

# Glucose uptake and regulation by intestinal tissues: Implications and whole-body energetics<sup>1</sup>

D. L. Harmon\* and K. R. McLeod†

\*Department of Animal Sciences, University of Kentucky, Lexington 40546-0215  
and †USDA, ARS, Beltsville, MD 20705

**ABSTRACT:** The purpose of this review is to examine mechanisms of glucose absorption by the ruminant small intestine and to relate these processes to available information on the theoretical advantages of shifting site of starch digestion in ruminants. The primary mechanism for glucose absorption across the brush-border membrane of enterocytes is the Na<sup>+</sup>-dependent glucose transporter, SGLT1. This transport protein is a high-affinity, concentrative, glucose transporter that couples glucose transport to an inwardly directed Na<sup>+</sup> gradient. This Na<sup>+</sup> gradient is maintained by the activity of Na<sup>+</sup>/K<sup>+</sup>-ATPase in the basolateral membrane. The activity of SGLT1 is highest in the developing ruminant and declines after weaning. Glucose transporter activity can be increased by intraluminal glucose; however, glucose absorption or metabolism is not necessary to induce transporter activity. Changes in SGLT1 activity are proportional to SGLT1 protein content. In contrast, SGLT1 mRNA levels are poorly correlated with SGLT1 activity, suggesting post-transcriptional regulation.

Forage-fed ruminants have little glucose available in the lumen of the small intestine, whereas considerable quantities can be available in animals fed concentrates. Because of this, glucose absorptive capacity in the small intestine is thought to vary greatly and has made the ruminant, particularly the sheep, a useful model to study the regulation of glucose transport. Theoretical calculations and experimental observations indicate that fermentation losses and differences in partial efficiencies of absorbed substrate use result in ruminally fermented starch or glucose being only 70 to 75% as energetically efficient as starch or glucose that is digested and absorbed in the small intestine. Accordingly, dietary approaches resulting in starch escaping ruminal fermentation should be energetically advantageous if no limitations occur in small intestinal starch assimilation. However, data demonstrating complete digestion of starch in the small intestine and improvements in animal energetic efficiency are limited.

Key Words: Absorption, Digestion, Glucose, Ruminants, Small Intestine

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## Introduction

Great progress has been made in the ability to supply nutrients for maximizing productivity of ruminants. Although pregastric fermentation offers the advantage of deriving both energy and protein from the fermentation of cellulose, it also suffers in that all dietary inputs are altered in an often unpredictable manner. The result of this process is that the flow of nutrients to the small intestine has been difficult to describe and predict based on diet formulation. The development and application of intestinal cannulas (Harmon and Richards, 1997)

has permitted the measurement of nutrients flowing from the stomachs into the small intestine, and from the small intestine into the large intestine. Armed with a database of nutrient flows and intestinal disappearances, systems for applying these estimates for diet formulation and performance predictions have arrived (NRC, 1996) and new model systems for interrelating ruminal starch digestion and small intestinal starch assimilation are being developed (Mills et al., 1999a,b). Despite these apparent successes, conclusions on the efficacy of small intestinal starch digestion and the subsequent absorption of glucose vs ruminal fermentation of starch remains controversial. Fermentation, although advantageous, is theoretically less energetically efficient. However, for the benefits of the increased efficiency of intestinal digestion to be realized, carbohydrate assimilation in the small intestine must be adequate or large intestinal fermentation will mask any gains in efficiency. It is the purpose of this review to examine information on the processes of glucose absorp-

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<sup>2</sup>Correspondence: 809 W. P. Garrigus Bldg. (phone: 859-257-7516; fax: 859-257-3412; E-mail: dharmon@ca.uky.edu).

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tion from the small intestine of the ruminant and to relate these processes to available information on the theoretical advantages of shifting site of starch digestion in ruminants.

### *Processes in the Small Intestine*

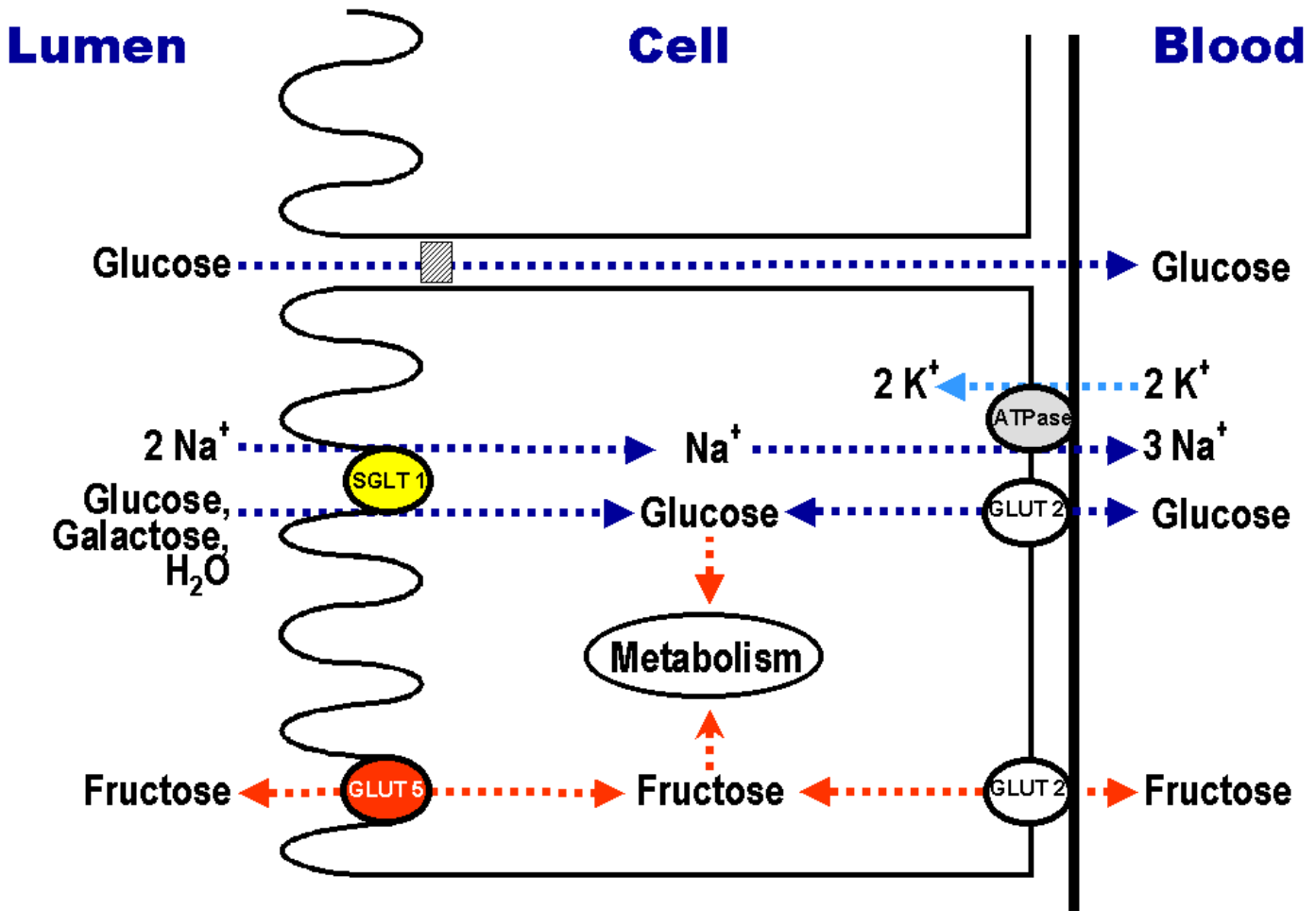
**Starch Supply.** The primary determinant of the amount of starch digested in the small intestine is the quantity of starch flowing there. Increasing the flow of starch into the small intestine increases the quantity that disappears. However, the efficiency of small intestinal digestion is less clear. Studies in which starch was infused into the abomasum (Little et al., 1968; Kreikemeier et al., 1991) or increasing quantities of ground corn were fed (Karr et al., 1966) have demonstrated that increasing the quantity of starch reaching the small intestine increases the daily starch disappearance; however, starch digestibility decreases as starch flow increases. This is in contrast to the review of Owens et al. (1986), who summarized results from 11 experiments encompassing 44 observations and found that on average 55% of starch reaching the small intestine disappeared there and that the relationship was linear. The reasons for these apparent discrepancies remain unclear. Linear relationships are not normally expected in biology, but we may not achieve a plateau in efficiency under practical feeding conditions. Whether the average digestibility is 55% (Owens et al., 1986) or digestibility decreases as starch flow increases (Little et al., 1968) is not the concern. Both are low and indicate an inefficient process. Huntington (1997) reviewed more recent digestion experiments covering 24 published reports and found that postruminal starch digestibility averaged 75% across a wide range of grains and processing conditions. These reports suggest that there must be limits in the small intestinal assimilation of starch, and these limits have been reviewed (Owens et al., 1986). However, they also indicate that considerable quantities of starch can be digested postruminally (Harmon, 1992) and, as nutritionists, we need to supply amounts of starch that do not exceed the capacity of the small intestine for efficient digestion and absorption.

**Digestive Processes.** Few studies have characterized ruminal  $\alpha$ -amylase activity (Mendoza et al., 1993), and it is not known whether ruminal enzymatic activity survives the abomasum and contributes to intestinal hydrolysis. Carbohydrate assimilation in the small intestine begins in the lumen of the duodenum with the entry of pancreatic  $\alpha$ -amylase.  $\alpha$ -Amylase is an endoglucosidase (Walker and Harmon, 1996) that attacks the amylose and amylopectin molecules of the starch granule and releases maltose and a collection of oligosaccharides termed  $\alpha$ -limit dextrins (Alpers, 1994). "Limit dextrins" occur because the  $\alpha$ -1-6 branch points of the amylopectin "limit" the activity of  $\alpha$ -amylase to no closer than one glucose molecule from an  $\alpha$ -1-6 bond. Most researchers (Huntington, 1997) have concluded that pancreatic  $\alpha$ -amylase is the major limitation to

small intestinal carbohydrate assimilation. However, Kreikemeier and Harmon (1995) infused glucose, corn dextrin, and raw cornstarch into the abomasum of steers fitted with portal-arterial catheters and ileal canulas to determine intestinal disappearance of carbohydrate and portal appearance of glucose. They also fractionated the oligosaccharides appearing in ileal digesta to estimate their average chain length. They found in ileal digesta that 44 and 24% of the  $\alpha$ -glucosides were ethanol-soluble (< 9 to 10 glucose units) and had average chain lengths of 2.1 and 2.4 glucose units for the corn dextrin and raw cornstarch treatments, respectively. Based on this accumulation of  $\alpha$ -amylase products in the terminal intestine they concluded that  $\alpha$ -amylase activity was not limiting carbohydrate assimilation.

Although studies of this type (Kreikemeier and Harmon, 1995) are useful, they do not provide an unbiased determination of limitations. Estimates made only at the terminal ileum may simply represent a mismatch of sites of hydrolysis and absorption. Both mucosal carbohydrase activities (Kreikemeier et al., 1990) and intestinal glucose transport activities (Bauer, 1996) are differentially distributed throughout the small intestine. However, a mismatch of transport and hydrolysis in the terminal intestine may falsely indicate overall limitations to carbohydrate assimilation. For example, Bauer (1996) reported that in the terminal small intestine SGLT1 activity decreased more rapidly than did mucosal maltase activity. Similarly, mucosal maltase and isomaltase activities were maintained throughout the small intestine of steers when expressed per centimeter of intestine (Kreikemeier et al., 1990). Combined, these results suggest that glucose transport is limiting in the terminal small intestine. However, either glucose transport is noninducible in this region of the small intestine or enzymatic activity is insufficient to supply adequate free glucose to induce SGLT1.

Following luminal hydrolysis by  $\alpha$ -amylase there are two brush-border proteins responsible for the second and final phase of hydrolysis. Sucrase-isomaltase is the primary mucosal maltase in nonruminants (Harmon, 1993). However, there is no detectable sucrase activity in ruminants (Kreikemeier et al., 1990), and it is not inducible by supplying sucrose to the small intestine (Swanson and Harmon, 1997) despite the presence of the sucrase-isomaltase gene in the bovine (Threadgill and Womack, 1991). This could be a major evolutionary limitation for carbohydrate assimilation in ruminants. The second protein, maltase-glucoamylase (Galand, 1989) has not been characterized in ruminants. The phase of hydrolysis occurring at the brush-border of the intestine in ruminants has received comparatively little research attention. Mucosal enzyme activity does not seem to respond to luminal substrate (Kreikemeier et al., 1990) as it does in nonruminants (Brannon, 1990), and determinations of whether mucosal enzymes truly limit carbohydrate assimilation have not been made.



**Figure 1.** Glucose transport in enterocytes. The Na<sup>+</sup>-dependent glucose transporter (SGLT1) is located in the apical membrane and transports Na<sup>+</sup> (two) coupled with glucose or galactose and water. This transport is driven by the inwardly directed Na<sup>+</sup> gradient, which is maintained by the activity of Na<sup>+</sup>/K<sup>+</sup>-ATPase in the basolateral membrane. The facilitative transporter GLUT2 transports sugars across the basolateral membrane, whereas the facilitative transporter GLUT5 transports fructose across the apical membrane (adapted from Wright, 1993).

### Glucose Absorption

**Enterocyte Transport.** Several processes have been proposed for the entry of luminal sugars into the vasculature draining the small intestine. A mechanism of absorption has been proposed whereby sugars exit the lumen via the intercellular spaces (Figure 1), a process termed *solvent drag* (Madara and Pappenheimer, 1987; Pappenheimer and Reiss, 1987; Pappenheimer, 1990). For this process to occur, luminal glucose must be present at high concentrations (> 25 mM), and concentrations must exceed approximately 200 mM before paracellular absorption would exceed active transport (Pappenheimer and Reiss, 1987), which may not occur under physiological conditions (Ferraris et al., 1990).

The second means whereby sugars may cross the luminal membrane is the facilitated transporter GLUT5. This transporter is responsible for the entry of fructose into the intestinal enterocytes (Burant et al., 1992) but does not transport glucose or galactose. Being a facilitated transporter, GLUT5 will transport fructose down

a concentration gradient. Fructose, as a component of sucrose, would represent a significant contribution to the supply of luminal carbohydrate in humans. However, its significance in ruminants is unknown because little fructose passes to the small intestine in typical ruminant diets.

The third and major means whereby glucose crosses the brush-border membrane is via the Na<sup>+</sup>-dependent glucose transporter, SGLT1 (Hediger and Rhoads, 1994). The SGLT1 is a high-affinity glucose transporter ( $K_m \gg 100 \mu M$ ; Wright, 1993) that couples glucose transport to an inwardly directed Na<sup>+</sup> gradient (Figure 1). This Na<sup>+</sup> gradient is maintained by Na<sup>+</sup>/K<sup>+</sup>-ATPase in the basolateral membrane. Excellent detailed reviews describing the structure and function of SGLT1 are available (Wright, 1993; Hediger and Rhoads, 1994).

The stoichiometry of the process dictates that two Na<sup>+</sup> cross the membrane with each glucose molecule. Recently, SGLT1 has been demonstrated to transport 210 water molecules along with each glucose and 2 Na<sup>+</sup> (Meinild et al., 1998), resulting in passive Na<sup>+</sup> (Loo et

al., 1999) and urea transport (Leung et al., 2000). These authors (Meinild et al., 1998) have postulated that this glucose-linked water pumping is a major contributor to intestinal water reabsorption.

The final transporter that contributes to sugar entry and exit from enterocytes is GLUT2, which is present in the basolateral membrane (Figure 1). The GLUT2 transporter serves as the major route of glucose exit from the cells as well as entry of glucose from the blood into enterocytes (Thorens, 1993). Fructose also crosses the basolateral membrane via the activity of GLUT2 (Cheeseman, 1993).

### Glucose Absorption in Ruminants

Glucose availability in the small intestine of ruminants is highly dependent on diet. Forage-fed ruminants have little glucose available in the lumen of the small intestine, whereas considerable quantities can be available in animals fed concentrates. Because of this, glucose absorption in the small intestine varies greatly and has made the ruminant, particularly the sheep, a subject of considerable interest as a model to study the regulation of glucose transport.

*Transporter Activity.* The study of transporter function in the brush-border membrane has been greatly enhanced by the use of brush-border membrane vesicles (BBMV; Stevens et al., 1984). The first report of the application of BBMV to the study of glucose transport in cattle was published by Kaunitz and Wright (1984). Jejunal BBMV collected from steers at slaughter were used to demonstrate the presence of a Na<sup>+</sup>-dependent, saturable system of glucose transport. Moe et al. (1985) used BBMV to study nutrient transport in bovine enterocytes and reported characteristics of Na<sup>+</sup>-dependent glucose transport; glucose transport was not inhibited by fructose but was inhibited by galactose > xylose, and 100 mM phlorizin (a competitive inhibitor of SGLT1) completely inhibited Na<sup>+</sup>-dependent transport. Their report focused primarily on methods of vesicle preparation; however, they did compare glucose transport in cows and young bulls and reported similar rates of glucose transport. Crooker and Clark (1986) used tissues from Holstein steers and cows and they too demonstrated Na<sup>+</sup>-dependent glucose transporter activity using BBMV from both. Zhao et al. (1998) prepared BBMV from lactating dairy cows and observed SGLT1 activity throughout the intestine. Zhao et al. (1998) also determined SGLT1 expression in several tissues and, surprisingly, found high amounts in the stomach tissues, rumen, and omasum, as well as the intestinal tissues, the duodenum, jejunum, and ileum. The importance of transporter expression in stomach tissues remains unclear. Recent findings suggest that the ruminal SGLT1 transporter does function in sheep and may play a significant role during times of heavy glucose loads such as those that precede acidosis (Aschenbach et al., 2000a,b).

Wolffram et al. (1986) was the first to compare transporter activity for ruminants with that for nonruminants using BBMV from the midjejunum of 3- to 4-month old growing sheep and pigs obtained at slaughter. They compared transport of glucose and leucine. Kinetics of leucine transport revealed a similar capacity for leucine transport but a lower affinity for leucine in ruminants. Glucose transport kinetics revealed a lower capacity for glucose transport in ruminants, but with a much higher affinity. Wolffram et al. (1986) concluded that ruminant glucose transport was adapted to the smaller amounts of glucose reaching the small intestine.

*Developmental Changes in Transport.* The first detailed studies of glucose transport in developing ruminants were reported for lambs. Lambs differing in age and rumen development were used to measure glucose and galactose disappearance from isolated intestinal loops (Scharrer et al., 1979a) or uptake was measured in vitro using isolated pieces of jejunum (Scharrer et al., 1979b). Both studies demonstrated that sugar uptake was greater in milk-fed lambs. The rate of absorption decreased as age increased and decreased most in the distal small intestine (Scharrer et al., 1979a). More recently, Shirazi-Beechey et al. (1989) prepared BBMV from lambs at 1 and 3 wk of age (milk-fed), 5 wk of age (transition period), and 12 wk of age. They reported that Na<sup>+</sup>-dependent glucose transport was present in all regions of the small intestine in preruminant lambs but was absent in the small intestine of ruminant lambs. In a more detailed report of developmental changes in glucose transport in lambs Shirazi-Beechey et al. (1991) found that glucose transporter activity peaked at 2 wk of age and declined to negligible levels by 8 wk of age. This decreased glucose transporter activity was observed in adult sheep at 2 to 3 yr of age; however, the decline could be prevented by maintaining the lambs on a milk-replacer diet beyond the normal weaning period. Furthermore, when 2- to 3-yr-old sheep were intraduodenally infused with a 30 mM glucose solution for 4 d, glucose transporter activity in BBMV increased 40- to 80-fold. This increase in glucose transporter activity was accompanied by an increase in expression of SGLT1 protein in the brush-border membrane. This was the first study to demonstrate that the presence of glucose in the intestinal lumen regulates glucose transporter expression in the brush-border membrane of ruminants.

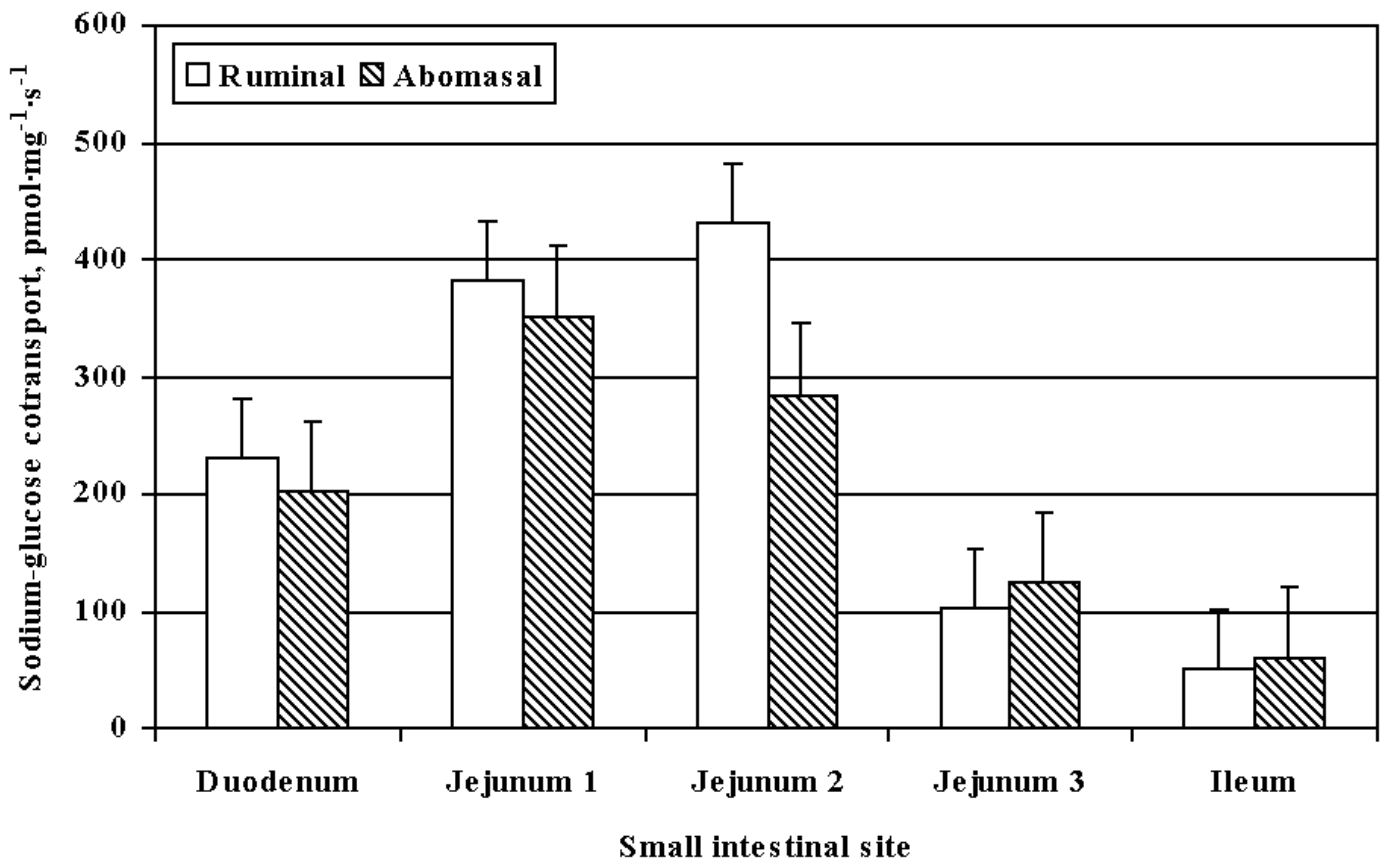
Whereas an adaptive response to increased luminal glucose is indicative that ruminants can adapt to increase their carbohydrate assimilation, adaptive responses in the intestine to starch have been less clear (Mayes and Orskov, 1974; Bauer et al., 1995). Bauer (1996) used cattle and sheep in an experiment to study adaptation of glucose transport in the proximal jejunum. Animals were fed fescue hay and infused either ruminally (control) or abomasally (adapted) with a partially hydrolyzed cornstarch solution for 7 d. Animals were killed and 1 m of jejunum was harvested and used to prepare BBMV. Animals that were adapted to the

hydrolyzed starch (infused abomasally) had higher (twofold) rates of  $\text{Na}^+$ -dependent glucose transport. This adaptive response was studied in more detail in a second experiment using 13 steers (Bauer, 1996). Steers were fed fescue hay and infused for 7 d either ruminally (control,  $n = 6$ ) or abomasally (adapted,  $n = 7$ ) with a partially hydrolyzed cornstarch solution. On d 7 steers were killed, the entire intestine was removed, and five equally spaced, 1-m segments of small intestine were used for BBMV preparation and analysis of SGLT1 activity. In this experiment, adaptation (abomasal infusion) did not affect SGLT1 activity in the small intestine (Figure 2). Activity of SGLT1 was greatest in the midjejunum and declined toward the ileum. This pattern of distribution of glucose transport was first suggested for sheep (White et al., 1971) and later confirmed in steers (Krehbiel et al., 1996) and dairy cows (Zhao et al., 1998). The lack of adaptive response reported by Bauer (1996) brings into question the ability of ruminants to adapt to increase their use of complex carbohydrates and suggests that processes other than glucose transport may be limiting intestinal carbohydrate assimilation.

*Regulation of Glucose Transporter Expression.* Lescafe-Matys et al. (1993) determined the relative changes in SGLT1 mRNA abundance in intestinal tissue of lambs and sheep described above (Shirazi-

Beechey et al., 1991). Unlike the dramatic changes in SGLT1 activity during weaning (200-fold decrease), SGLT1 mRNA decreased only fourfold. When glucose was infused into the duodenum SGLT1 mRNA increased twofold compared with the 60- to 90-fold increase in transporter activity. Because transporter activity and protein expression were highly correlated in the initial study (Shirazi-Beechey et al., 1991) and in subsequent, more detailed studies (Dyer et al., 1997), and changes in mRNA did not account for these changes, the authors concluded that regulation by luminal sugar must be translational or post-transcriptional. Freeman et al. (1993) examined the expression of SGLT1 along the crypt-villus axis of the small intestine from 1-, 14-, and 35-d-old lambs. Detection of SGLT1 mRNA first occurred just below the crypt-villus axis, peaked in the lower villus, and continually declined toward the tip. This pattern of expression was similar throughout the small intestine and across age groups. A decrease in mRNA abundance occurred first in the distal small intestine, a response apparently disassociated from changes in SGLT1 activity, suggesting that regulation is post-transcriptional.

The induction of SGLT1 by luminal glucose has also been examined using a nonabsorbable, nonhydrolyzable, glucose analog (Bagga et al., 1997). When this



**Figure 2.** Changes in  $\text{Na}^+$ -dependent glucose uptake and maltase activities along the small intestine as measured in the brush-border fraction. Each value is the mean  $\pm$  pooled SE ( $n = 6$  for ruminal infusion and 7 for abomasal). Glucose uptake site effect: linear and quadratic ( $P < 0.001$ ; Bauer, 1996).

**Table 1.** Summary of reported modulators of Na<sup>+</sup>-dependent glucose transport

Modulator	Response	Target	Source
Epidermal growth factor	Increase	Mouse intestine	Bird et al., 1994
Glucagon-like peptide 2	Increase	Rat intestine	Cheeseman, 1997
Peptide YY	Increase	Mouse intestine	Bird et al., 1996
Insulin-like growth factor I	Increase	Mammary cells	Prosser et al., 1987
Thyroid hormone	Increase	Caco-2 cells	Matosin et al., 1996
Somatotropin	Increase <sup>a</sup>	Sheep	Bird et al., 1996
Bradykinin	Increase	Rat enterocytes	Sharp and Debnam, 1992
Gastrin	Increase <sup>b</sup>	Rat intestine	Schwartz and Storozuk, 1986
Increased dietary sodium	Increase	Chicken colon	Bindslev et al., 1997
Insulin	Decrease	Streptozotocin diabetic rats	Fujii et al., 1991
Cholecystokinin	Decrease	Rat intestine	Hirsh et al., 1996; Hirsh and Cheeseman, 1998
Prostaglandin E <sub>2</sub>	Decrease	Sheep intestine	Hyun et al., 1997a,b

<sup>a</sup>Increase occurred in the duodenum and not the jejunum or the ileum.

<sup>b</sup>Increase was seen for galactose.

analog was infused intraduodenally into sheep (Shirazi-Beechey et al., 1997) SGLT1 protein expression increased, indicating that glucose can induce SGLT1 through interactions on the luminal membrane. This relation is supported by the fact that 2-deoxy-D-glucose also induces SGLT1 despite the fact it is not transported by SGLT1 (Shirazi-Beechey, 1996). Shirazi-Beechey (1996) also demonstrated that other nonmetabolizable, nonabsorbable alditols, D-mannitol and D-sorbitol, would not stimulate SGLT1. Other nonmetabolizable analogs (methyl- $\alpha$ ,D-glucopyranoside and 3-O-methyl- $\alpha$ ,D-glucopyranoside) that are absorbable did induce SGLT1 activity. Combined, these results indicate the presence of a sugar sensor on the luminal membrane responsible for inducing SGLT1 activity.

**Regulatory Influences.** Numerous dietary and regulatory factors have been shown to influence SGLT1 activity in the small intestine. A detailed description of all of their actions is beyond the scope of this review. However, a summary of the responses to several compounds is presented in Table 1.

Although the most obvious stimulator is glucose, which increases transporter activity (Shirazi-Beechey et al., 1991) and transporter protein (Dyer et al., 1997), several other regulatory peptides have been shown to influence SGLT1, and their actions have been reviewed (Bird et al., 1996). Two peptides producing dramatic stimulatory effects are epidermal growth factor (**EGF**) and glucagon-like peptide 2 (**GLP-2**).

Epidermal growth factor was first shown to influence intestinal absorption by Schwartz and Storozuk (1988). When injected subcutaneously into mice, EGF causes a dose-dependent increase in intestinal glucose transport (Bird et al., 1994). Perfusing the small intestinal lumen of the rabbit with EGF also increased the maximal rate of glucose transport; a response that was abolished by a tyrosine kinase inhibitor, indicating that this response was mediated via the EGF receptor (Hardin et al., 1996). Further research on this response to EGF in the rabbit demonstrated that the up-regulation of glucose transport was mediated by an increase in the absorptive surface area and the insertion of SGLT1 into the mem-

brane from an internal pool (Chung et al., 1999). A similar response can be induced by GLP-2 (Cheeseman, 1997). Vascular infusion of GLP-2 into rats caused a maximal increase in SGLT1 activity after only 1 h, and this increase was the result of increased transporter expression in the membrane. Few of these compounds have been examined in ruminants. However, they do provide a means to manipulate SGLT1 and may prove to be useful tools for the study of intestinal starch assimilation.

**Capacity for Glucose Absorption.** Because much of the dietary carbohydrate is ruminally fermented and often limited quantities of carbohydrate reach the small intestine, the ability of ruminants to absorb carbohydrate has been questioned for some time. White et al. (1971) measured disappearance of glucose from isolated loops along the length of the small intestine of anesthetized sheep. They reported that the glucose absorptive capacity of adult grazing sheep was only 25% that of lambs less than 1 wk of age, and that glucose absorptive capacity decreased along the intestine from the duodenum to the ileum. Additionally, glucose absorptive capacity of lambs was greater when intake of lactose was increased before an experiment. These results have been confirmed in more recent studies (Shirazi-Beechey et al., 1991) and were suggested in earlier studies of intestinal adaptation to carbohydrate in sheep (Mayes and Orskov, 1974).

Using dairy cows fitted with abomasal and ileal cannulas, Pehrson and Knutsson (1980) reported that when 500 g of glucose was administered abomasally over 4 h, 73% disappeared, and when 1,500 g glucose was administered abomasally over 20 h, 77% disappeared. These results are similar to those in steers (Kreikemeier et al., 1991) fitted with abomasal and ileal cannulas and infused abomasally with 480, 960, or 1,440 g/d of glucose. Intestinal disappearance was 97, 85, and 71% for the 480, 960, and 1,440 g/d infusions, respectively. The Kreikemeier et al. (1991) experiment differed in that steers were also equipped with portal vein catheters to estimate glucose leaving the portal-drained viscera. At the highest glucose infusion, 94%

of glucose disappearing from the intestine appeared in portal blood. These studies indicate a significant capacity for ruminants to absorb glucose, even when fed forage. Questions as to the actual mechanism of absorption arise because of the types of studies that have been employed. All of these experiments (White et al., 1971; Pehrson and Knutsson, 1980; Kreikemeier et al., 1991) infused comparatively high concentrations of glucose (166 to 1300 mM). Whether these high concentrations of glucose would result in largely paracellular absorption (Pappenheimer and Reiss, 1987) is not known. Krehbiel et al. (1996) infused glucose (216 or 432 g/d) into the small intestine of steers containing either 24 or 48 g/d of 2-deoxyglucose, a nonmetabolizable glucose analog that is not transported by SGLT1 (Shirazi-Beechey, 1996). They found that although the 2-deoxyglucose represented 10% of the glucose infused, it represented only 0.7 to 1.7% of the glucose reaching portal blood, suggesting that paracellular diffusion was a minor component under their experimental conditions (approximately 200 to 400 mM infusion solutions). Similar conclusions were drawn regarding a minimal role for paracellular absorption in the dog (Lane et al., 1999). Dogs were given infusions of glucose solutions containing L-glucose as the nonmetabolizable, nontransportable marker into jejunal Thiry-Vella loops. At luminal glucose concentrations up to 150 mM, only 2 to 5% of L-glucose was absorbed.

Bauer et al. (1995) reported no effects of adaptation on the capacity for glucose absorption from a partially hydrolyzed cornstarch solution in steers and lambs. All animals were fed alfalfa hay and were adapted (abomasal infusion of partially hydrolyzed cornstarch solution for 4 or 5 d) or were not adapted (ruminal infusion of partially hydrolyzed cornstarch solution for 4 or 5 d) before receiving abomasal infusions of partially hydrolyzed cornstarch. They saw dramatic changes in net portal glucose absorption when phlorizin, a competitive inhibitor of SGLT1, was added to the infusate. The capacity for absorption was estimated to be 39 and 173 g/d for lambs and steers, respectively, and this capacity was maintained regardless of adaptation protocol. A mathematical model of glucose uptake has been developed to test whether uptake capacity can be up-regulated in the bovine (Cant et al., 1999). Four heifers were duodenally infused with glucose continuously and glucose disappearance at the ileum was measured. The amount of glucose infused was increased every 3 d by 34 mMol/h. For each increase in infusion, uptake capacity increased 0.55 units such that capacity relative to glucose supply actually decreased. Croom et al. (1998) reviewed the regulation of intestinal glucose absorption and suggested that absorptive capacity was closely matched to nutrient supplies, and that absorptive capacity could become limiting under some production conditions. Huntington (1997) concluded that enzymatic hydrolysis was the primary limitation to intestinal carbohydrate assimilation in cattle, at least up to

intestinal supplies of 1.5 kg/d for steers and 3.0 kg/d for dairy cows.

*Impact of Intestinal Digestion on Glucose Supply.* Several experiments have used animals fitted with hepatic portal vein and hepatic vein catheters to measure the quantity of glucose exiting the portal-drained viscera (PDV) and entering the liver (Huntington et al., 1989). This provides a means of determining the net contributions to the liver or peripheral tissues and measures the sum of glucose absorption and metabolism. Across a wide range of experiments encompassing varied diets, intakes, and physiological states, net glucose absorption is almost always zero or negative (Reynolds et al., 1994). This is not to say glucose is not being absorbed, but rather very large amounts are being metabolized. In a study designed to quantify intestinal contributions to portal glucose supply, Huntington and Reynolds (1986) abomasally infused glucose and cornstarch into heifers. Overall, they recovered an average of 65% of the glucose and 35% of the starch as glucose in portal blood. No differences were observed for the amounts of glucose recovered from animals fed alfalfa hay or a high-concentrate diet at two intakes, suggesting little effect of adaptation for carbohydrate assimilation. Kreikemeier et al. (1991) fed steers alfalfa hay to minimize intestinal carbohydrate supply and abomasally infused them with glucose, cornstarch, or corn dextrins at 20, 40, and 60 g/h. Infusions were all 10 h, with samples taken the final 6 h. Glucose infusion resulted in 90% recovery of intestinal glucose disappearance in portal blood, whereas only 19 and 32% of the dextrin and starch intestinal disappearance were recovered in portal blood, respectively. Factors such as microbial fermentation and gut tissue metabolism must certainly make a large contribution to small intestinal carbohydrate disappearance; this emphasizes the need for measures of tissue metabolism and intestinal disappearance to more accurately describe processes of digestion and absorption.

The very high metabolic activity of the portal-drained visceral tissues has been shown to be a major factor in the apparently low net rates of glucose absorption (Reynolds and Huntington, 1988a). These authors (Reynolds and Huntington, 1988a,b) directly measured the contribution of stomach and intestinal tissues to nutrient absorption in beef steers. When steers were fed a concentrate diet comparatively large amounts of glucose were absorbed from the intestines; however, the amounts utilized by ruminal and other stomach tissues were so great that the overall net PDV absorption was negative. Attempts were made in previous studies to account for this negative net glucose absorption and thereby obtain a better estimate of net glucose absorption by including control (water) infusions (Kreikemeier et al., 1991). However, more recent work has shown that increasing the peripheral supply of carbohydrate either through intraduodenal or intrajugular infusion of glucose increases the metabolism of arterially supplied glucose by the PDV (Balcells et al., 1995).

More recent work in steers (Richards, 1999) compared the impact of ruminally vs abomasally supplied starch on the glucose economy and PDV glucose metabolism. Beef steers were infused ruminally or abomasally with 800 g/d of partially hydrolyzed starch. Shifting the site of starch digestion from the rumen to the small intestine increased glucose utilization by PDV tissues (132%), PDV glucose flux (310%), and irreversible loss of glucose (59%). Abomasal infusion resulted in greater total energy (28%) from the total splanchnic tissues. Thus, shifting starch digestion to the intestine increases PDV glucose uptake and utilization without a decrease in hepatic glucose production, resulting in greater glucose supplies to the periphery.

### Impact of Ruminal vs Small Intestinal Glucose Supply on Whole-Body Energetics

It has generally been contended for the past 35 to 40 yr that the conversion of dietary starch energy to tissue energy is greater if assimilation occurs via intestinal glucose absorption rather than ruminal fermentation and subsequent VFA absorption. However, there is a paucity of scientific data that directly support this contention or quantify the divergence in energetic efficiency associated with site of starch delivery. Regardless, inferences can be made regarding this divergence based on energetic losses attributed to 1) methane formation, 2) heat of fermentation or digestion and absorption, and 3) partial efficiencies of use of absorbed substrates.

*Methane Formation.* Methane is an end product of anaerobic fermentation and is unavailable for reconversion into usable substrates by either the microbes or the host animal. Thus methanogenesis, 90 to 95% of which occurs in the rumen, represents a net energetic loss in the conversion of dietary DE to animal tissue or milk energy (Hungate, 1966). In fact, stoichiometric relationships indicate that 0.57 mol of methane is produced per mole of hexose fermented; however, assuming direct incorporation of 10 to 30% of the hexose into microbial cells, this molar relationship would be reduced to a range of 0.52 to 0.40 (Hungate, 1966; Baldwin et al., 1970). This equates to a loss of approximately 13 to 18% of available carbohydrate energy. Measurements of methane production in vivo in ruminants range from 3 to 15% of DE (Blaxter and Clapperton, 1965; Hungate, 1966; Kreuzer et al., 1986). This observed variation may be due to differences in diet composition and DMI. Moe and Tyrrell (1980), summarizing data from 404 energy balance trails with dairy cows in open-circuit respiration chambers, reported that variation in methane production across diets was largely a function of the carbohydrate fractions digested. These researchers estimated that energy loss in the form of methane accounted for 6.5, 11.5, and 33.6% of the DE from the soluble carbohydrate, hemicellulose, and cellulose fractions, respectively. Greater amounts of methane formation are associated with diets high in fiber

because of the stimulation of cellulolytic-methanogenic microflora (Kirchgeßner et al., 1995). In contrast, diets containing large amounts of readily available carbohydrates (e.g., starch) alter the fermentation pattern so that H<sub>2</sub> is consumed for propionate synthesis rather than the reduction of CO<sub>2</sub> to methane (Beever, 1993). Additionally, the influence of DMI on methane production is variable and dependent on the carbohydrate fractions fermented. Increasing DMI from less than 1.5 to 3.5 × maintenance energy intake has little effect on methane production from soluble and hemicellulose fractions, whereas methane production from the cellulose fraction increases threefold per unit of carbohydrate fermented (Moe and Tyrrell, 1980). Accordingly, because of the large quantity of readily fermentable carbohydrate supplied to the rumen, the effect of DMI would be less pronounced for high-starch diets than for diets high in fiber.

In a summarization of in vivo measurements, Hungate (1966) estimated that 0.35 mol of methane is produced per mole of starch fermented. This is consistent with 0.38 mol of methane per mole of carbohydrate fermented calculated by Beever (1993) for a high-grain diet. Based on the heat of combustion of starch (672 kcal/mol) and methane (212 kcal/mol) this equates to 11 to 12% of the DE from starch lost as methane. These values are higher than recent observations (K. R. McLeod and D. L. Harmon, unpublished data) wherein 8.5% of DE from starch was accounted for by methane formation when partially hydrolyzed starch was infused ruminally. Based on these values, it can be estimated that a typical feedlot steer consuming 6.0 kg of starch (25.2 Mcal of intake energy), with a ruminal starch digestibility of 80%, will lose between 1.7 to 2.4 Mcal DE from starch, or 6.8 to 9.6% of starch intake energy, as methane from the rumen. This is contrasted with essentially no loss of energy in the form of methane when starch is digested in the small intestine and absorbed as glucose, because negligible amounts of methane are produced in the small intestine (Hungate, 1966).

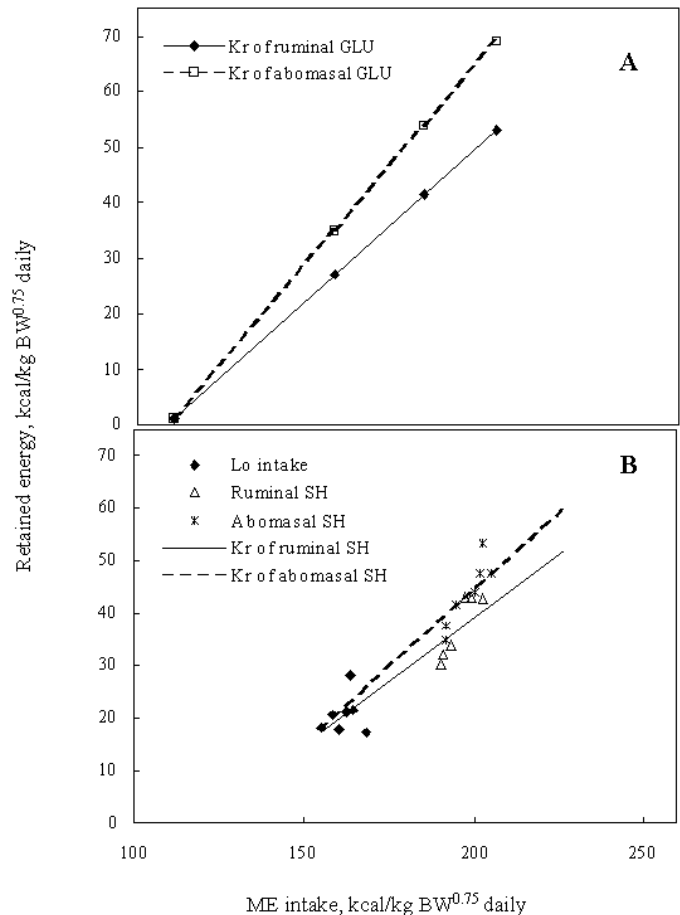
*Heat of Fermentation or Digestion and Absorption.* Heat of fermentation refers to the amount of energy dissipated, in the form of heat, as a result of the conversion of substrate to end products of fermentation. Therefore, heat of fermentation can be calculated as the difference between heats of combustion of substrate and products formed. Assuming a strict anaerobic environment, theoretical stoichiometric relationships describing the fermentation of starch to an average ratio of VFA (62 acetate:22 propionate:16 butyrate) indicate that 6.4% of the fermentable starch would be lost as heat (Hungate, 1966). This calculation assumes a static microbial mass with no net capture of hexose energy by the microbiota. Because up to 30% of the hexose may be incorporated by microbial cells (Baldwin et al., 1970), this would be an overestimation of energy lost as heat. However, for starch digested in the rumen, a portion of hexose energy captured in the form of bacterial poly-

saccharides and amino acids would subsequently be released as heat as a result of bond breakage via enzymatic hydrolysis in the small intestine. In vitro and in vivo estimates of the heat of fermentation of purified substrates and mixed diets range from 3 to 12% of DE (Blaxter, 1962; Webster, 1980). The variation observed as well as the deviation from stoichiometric-based estimates are likely due to differences in microbial populations, and thus molar ratios of VFA produced, and the precision of the experimental techniques used to quantify heat production. Although heat of fermentation of starch in the small intestine is assumed to be zero, heat is released as a result of glucosidic bond cleavage by host enzymes. Baldwin (1968), based on a free energy of hydrolysis of glucosidic bonds of 4.3 kcal/mol of starch, estimated that the heat released from digestion of starch in the small intestine would equal 0.6% of DE.

The absorption of VFA from the rumen and large intestine of ruminants is primarily a passive process and, as such, negligible energy costs are directly associated with absorption (Rechkemmer et al., 1995). Conversely, small intestinal absorption of glucose occurs via a  $\text{Na}^+$ -dependent cotransporter coupled with  $\text{Na}^+/\text{K}^+$ -ATPase and thus is an energy-dependent process (Shirazi-Beechey et al., 1995). Considering that absorption of 1 mol of glucose (686 kcal) requires the use of 1 mol of ATP (18 kcal), then 2.6% of glucose energy would be expended during absorption (Baldwin, 1968).

Indirect energetic costs associated with pancreatic enzyme secretion and maintenance of gut cell ion balance are difficult to attribute to individual dietary substrates. However, the relative change due to site of glucose supply to the gut is considered to be small. Therefore, the energetic cost directly associated with starch digestion and subsequent glucose transport in the small intestine equates to 3.2% of starch DE, or approximately 50% of the DE lost as heat of fermentation if starch is digested in the rumen or hindgut. Assuming an intake of 6 kg of starch and a rumen digestibility of 100%, 1.6 Mcal of energy would be dissipated as heat resulting from fermentation. In contrast, when 75% of the intake starch is assumed to be digested in the rumen and the remainder digested in the small intestine, 1.4 Mcal of energy would evolve as heat. Thus, this shift in site of digestion results in a 12.5% increase in the conversion of intake energy to absorbed energy.

*Partial Efficiencies of Absorbed Substrates.* Classic experiments by Kellner were the first to describe the energetic efficiency by which ME supplied from individual dietary nutrients is converted to tissue energy in cattle (Blaxter, 1962). The approach adopted by Kellner entailed addition of individual nutrients to a basal diet supplied at maintenance energy intake. The partial efficiency ( $K_r$ ) for the individually supplied nutrients above maintenance was then calculated as the energy retained in tissue divided by the ME supplied by the nutrient. Using a similar approach in mature sheep, Armstrong et al. (1960) estimated the  $K_r$  of glucose to be 0.55 and 0.72 for ruminally and abomasally supplied



**Figure 3.** Partial efficiency of converting ME to retained energy ( $K_r$ ) for (A) sheep infused ruminally and abomasally with increasing amounts of glucose (GLU); adapted from Armstrong et al. (1960) and (B) steers fed two energy intakes and infused ruminally and abomasally with partially hydrolyzed starch. (SH; K. R. McLeod and D. L. Harmon, unpublished data).

glucose, respectively (Figure 3). Considering that the  $K_r$  value observed by Armstrong et al. (1960) for ruminally supplied glucose includes heat loss associated with fermentation of glucose, it is strikingly comparable to the average  $K_r$  value of 0.61 reported by Orskov et al. (1979) for mixtures of VFA when infused intragastrically in sheep. In recent experiments (K. R. McLeod and D. L. Harmon, unpublished data), we infused a partial hydrolysate of starch ruminally and abomasally to determine the implications of site of starch delivery on  $K_r$  in growing beef steers. Starch was infused at approximately 20% of total ME intake ( $12.6 \text{ g}/[\text{d}\cdot\text{kg BW}^{0.75}]$ ) and a basal diet was supplied to exceed metabolizable protein requirements by 20% and to meet  $1.5 \times$  maintenance energy requirements in order to circumvent potential limitations associated with synthesis and secretion of digestive enzymes. Estimates for  $K_r$  values (Figure 3) averaged 0.48 and 0.60 for ruminal and abomasal starch infusion, respectively. Although our  $K_r$  values are lower than those determined for glucose by Arm-

strong et al. (1960), the relative increase in  $K_r$  observed (25 and 31%) for abomasal vs ruminal glucose or starch supply is reasonably consistent between studies. In fact, if the  $K_r$  for starch is adjusted by adding heat loss associated with glucosidic bond cleavage (0.6% of DE from starch) to retained energy, the relative increase (29%) in  $K_r$  for abomasal vs ruminal starch would be very similar to that reported by Armstrong et al. (1960) for glucose. It is possible that some of the infused starch in our experiment may have escaped small intestinal digestion and was subsequently fermented in the large intestine. Branco et al. (1999) determined that 88% of duodenally infused starch hydrolysate disappeared from the small intestine of steers. We used a similar rate of infusion in our energy balance experiments (K. R. McLeod and D. L. Harmon, unpublished data), and when the ME supplied from abomasal starch is adjusted by 0.88 a theoretical maximum  $K_r$  value for small intestinally supplied starch of 0.68 is generated. Therefore, it is likely that the actual  $K_r$  value for small intestinally supplied starch falls between the observed 0.60 and the calculated maximal value of 0.68.

**Efficiency of Glucose Utilization.** Total energetic efficiency of a diet or nutrient (Kleiber, 1961) is defined as retained energy divided by intake energy supplied by the diet or nutrient. It reflects the summation of energy losses due to digestion and absorption as well as partial

efficiencies associated with maintenance and production. To illustrate the potential divergence in total energetic efficiency of nutrients according to site of nutrient digestion, Black (1971) simulated the energetic efficiency of a ruminant and nonruminant growing lamb (Figure 4). For the purposes of his simulation, Black (1971) assumed a 20-kg lamb consuming a diet containing 85% linked-hexose units and 15% casein at 2 × maintenance energy intake. Furthermore, diets were delivered and totally digested either ruminally or post-ruminally by host enzymes. Based on these constraints, Black (1971) estimated that conversion of intake energy to net available energy was 61 and 81% for the ruminant and nonruminant lamb, respectively. However, after accounting for maintenance energy costs, the net energy available for tissue accretion for the ruminant lamb was reduced to only one-third (11 vs 31% of intake energy) of that of the nonruminant lamb. The diet simulation of Black (1971) seems to overestimate the difference in total energetic efficiency of ruminally fermented or small intestinally digested starch. In our recent experiments (K. R. McLeod and D. L. Harmon, unpublished data; Table 2) using steers fed a basal diet and infused with a partial hydrolysate of starch, we demonstrated that under these experimental conditions 32% of ruminal and 44% of abomasal infused starch energy was retained in tissue. These results indicate that the

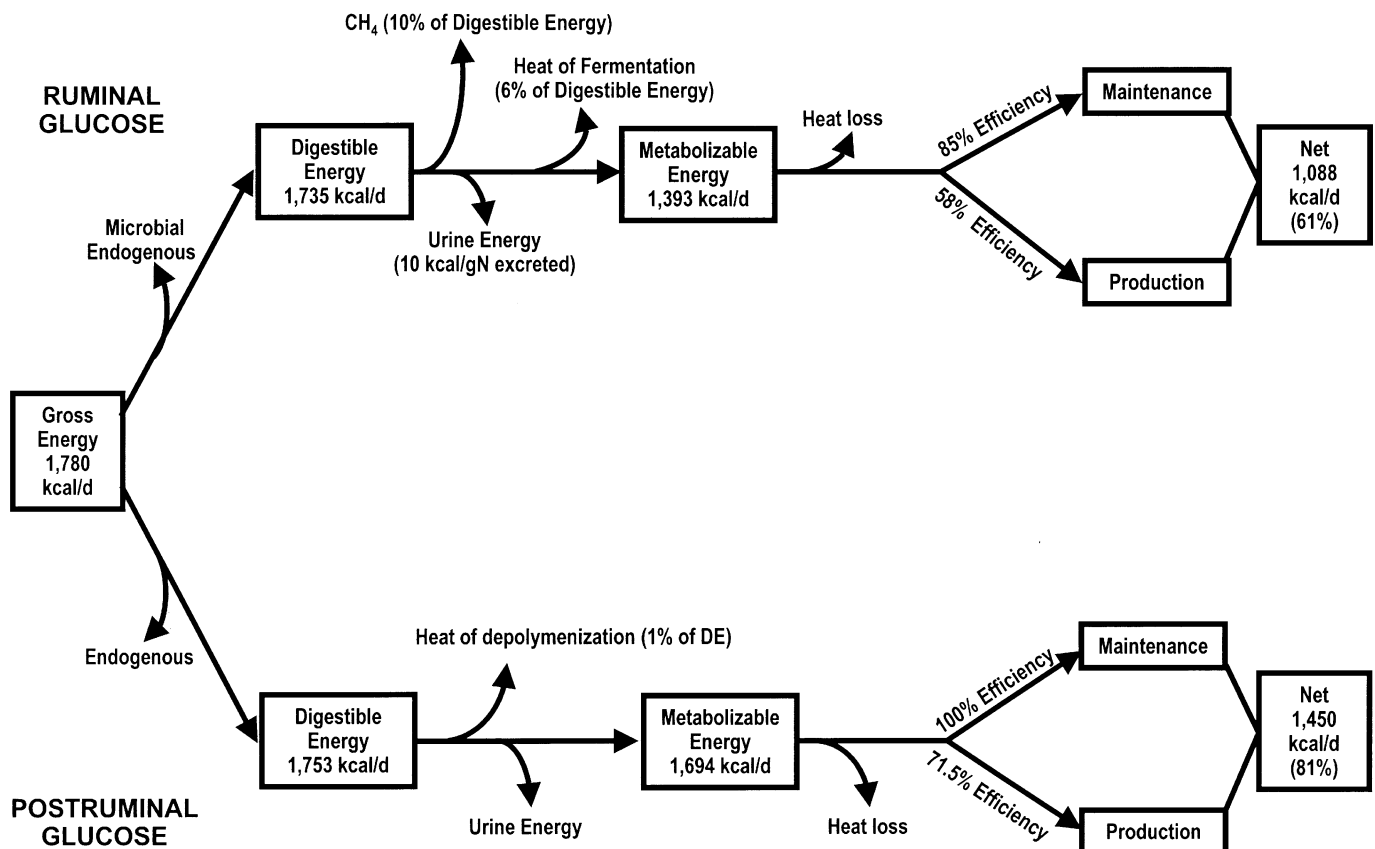


Figure 4. Energy partitioning as influenced by site of glucose metabolism in ruminants (Black, 1971).

**Table 2.** Partitioning of energy (kcal/kg<sup>0.75</sup>) in steers infused ruminally or postruminally with partially hydrolyzed starch (SH) and fed at two energy intake (K. R. McLeod and D. L. Harmon, unpublished data)

Item	Low intake			High intake		Significance, <i>P</i> <		
	Water	Ruminal starch	Abomasal starch	Water	SEM <sup>a</sup>	Intake	Starch	Rumen vs abomasum
Intake	324.0	375.4	374.5	431.6	1.3	.01	.01	NS
Diet	324.0	324.2	323.2	431.6	1.4	.01	NS <sup>b</sup>	NS
Infused SH	0	51.2	51.3	0	0.2	NS	.01	NS
DE	203.5	236.6	235.9	266.5	2.5	.01	.01	NS
CH <sub>4</sub>	23.6	26.4	22.4	29.5	0.6	.01	NS	.01
ME	162.0	195.9	197.9	213.9	2.0	.01	.01	NS
Heat production	140.3	157.8	154.1	171.4	1.8	.01	.01	0.13
Retained energy	21.7	38.1	43.8	42.5	2.5	.01	.01	0.10

<sup>a</sup>Standard error of mean, *n* = 8.

<sup>b</sup>*P* > 0.15.

total energetic efficiency of ruminally fermented starch is only 73% of that for starch digested in the small intestine. This agrees reasonably well with Armstrong et al. (1960), who reported that the total energetic efficiency in sheep of ruminally infused glucose was 68% of that for glucose infused abomasally.

Although the infusion data described above clearly demonstrate improved energetic efficiency when site of carbohydrate digestion and/or absorption is shifted to the small intestine, few experimental data are available that have directly tested this contention using diets containing intact starch. This limitation is due in part to the difficulty in manipulating site of starch digestion in a predictable manner. In an attempt to indirectly quantify the impact of site of starch digestion on efficiency of converting feed to body weight gain, Owens et al. (1986) used a multiple regression analysis of gain-to-feed ratios and site of starch digestion in cattle derived from a compilation of data to determine that efficiency of feed use was equal to 0.159 times ruminal starch digestion plus 0.227 times small intestinal starch digestion. Based on this equation, Owens et al. (1986) inferred that starch digested in the rumen is used only 70% as efficiently as starch digested in the small intestine. This is surprisingly close to the experimentally obtained values described above, indicating that if starch can be supplied to the small intestine and digested and absorbed there, improvements in production efficiency can be realized.

In practice, clear examples of the relationships between site of starch digestion and energetic efficiency are few. This can in part be ascribed to the difficulty of accurately predicting the digestive response to a given diet. Rare would be the occasion when some fraction of dietary starch were not digested in the small intestine and these energetic benefits were realized. A greater digestive capacity of the small intestine would perhaps make these concepts easier to demonstrate. Research can, however, determine the flow of dietary starch into the large intestine, the point at which production efficiency declines.

Large intestinal starch fermentation would be associated with the same energetic costs of fermentation and nutrient transport as the rumen; however, unlike the rumen, hexose energy incorporated into microbial mass (15 to 30% of DE; Baldwin, 1968) would be lost in the feces. Thus, a comparison of the energetic efficiency of large intestinal fermentation with small intestinal digestion and glucose absorption reveals that the large intestine is only 54 to 74% as efficient. This point can be further emphasized using the same data summarized by Owens et al. (1986). If one regresses the percentage of intake that is digested in the large intestine for steers fed corn against gain/feed one obtains a negative relationship with an  $r^2 = 0.97$ . This indicates that although improvements in efficiency associated with increases in small intestinal digestion are significant, any excess starch that is fermented in the large intestine is highly associated with decreases in efficiency. This further indicates that optimal performance may be highly dependent on our ability to accurately predict the quantity of starch flowing to and disappearing from the small intestine.

## Implications

Glucose absorption typically makes little or no apparent net contribution to energy derived from portal-drained tissues. However, substantial quantities of glucose may be absorbed from the small intestine when high-starch diets are fed. Origins of this apparent anomaly are many. Processes for starch assimilation and glucose transport are similar for ruminants and nonruminants. However, the ability of ruminants to up-regulate digestive and absorptive processes in response to increased small intestinal starch remains in question. Small intestinal digestion is more efficient than ruminal fermentation. Practical application of this concept is diminished by the limited capacity of the small intestine to hydrolyze starch and absorb glucose. Fermentation of starch in the large intestine must be avoided if these improvements are to be realized.

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