is less responsive to changes in diet. Some of the apparent differences in relative changes may occur because much lower activities occur in the fasting and protein deficient non-ruminant models making relative changes much greater. In the fed ruminant, fermentation produces a nearly continuous flow of microbial protein to the small intestine, and changes in diet produce much more subtle changes in protein flow and changes in pancreatic proteases may be more subtle as well. However, adaptation or stimulation of synthesis and secretion does occur.

Mucosal peptidases

A complete accounting of mucosal peptidases in ruminants is not available at the present time. A summary of current information is available (Hooton *et al.*, 2015) and a partial summary of the most common brush border peptidases is in Table 2. The majority have been identified in bovine tissues (Uniprot, 2017) and characterized. Nomenclature for many peptidases has changed, and the identity of all present in any species remains elusive.

Peptidases are ubiquitous and multifunctional in that the same peptidase may be anchored in the brush border membrane, present in the cytosol of the enterocytes and present in the intestinal lumen. Peptidases have broad specificities allowing them to act on a variety of substrates

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Table 2 *Common peptidases in the mammalian small intestine brush border*

Peptidase	Site	Amino acid	Product	Bovine
Enteropeptidase	Trypsinogen		Trypsin	Yes
Aminopeptidase A	N	Asp, Glu	Amino acids	Yes
Aminopeptidase N	N	Ala	Amino acids	Yes
Aminopeptidase P	N	Pro	Di-tripeptide	Unknown
Dipeptidase 1	Dipeptides	Many	Amino acids	Yes
Dipeptidylpeptidase IV	N	Pro	Peptide	Yes
Angiotensin-converting enzyme	C	Pro	Peptide	Yes

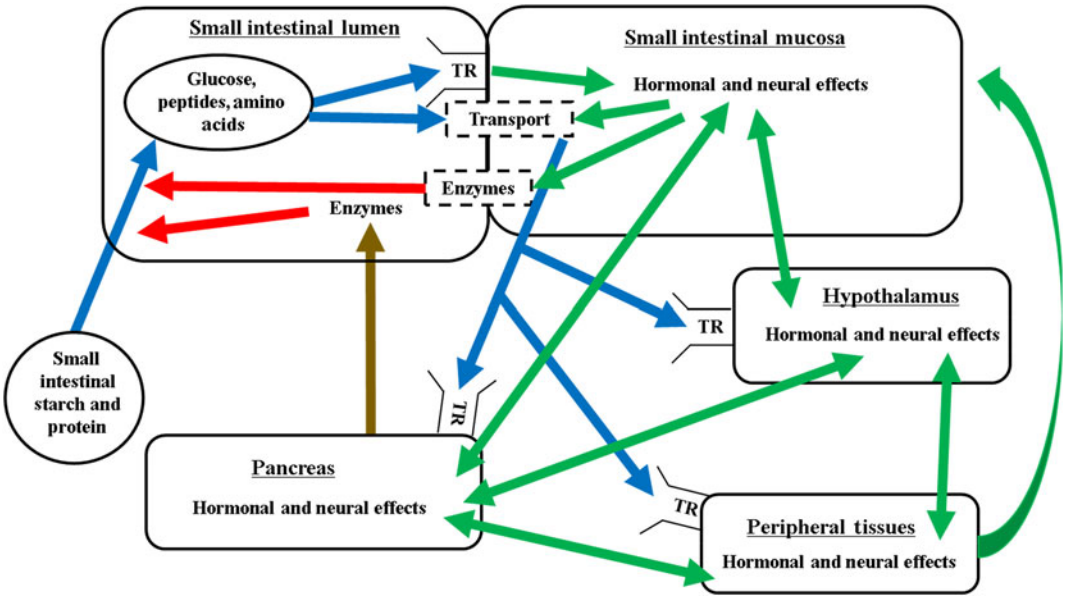

Figure 2 Proposed interrelationships of factors controlling digestion and absorption in ruminants. Blue lines represent nutrient flow, green lines represent hormonal and neural signalling, brown line represents secretion through the pancreatic duct, red lines represent digestive enzyme activity, dashed boxes indicate brush border. Enzymes = pancreatic and brush border carbohydrases and proteases; TR = taste receptor; transport = glucose or amino acid/peptide transporter.

generated from the hydrolysis of proteins by pancreatic enzymes. In general, peptidases are complementary to pancreatic enzymes in that multiple peptidases target proline containing residues where pancreatic enzymes have little or no activity (Erickson and Kim, 1990), others may act on intact proteins producing small peptides and amino acids eliminating the need for pancreatic proteases (Guan *et al.*, 1988). Brush border peptidases are highest in the proximal to the mid-gut region (Yoshioka *et al.*, 1988) in concert with their role in protein assimilation.

Peptide and amino acid transporters

The process of moving the products of digestion from the intestinal lumen across the brush border membrane is multi-faceted involving numerous amino acid and peptide transporters. A thorough description of these processes is beyond the scope of this paper. However, numerous excellent reviews are available describing both amino acid (Bröer, 2008) and peptide transporters (Daniel, 2004; Gilbert *et al.*, 2008; Daniel and Zietek, 2015).

Multiple systems have been described for both amino acid (Matthews *et al.*, 1996b; Knapp, 2004; Liao *et al.*, 2009) and peptide (Matthews and Webb, 1995; Matthews *et al.*, 1996a) transport in ruminants similar to other species. To date, aspects of amino acid or peptide transport in ruminants have not been reported limiting to protein assimilation.

Mechanisms regulating the nutritional modulation of digestive function in the small intestine

The mechanisms regulating the nutritional modulation of digestive function in the small intestine are complex and coordinated via the substrate, neural and hormonal effects in the small intestine, pancreas, peripheral tissues and the pituitary–hypothalamic axis (Figure 2). The overall regulation is also closely linked with factors regulating feed intake, glucose and amino acid metabolism, and energy balance.

The small intestine plays a vital role in the sensing, digestion and absorption of nutrients. Nutrients are an essential signal for the release of gut peptides (Bauer *et al.*, 2016)

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within the small intestine and absorbed nutrients can have intestinal, pancreatic or other peripheral effects in mediating dietary effects on pancreatic exocrine function (Call *et al.*, 1975; Blouet and Schwartz, 2010).

The importance of taste receptors on nutrient sensing in the digestive tract and other tissues in animals and humans is becoming more apparent (Moran *et al.*, 2014; Lushchak *et al.*, 2019). Taste receptors for sweet and umami (T1R), bitter (T2R) and salty (ENaC) have been described in vertebrate animals (Bachmanov *et al.*, 2014) with much of the research conducted using laboratory animals. Initially, the taste receptors were identified not only in the oral cavity but also in many metabolically active tissues in the body including the small intestine (Kochem, 2017). In the small intestine, the taste receptors are primarily concentrated in the enteroendocrine cells (Herzig *et al.*, 1994; Lee and Owyang, 2017). The gastrointestinal hormones that are secreted from the neuroendocrine cells containing taste receptors in response to stimulation of the taste receptors include secretin (S-cells), CCK (I-cells), ghrelin (X/A-like cells), GIP (K-cells), and peptide YY, glucagon peptide 1 and glucagon peptide 2 (GLP-2; L-cells) (Calvo and Egan, 2015). There is also a recent evidence suggesting that multiple gastrointestinal regulatory proteins can be co-localized within the enteroendocrine cells of the small intestine (Fothergill and Furness, 2018). The primary functions of the gastrointestinal hormones are to regulate feed intake, feed digestion and whole animal metabolism (Gribble and Reimann, 2017; Fothergill and Furness, 2018).

Cholecystokinin and secretin have long thought to be key regulators of pancreatic exocrine function (Miyasaka and Funakoshi, 1998; Chey and Chang, 2014) with CCK thought to have primary effects on enzyme secretion and secretin on the buffer and fluid secretion. These effects may be mediated by stimulating neural effects in the small intestine that regulate pancreatic exocrine function or directly on the pancreas via CCK receptors (Bourassa *et al.*, 1999). In pigs, this effect is likely mediated at the intestinal level via CCK receptors located in the duodenum which activate neural signals to increase pancreatic enzyme secretion (Evilevitch *et al.*, 2004). Less is known in ruminants. However, incubation of pancreatic tissue explants with caerulein, a CCK mimic, was shown to increase α-amylase release in bovine pancreas from steers previously abomasally infused with casein or when incubated with amino acids (Swanson *et al.*, 2003). The role of other gut peptides on pancreatic function is less well defined, especially in ruminants.

The primary nutrients that activate taste receptors in the small intestine are likely amino acids (Bachmanov *et al.*, 2016) and monosaccharides (Moran *et al.*, 2014). For example, recent research suggests that the positive effect of increased luminal glucose has on SGLT1 expression is mediated through neuroendocrine cells producing GLP-2 (Moran *et al.*, 2018). Similarly, amino acids have been shown to elicit CCK secretion via taste receptor activation in mice (Daly *et al.*, 2013). The physiological effects of taste receptors in the gastrointestinal tract are less well understood in ruminants. However, it has been shown that ruminants do express taste receptors in the small intestine and the artificial sweetener, Sucram, increases SGLT1 mRNA abundance, Na^+-dependent glucose uptake, maltase activity, and villus height and crypt depth in the small intestine in lambs and calves (Moran *et al.*, 2014). Although it seems that the small intestine in ruminants responds to increased glucose supply by increasing mass and carbohydrase activity, in past research from our laboratory, post-ruminal infusion of glucose decreased α-amylase secretion in steers (Swanson *et al.*, 2002b) suggesting a complex and perhaps uncoordinated regulation between intestinal and pancreatic responses related to the adaptation of post-ruminal starch digestive function.

Insulin also has long been implicated as an important regulator of pancreatic exocrine function (Brannon, 1990). Diabetic sheep have decreased α-amylase and lipase secretion (Pierzynowski and Barej, 1984) suggesting a role for insulin in regulating exocrine pancreatic function in ruminants. Also, an insulin-dependent element has been identified in the α-amylase gene in mice (Keller *et al.*, 1990) suggesting a direct role for insulin in regulating pancreatic exocrine function.

The hypothalamus is critical in sensing whole body signals (substrate, hormonal and neural) related to nutrient and energy balance and coordinating whole body responses to stimuli (Blouet and Schwartz, 2010) including factors related to feed intake, digestion and glucose homeostasis. There is also a strong evidence suggesting the importance of the brain–gut axis in regulating pancreatic secretion (Konturek *et al.*, 2003; Jaworek *et al.*, 2010). Interestingly, sweet/amino acid receptors also are located in the hypothalamus (Heeley and Blouet, 2016; Kohno, 2017) which likely are important in sensing systemic glucose and amino acid concentrations and along with neural and hormonal signals are sensed by the hypothalamus which allows for coordinated central control of metabolism, including intestinal and pancreatic function. Other hormones thought to influence pancreatic exocrine and intestinal function either directly or through neural signals include melatonin, C-natriuretic peptide, endocannabinoids and leptin to name a few (Chandra and Liddle, 2009). More research is needed in ruminants to help unravel the complexities by which small intestinal digestion is regulated with the aim of developing approaches to enhance and improve the efficiency of small intestinal digestion in ruminants.

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Declaration of interest

Both authors declare no conflict of interest and nor competing interest.

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Ethics statement

None.

Software and data repository resources

None of the data were deposited in an official repository.

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