INTRODUCTION

Proper gut development and function are essential for efficient nutrient absorption and use, particularly in the growing animal. Impaired gut function can have long-lasting effects on overall animal health, production performance, and product quality. For instance, diarrhea in early life can have a strong negative impact on milk production and component yields of dairy heifers (Heinrichs and Heinrichs, 2011). High-concentrate-fed dairy cows may exhibit hindgut acidosis, resulting in damage to the gut wall, intestinal inflammation, and...
laminitis (Gressley et al., 2011). Thus, therapies that mitigate intestinal inflammation and damage or improve nutrient absorption and intestinal function could benefit ruminant health and production.

Glucagon-like peptide-2 (GLP-2) has been a target of investigation for improving nutrient absorption and production efficiency of poultry (Hu et al., 2010) and livestock (Burrin et al., 2003; Sigalet, 2012; Ipharraguerre et al., 2013) because of its effects on the intestinal mucosa. Treatment of nonruminants with GLP-2 stimulates intestinal crypt cell proliferation, reduces apoptosis and inflammation in gut mucosal epithelium, and enhances nutrient absorption and gut integrity after injury (Lovshin and Drucker, 2000; Burrin et al., 2003; Drucker, 2005). Similar benefits may be achieved through GLP-2 therapy in cattle (Taylor-Edwards et al., 2011, 2012; Connor et al., 2013). However, hormone treatment of food animals to improve production performance has received criticism from consumers (Sibbald, 1999; Refsdal, 2000; Rainer, 2001; Johnson and Hanranah, 2010). Thus, methods that promote endogenous release of GLP-2 may have greater consumer acceptance and improve production efficiency of livestock. This review summarizes the biology of GLP-2 in ruminants and nonruminants, the use of GLP-2 in the treatment of human and livestock diseases, and the potential applications of GLP-2 to improve production and health of ruminants.

BIOLoGY OF GLP-2

GLP-2 Synthesis and Secretion

Glucagon-like peptide-2 is a 33–amino acid peptide hormone derived from the tissue-specific cleavage of a 160–amino acid precursor, proglucagon, by the actions of prohormone convertase-1 (Dhanvantari et al., 1996). The peptide is cosecreted with GLP-1 in an equal ratio from enteroendocrine L cells (Ørskov et al., 1986) located in the small and large intestines in response to nutrient ingestion (Roberge and Brubaker, 1991). Because GLP-2 is secreted in parallel with GLP-1, factors that influence GLP-1 release are assumed to be identical for GLP-2. The L cells are sparsely distributed throughout the intestinal tract where, in humans, they contribute to only 1% to 5% of mucosal cells (Sjolund et al., 1983); their abundance is reported to be greater in the distal portion of the jejunum, ileum, and colon of the mouse, human, rat, and pig (Larsson et al., 1975; Eissele et al., 1992).

Upon nutrient ingestion, L cells secrete GLP-2 in a biphasic manner (Fig. 1). The initial release occurs within 30 min of nutrient intake, which is believed to be mediated by indirect stimulation of subepithelial vagal afferent nerves (possibly via glucose-dependent insulinotropic peptide [GIP] secreted from enteroendocrine K cells located in the proximal small intestine) and then through subsequent effferent stimulation of the L cell by the enteric nervous system (possibly involving GRP). The second GLP-2 release occurs 1 to 2 h postprandially as a result of nutrients arriving in the distal SI and directly activating L cells through various sensors or nutrient transporters.

A second peak in GLP-2 release occurs 1 to 2 h postprandially as a result of nutrients arriving in the distal SI (possibly involving gastrin-releasing peptide [GRP; Brubaker and Anini, 2003]). This release may be mediated by direct stimulation of subepithelial vagal afferent nerves via GRP secreted from enteroendocrine K cells located in the proximal SI, followed by catterrent stimulation of the L cell by enteric nerves (possibly involving GIP). The second GLP-2 release occurs 1 to 2 h postprandially as a result of nutrients arriving in the distal SI and directly activating L cells through various sensors or nutrient transporters (Akiba and Kaunitz, 2014).

The GLP-2 release in response to feeding is highly nutrient specific. For instance, fatty acids administered parenterally to rats (Tappenden and McBurney, 1998) and in the diet (Xiao et al., 1999) or directly to the duodenum (Feltrin et al., 2006) of healthy men stimulate GLP-2 release. Likewise, carbohydrate feeding increases plasma concentrations of GLP-2 in men (Xiao et al., 1999), and isolated perfused pig ileum stimulated with luminal glucose exhibits increased GLP-2 secretion (Ørskov et al., 1986). However, complex carbohydrates do not appear to activate GLP-1 (hence GLP-2) release in humans (Elliott et al., 1993). Similarly, dietary proteins do not consistently elicit a GLP-2 response in humans (Xiao et al., 1999; Dubé and Brubaker, 2004), whereas oral administration of the amino acid glutamine does increase GLP-1 (hence GLP-2) secretion in humans (Greenfield et al., 2009). Independent of nutrient type, there may be a minimum caloric threshold required for induction of GLP-2 secretion because low-
level energy infusion or low-calorie meals did not result in GLP release in multiple studies involving human and porcine subjects (Dubé and Brubaker, 2004).

**Physiological Effects of GLP-2 in Nonruminants**

Most knowledge regarding the biological actions of GLP-2 is derived from studies involving rodents, swine, and humans. Its effects on the gut have been reviewed extensively by Burrin et al. (2003), Estall and Drucker (2006), and Drucker and Yusta (2014). Therefore, the physiological effects of GLP-2 in non-ruminant species are discussed here only briefly and are summarized in Fig. 2.

As described previously, the release of GLP-2 is initiated by nutrient ingestion; thus, the effects of GLP-2 on the gut appear to serve largely to facilitate the absorption and processing of these nutrients. For instance, GLP-2 increases nutrient uptake by stimulating the expression or activity of hexose and peptide transporters in enterocytes, including sodium-glucose cotransporter-1 (SGLT1; Cheesman, 1997), glucose transporter-2 (Cheeseman and O’Neill, 1998; Au et al., 2002), and peptide transporter-1 (Hu et al., 2010). In addition, GLP-2 increases expression of the digestive enzymes maltase-glucoamylase and sucrase-isomaltase in the brush border that are required for digestion of starch and other sugars and aminopeptidase N involved in peptide digestion (Petersen et al., 2001, 2002). Increased absorption of intestinal lipids is also mediated by GLP-2 through its effects on fatty acid translocase (Hsieh et al., 2009; Newberry and Davidson, 2009). Furthermore, by decreasing gastric emptying, gastric acid secretion, and gut motility (Wojdemann et al., 1999; Nagell et al., 2004; Meier et al., 2006; Guan et al., 2012), GLP-2 provides an opportunity for increased enzymatic processing of complex molecules and nutrient transport and absorption. Additionally, GLP-2 increases the absorptive area and capacity of the gut by increasing intestinal epithelial and crypt cell proliferation and reducing apoptosis (Burrin et al., 2005, 2007). Ultimately, these changes extend the length of intestinal villi and increase intestinal weight (Drucker et al., 1996). Furthermore, GLP-2 increases mesenteric blood flow to support cell proliferation and

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**Figure 2.** Summary of the physiological effects of glucagon-like peptide-2 (GLP-2) on intestinal mucosa and intestinal function. Glucagon-like peptide-2 increases nutrient uptake by stimulating nutrient transporters in enterocytes, increasing digestive enzyme expression, and reducing gut motility. Mesenteric blood flow is increased by GLP-2, which supports nutrient delivery and cell proliferation. The absorptive capacity of the gut is increased by GLP-2 through its effects on growth of the intestinal villi due to increased crypt cell proliferation and reduced apoptosis. Gut barrier permeability is decreased by GLP-2, which may reduce inflammation by preventing passage of bacteria and their components from the lumen through the mucosal epithelium. Effects of GLP-2 are mediated by GLP-2 receptor (GLP-2R) expressed on enteric neurons, endocrine cells, and subepithelial myofibroblasts.
nutrient delivery through the release of nitric oxide from enteric neurons (Guan et al., 2003; Stephens et al., 2006; Dubé and Brubaker, 2007; Bremholm et al., 2009).

Beyond nutrient uptake, GLP-2 functions to protect the intestinal mucosa from inflammation and to promote barrier function and healing after intestinal injury. For instance, impaired barrier function and increased mucosal permeability due to factors such as psychological stress are thought to lead to inflammation associated with inflammatory bowel disease. Using a model of chronic psychological stress in mice, Cameron and Perdue (2005) found that daily administration of a long-acting human GLP-2 containing a glycine substitution at the second amino acid position ([Gly²]-GLP-2) shortly before a 1-h stress exposure (water avoidance) for a 10-d period attenuated stress-induced increases in intestinal permeability and bacterial penetration of the epithelial barrier relative to saline-treated controls. Furthermore, [Gly²]-GLP-2 reduced intestinal inflammation as measured by infiltration of mononuclear cells into the colonic mucosa. Using rat models, Sigalet et al. (2007) demonstrated that twice-daily subcutaneous injections of GLP-2 for 3 to 5 d shortly after chemical induction of ileitis and ulcerative colitis reduced granulocyte infiltration of intestinal mucosa and associated mucosal damage; reduced mucosal inflammatory cytokine levels, including IL-1β, interferon-γ, and tumor necrosis factor-α; and reduced cytokine-induced apoptosis in affected epithelial tissue. In their model of ileitis, GLP-2 treatment also increased the expression of the anti-inflammatory cytokine IL-10. In general, these effects of GLP-2 were blocked by coadministration of a vasoactive intestinal peptide (VIP) antagonist, and GLP-2 treatment of healthy rats increased the number of VIP-expressing neurons in the ileum relative to saline treatment, indicating that anti-inflammatory actions of GLP-2 are mediated by VIP. In a later study using a rat model of colitis, Sigalet et al. (2010) also showed that twice-daily subcutaneous GLP-2 injections for 5 d could prevent the loss of VIP-expressing neurons in the distal colonic submucosal plexus caused by inflammation and increased the number of VIP-expressing neurons in the colon of normal rats.

In a similar study using a mouse model of post-operative ileus, Moore et al. (2010) found that long-acting forms of GLP-2 administered 1 to 24 h prior to surgical manipulation had multiple beneficial effects, including reduced inflammation and granulocyte infiltration of the small intestine; altered mucosal expression of genes participating in inflammation such as EGR-1 (early growth response gene), IL-6, IL-1β, and MIP-1α (macrophage inflammatory protein-1α) and barrier function, including occludin and claudins 1 and 3; and improved overall intestinal motility 48 h postsurgery. Moore et al. suggested that the effects of GLP-2 pretreatment on intestinal barrier function may further help to reduce inflammation in the small intestine by preventing passage of bacteria and their components from the lumen through the mucosa. They also indicated that GLP-2 pretreatment helped to prevent the decrease in gut motility associated with reductions in intestinal smooth muscle contraction caused by inflammation.

**GLP-2 Receptor and GLP-2 Intermediates**

Glucagon-like peptide-2 exerts its effects by binding to a specific G protein–coupled receptor, the GLP-2 receptor (GLP-2R), which is a member of the β-secretin family of receptors (Munroe et al., 1999). The GLP-2R is expressed in relatively low abundance, but its mRNA transcripts have been detected in the stomach, small and large intestines, brain, lungs, and central nervous system in rodents, humans, and pigs (Munroe et al., 1999; Yusta et al., 2000; Bjerknes and Cheng, 2001; Petersen et al., 2001) and, more recently, in human-derived osteoblastic cell lines (Pacheco-Pantoja et al., 2011) and rat heart (Angelone et al., 2012). Among specific cell types of the gastrointestinal tract, GLP-2R protein has been localized to human enteroendocrine cells (Yusta et al., 2000), murine enteric neurons (Bjerknes and Cheng, 2001), and subepithelial myofibroblasts of rodents and primates (Ørskov et al., 2005). Once activated, GLP-2R on enteric neurons and subepithelial myofibroblasts is believed to function through the phosphatidylinositol 3-kinase-γ intracellular signaling pathway and Akt phosphorylation (Leen et al., 2011; de Heuvel et al., 2012). Because of the lack of expression of GLP-2R on intestinal epithelial cells (Bjerknes and Cheng, 2001), the effects of GLP-2 on these cells must be mediated indirectly through paracrine-acting effector molecules (Rowland and Brubaker, 2011).

Several growth factors, including IGF-1, IGF-2, keratinocyte growth factor (KGF), and members of the ErbB family, have been identified as mediators of GLP-2-induced effects on the intestinal mucosa (reviewed by Dubé and Brubaker [2007] and Rowland and Brubaker [2011]). For instance, GLP-2 treatment of primary submucosal neurons isolated from rodent intestine exhibit increased expression of multiple growth factors, including epidermal growth factor (EGF), IGF-1, and ErbB ligands and their receptors (de Heuvel et al., 2012). The importance of KGF was also demonstrated by the loss of GLP-2-induced growth of the large intestine and colon of mice subjected to KGF immunoneutralization (Ørskov et al., 2005). Using GLP-2R knockout mice with fasting-induced atrophy of the small intestine, it
was further demonstrated that \( GLP-2R \) is central to the proliferative response of the gut to refeeding and that the EGF-ErbB pathway mediates the observed growth responses, which presumably are induced by GLP-2 (Bahrami et al., 2010).

Multiple studies have demonstrated the roles of IGF pathway members in mediating the effects of GLP-2 on proliferation of the intestinal mucosa, particularly through the use of knockout mouse models. Dubé et al. (2006) first demonstrated that mice treated with GLP-2 exhibit increased intestinal IGF-1 mRNA transcription and that cultured fetal rat intestinal cells have increased expression of both IGF-1 mRNA and protein in response to GLP-2-treatment. The same group demonstrated that IGF-1 knockout mice exhibit no GLP-2-induced increases in intestinal weight, villus height, crypt depth, or crypt cell proliferation, as had been observed in GLP-2-treated wild-type mice, and that partial IGF-2 knockout mice showed significantly impaired proliferative responses to GLP-2 treatment in various segments of the intestine. Likewise, the proliferative effects of GLP-2 on intestinal crypts were lost in IGF-1 receptor knockout mice (Rowland et al., 2011). Certainly, development of novel tissue- and cell-specific models, as well as specific gene knockout mouse models, will continue to enable the identification of the complex intermediate pathways and their members contributing to the intestinal actions of GLP-2 (Rowland and Brubaker, 2011).

### GLP-2 Degradation and Clearance

Upon release from L cells, the bioactive GLP-2(1-33) peptide has a short half-life in circulation, estimated to be approximately 7 min in humans (Hartmann et al., 2000a). This short half-life is due to N-terminal cleavage of the first 2 amino acids of the peptide by the ubiquitously expressed dipeptidyl peptidase IV enzyme (\( DPP-4; \) Drucker et al., 1997) to an inactive form, GLP-2(3-33), and removal by the kidneys (Tavares et al., 2000). In rats, a greater activity of DPP-4 on intestinal crypts were lost in IGF-1 receptor knockout mice (Rowland et al., 2011). Certainly, development of novel tissue- and cell-specific models, as well as specific gene knockout mouse models, will continue to enable the identification of the complex intermediate pathways and their members contributing to the intestinal actions of GLP-2 (Rowland and Brubaker, 2011).

#### Luminal Nutrient Detection and GLP-2 Release

Until recently, the mechanisms by which the presence of various nutrients in the intestinal lumen was detected and transduced to afferent nerves and L cells to activate GLP-2 secretion were unknown. The discovery and characterization of a large group of G protein–coupled receptors that “taste” the luminal contents provides a basis for how specific nutrients may regulate their absorption, as well as hormonal release and overall metabolism (Akiba and Kaunitz, 2014). These nutrient-sensing receptors are expressed on the apical membrane of L cells and include multiple types known to influence GLP-2 secretion in nonruminant species. These receptors include the umami taste receptor (\( \text{T1R1-T1R3} \)), the bile acid receptor (\( \text{TGR5} \)), free fatty acid receptors (\( \text{GPR40, GPR41, GPR43, and GPR120} \)), and the sweet taste receptor (\( \text{T1R2-T1R3} \)), which are described briefly below. For more
complete reviews of these G protein–coupled receptors, the reader is referred to Reimann et al. (2012), Ulven (2012), Mace and Marshall (2013), Akiba and Kaunitz (2014), and Shirazi-Beechey et al. (2014).

First, the umami T1R1-T1R3 receptor is activated by most of the l–amino acids, including l-glutamate (Nelson et al., 2002), and its activation has been shown to stimulate GLP-2 release from L cells in the duodenum of rats (Wang et al., 2011). This receptor is conserved across multiple mammalian species (Kaji et al., 2013), and it is likely through its stimulation and subsequent GLP-2 secretion that dietary glutamate or glutamine supplementation is able to improve gut function and health in pigs, including reduced jejunal villus atrophy during weaning (Wu et al., 1996), attenuated intestinal damage induced by E. coli challenge (Yi et al., 2005), and reduced prevalence and severity of diarrhea in young pigs postweaning (Bannai and Torii, 2013). Second, the receptor TGR5 is stimulated by bile acids, and its activation has been shown to stimulate GLP-1 release in a mouse enteroendocrine cell line (Katsuma et al., 2005) and GLP-2 secretion in perfused rat duodenum (Inoue et al., 2012). Furthermore, it is through this receptor that feeding of the bile acid, chenodeoxycholic acid, was believed to stimulate GLP-2 release in early weaned pigs (Ipharraguerrre et al., 2013).

A third nutrient sensor expressed on L cells is the free fatty acid receptor, which exists as 4 different subtypes, each of which are activated by fatty acids of differing carbon chain lengths (Covington et al., 2006; Ulven, 2012). Specifically, the receptors GPR41 and GPR43 are activated by short-chain fatty acids (<C6), and GPR40 and GPR120 are activated by saturated and unsaturated medium-chain (C7 to C12) to long-chain (C12 to C24) fatty acids (Ulven, 2012; Mobraten et al., 2013). For instance, in the large intestine, GPR41 and GPR43 detect short-chain fatty acids generated by microbial fermentation of dietary fiber and stimulate GLP secretion, providing a mechanism for the beneficial effects of a high-fiber diet and prebiotics on preventing and ameliorating inflammatory bowel diseases (Cani et al., 2009; Ulven, 2012).

Last, the sweet taste receptor T1R2-T1R3 expressed on L cells is stimulated by carbohydrates and other nonnutritive sweeteners, resulting in GLP release and increased expression of glucose transporters on nearby intestinal epithelial cells (Shirazi-Beechey et al., 2014). For instance, Daly et al. (2012) demonstrated that treatment of murine small intestinal explants with glucose or the artificial sweetener sucralose increased GLP-2 secretion, which was blocked in the presence of an inhibitor of the T1R3 domain of the sweet taste receptor. It is likely through the activation of T1R2-T1R3 receptors and subsequent GLP-2 release and increased glucose transporter expression that Sterk et al. (2008) observed improved fecal consistency and ADG in weanling pigs fed diets supplemented with artificial sweeteners.

**THERAPEUTIC USES OF GLP-2**

**Applications in Nonruminants**

Because of the many effects of GLP-2 on the gut, therapies including long-acting GLP-2 derivatives or activators of GLP-2 secretion or the GLP-2R have been proposed for the treatment of intestinal disorders or conditions of humans to improve nutrient absorption and intestinal healing (reviewed by Wallis et al., 2007; Tee et al., 2011; Yamazaki et al., 2012; Drucker and Yusta, 2014). These conditions include short bowel syndrome (nutrient malabsorption generally due to intestinal resection); inflammatory bowel disease; colitis or colonic injury; enteritis caused by chemotherapies, prolonged nonsteroidal anti-inflammatory drug use, infectious agents, and radiation treatment; gut ischemia; necrotizing enterocolitis, particularly in premature infants; total parenteral nutrition-induced gut atrophy; and impaired gut barrier function (e.g., from acute necrotizing pancreatitis, diet-induced allergy, or stress). Currently, the prescription drug Gattex (teduglutide, recombinant human [Gly²]-GLP-2) from NPS Pharmaceuticals (Bedminster, NJ) for subcutaneous injection is approved by the U.S. Food and Drug Administration for the treatment of patients receiving parenteral nutrition or exhibiting short bowel syndrome.

The effects of GLP-2 treatment have been evaluated in a limited number of studies as a means to improve growth performance in poultry and in swine during weaning. For instance, Hu et al. (2010) modeled stress in broiler chickens using daily corticosterone feeding (30 mg/kg diet) for a 2-wk period, then evaluated the impacts of intraperitoneal GLP-2 injection (26.3 μg/kg of BW) for 14 d on their ADG, G:F, gut morphology, and nutrient transporter mRNA transcription in the small intestine over a 21-d period. In the stressed broilers, GLP-2 increased G:F, increased villus height and crypt depth in the small intestine, and increased nutrient transporter expression in the small intestine relative to saline-treated birds. In nonstressed broilers, GLP-2 also increased final BW, ADG, G:F, and selected nutrient transporters in the intestine relative to saline-treated controls. These results indicate that GLP-2 treatment can improve production efficiency of both healthy and stressed poultry.

In contrast, however, Thymann et al. (2014) found that weanling pigs reared in either a highly sanitary or an unsanitary environment and treated with native...
or long-acting GLP-2 exhibited no benefits related to growth performance and only limited benefits on fecal scores when treated with long-acting GLP-2 and raised under unsanitary conditions. Impacts on gut morphology and intestinal enzyme activities were also limited. Similarly, Sigalet et al. (2014) found that GLP-2 treatment of healthy 2-d-old pigs for 42 d had no effect on BW gain or feed intake but did increase villus height, crypt depth, and cell proliferation in the small intestine and reduced apoptosis and GLP-2R mRNA transcription in the small intestine and colon. These results indicate GLP-2 treatment has no substantial benefits for growth performance in healthy weaning pigs but indicate that GLP-2 may improve gut function in compromised pigs during weaning.

**GLP-2 Biology and Potential GLP-2 Applications in Ruminants**

The role of GLP-2 in gut development and function in ruminants was investigated recently, and results indicate that pathways and mechanisms of GLP-2 biology equivalent to those in nonruminants exist in these species. For example, mRNA transcription of both proglucagon, the peptide from which GLP-2 is derived, and GLP-2R was demonstrated throughout the bovine gastrointestinal tract, including very low levels in the rumen and omasum (Taylor-Edwards et al., 2010) and moderate levels in the duodenum, jejunum, ileum, cecum, and rectum (Connor et al., 2010; Taylor-Edwards et al., 2010). In addition, expression of GLP-2R protein was detected in all 3 segments of the small intestine, cecum, and rectum of mature dairy cows, and GLP-2R mRNA was differentially expressed in the ileum and rectum across different stages of the lactation cycle (Connor et al., 2010). Transcription of GLP-2R mRNA was also increased in the ileum in response to an increased level of dietary energy intake (Taylor-Edwards et al., 2010). Furthermore, circulating concentrations of GLP-2 in ruminating steers tended to increase with increased dietary energy intake (Taylor-Edwards et al., 2010) and increased in newborn calves supplemented with dietary sodium butyrate (Górka et al., 2009, 2011). Interestingly, the increase in GLP-2 among calves correlated with increased rumen mucosal development, which the authors suggested could be mediated indirectly by the effects of GLP-2 on the development of the small intestine. These findings indicate a functional role of GLP-2 in the intestinal tract and the potential for modulation of GLP-2 action in cattle.

Taylor-Edwards et al. (2011) further confirmed that consistent with the physiological effects of GLP-2 in nonruminants, a 10-d GLP-2 treatment of ruminating calves increases blood flow to the small intestine via the superior mesenteric artery and stimulates intestinal mucosal growth, although effects on blood flow were greater in response to acute GLP-2 exposure and were dampened by chronic GLP-2 treatment. Their study estimated a 24% increase in intestinal mass due particularly to increased cell proliferation and mucosal growth in the ileum and jejunum, although increases in cell proliferation, villus height, and crypt depth were also observed in the duodenum. In a later study, the same group confirmed increases in blood flow to the portal and hepatic veins in response to acute GLP-2 administration but not chronic (10-d) GLP-2 exposure, as well as increased metabolism of specific amino acids (but not glucose) in the intestine (Taylor-Edwards et al., 2012). Taylor-Edwards et al. (2012) concluded that GLP-2 promotes amino acid use by the gut of ruminants over the metabolism of glucose to support proliferation of the intestinal mucosa.

Recently, Connor et al. (2013) confirmed the benefits of GLP-2 therapy in ruminants with compromised gut health, consistent with previous findings in nonruminants. Specifically, the results of the study indicated that GLP-2 treatment of neonatal calves for 10 d increased intestinal weight and epithelial cell proliferation in the jejunum and substantially reduced protein tyrosine nitration (an indicator of nitro-oxidative stress induced by inflammation) in the ileum and cecum, particularly in calves with coccidiosis caused by *Eimeria bovis*. The latter finding is consistent with the antioxidant activities of GLP-2 demonstrated previously in rodents (Arda-Pirincci and Bolkent, 2011) and indicates that GLP-2 therapy should promote tissue recovery and reduce the negative consequences of inflammation (e.g., resulting from insult or infection) on intestinal function in ruminants.

Interestingly, the effects of GLP-2 therapy on intestinal barrier function as assessed by mRNA transcription of key proteins participating in cellular tight junction formation using gut tissues collected from the same calf study (Connor et al., 2013) indicate that GLP-2 may help to improve gut integrity of ruminants by affecting expression of multiple tight junction proteins in intestinal mucosa (M. P. Walker, C. M. Evock-Clover, T. H. Elsasser, and E. E. Connor, unpublished data). For example, mRNA abundance of multiple tight junction complex proteins, including claudin 4, F11 receptor, and occludin, was reduced in the cecum by *E. bovis* infection but was increased by GLP-2 treatment. The increases in mRNA abundance of tight junction proteins in response to GLP-2 treatment were most evident in noninfected calves. These findings further confirm similarities in GLP-2 biology between ruminants and nonruminants and indicate the potential prophylactic use of GLP-2 to enhance gut barrier function in young ruminants to reduce pathogen invasion and intestinal damage.
Last, consistent with observations in nonruminants, the results of Moran et al. (2014) confirmed the protein expression of sweet taste receptors T1R2-T1R3 on GLP-2-secreting L cells in bovine duodenum. This exciting finding indicates the potential to stimulate GLP-2 release in ruminants through the use of dietary carbohydrates or artificial sweeteners to gain its beneficial effects on the gut. Indeed, Moran et al.’s study demonstrated that feeding the artificial sweetener Sucram (composed of saccharin and neohesperidin dihydrochalcone; Pancosma SA, Geneva, Switzerland) to 110-d-old ruminating calves increased intestinal glucose transporter SGLT1 activity, increased intestinal villus height and crypt depth, and increased activity of the digestive enzymes maltase and alkaline phosphatase. Significant effects of Sucram on the gut of preruminating 50-d-old calves, however, were not observed in their study. Although GLP-2 release was not measured in calf tissues in the study by Moran et al. (2014), release of GLP-2 in response to treatment with 3 artificial sweeteners in ovine intestinal explants was shown. Additionally, feeding Sucram to mature, nonlactating dairy cows increased their expression of the intestinal glucose transporter SGLT1 protein (Moran et al., 2014). Thus, their results provide a practical means to stimulate GLP-2 release in dairy cattle to improve their gut function and health and indicate the need for additional research in this promising area of ruminant production.

**SUMMARY AND CONCLUSIONS**

Several opportunities exist for using GLP-2 to improve production efficiency and health in cattle. First, GLP-2 may be useful for increasing absorptive capacity in the gut of newborn calves and may improve feed conversion efficiency. Therapy with GLP-2 should increase barrier function and gut integrity, which can reduce the passage of toxins and pathogenic organisms and has implications for reducing negative impacts on the gut associated with conditions such as transport stress or heat stress. Direct or indirect effects of GLP-2 may reduce inflammation in the gut associated with damage or infections, such as acidosis, or diarrhea caused by parasitic organisms or associated with Johne’s disease and can be used to promote healing and regeneration of damaged gut tissues resulting from these conditions. Ultimately, practical means to administer GLP-2 therapy, such as dietary supplements (e.g., artificial sweeteners, bile acids, fatty acids, or prebiotics) that stimulate natural GLP-2 secretion via activation of taste receptors, need to be investigated.

**LITERATURE CITED**


