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Glucagon-like peptide 2 and its beneficial effects on gut function and health in production animals

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ABSTRACT

Numerous endocrine cell subtypes exist within the intestinal mucosa and produce peptides contributing to the regulation of critical physiological processes including appetite, energy metabolism, gut function, and gut health. The mechanisms of action and the extent of the physiological effects of these enteric peptides are only beginning to be uncovered. One peptide in particular, glucagon-like peptide 2 (GLP-2) produced by enteroendocrine L cells, has been fairly well characterized in rodent and swine models in terms of its ability to improve nutrient absorption and healing of the gut after injury. In fact, a long-acting form of GLP-2 recently has been approved for the management and treatment of human conditions like inflammatory bowel disease and short bowel syndrome. However, novel functions of GLP-2 within the gut continue to be demonstrated, including its beneficial effects on intestinal barrier function and reducing intestinal inflammation. As knowledge continues to grow about GLP-2's effects on the gut and its mechanisms of release, the potential to use GLP-2 to improve gut function and health of food animals becomes increasingly more apparent. Thus, the purpose of this review is to summarize: (1) the current understanding of GLP-2's functions and mechanisms of action within the gut; (2) novel applications of GLP-2 (or stimulators of its release) to improve general health and production performance of food animals; and (3) recent findings, using dairy calves as a model, that suggest the therapeutic potential of GLP-2 to reduce the pathogenesis of intestinal protozoan infections.

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1. Introduction

In 1902, the first factor produced in the gut and released into the bloodstream, which affected insulin secretion, was described and named 'secretin' [1]. Since that time, numerous subtypes of endocrine cells within the intestinal mucosa and their peptide products have been characterized [2]. These enteric peptides have become the subject of intensive scientific investigation regarding regulation of their release [3–5], mechanisms of action [6–8], and diverse physiological effects, including those outside the digestive system such as bone [9], liver [10], lung [11], and the central nervous system [12–14]. This primarily was due to the discovery that enteric peptides, such as glucagon-like peptide 1 (GLP-1), gastric inhibitory peptide, and peptide YY, play key roles in the regulation of appetite, energy metabolism [15–17], and gut function [18–20], making them targets for managing prevalent human diseases of obesity and diabetes. As knowledge has continued to grow, the potential to improve gut function and health of food animals through the manipulation of enteric peptide secretion has become increasingly more apparent [21–26].

Glucagon-like peptide 2 (GLP-2) is an enteric peptide gaining significant attention because of its roles in

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improving nutrient absorption, energy balance, and gut barrier function, and reducing intestinal inflammation and its subsequent impacts on human health (reviewed by [12,27–29]) and production animals (reviewed by [22,30]). The purpose of this review is to summarize (1) the current understanding of GLP-2's functions and mechanisms of action; (2) the potential use of GLP-2 or stimulators of its release to improve health and production performance of food animals; and (3) recent findings suggesting the therapeutic potential of GLP-2 to reduce the pathogenesis of intestinal protozoan infections in dairy calves.

2. Physiology of GLP-2

2.1. GLP-2 synthesis and degradation

GLP-2 is a 33-amino acid peptide hormone produced primarily in the gut as a result of tissue-specific post-translational cleavage of a prohormone, proglucagon, by the enzyme prohormone convertase 1/3 in intestinal L cells [22]. The L cells comprise less than 5% of mucosal cells; however, the greatest percentage of L cells is located in the distal small intestine and colon [30]. Processing of proglucagon by prohormone convertase 1/3 in L cells concurrently produces the incretin hormone, GLP-1, in addition to an appetite regulator named oxyntomodulin [31], and 3 peptides called glicentin, glicentin-related pancreatic polypeptide, and intervening peptide 2 (IP-2; [32,33]), the functions of which are not well characterized. Proglucagon is encoded by the *GCG* gene, the expression of which is regulated by a cyclic adenosine monophosphate-mediated pathway in intestinal cells [34], and transcription factors Pax-6 [35,36], β-catenin and/or T cell factor 4 [37], and factors in the Wnt signaling pathway [38]. Intestinal expression of *GCG* gene is increased by feeding and is suppressed by fasting [39]. In addition, specific nutrients including long-chain triglycerides, protein hydrolysates, dietary fiber, and short-chain fatty acids can induce *GCG* messenger RNA (mRNA) expression [22]. For additional details regarding the transcriptional regulation of *GCG* gene, the reader is referred to Jin [38].

The half-life of GLP-2 (1–33) in circulation is very short because of its removal by the kidneys, and enzymatic degradation by dipeptidyl peptidase IV (DPP-IV) of its N-terminal His-Ala residues to a truncated GLP-2 (3–33) form [40]. The GLP-2 (3–33) form lacks in vivo activity [41,42]; however it can weakly activate the GLP-2 receptor (GLP-2R) when administered at supraphysiological doses [43]. Because of GLP-2's short (approximately 7-min) half-life in humans [44], administration of DPP-IV inhibitors has been used to enhance the therapeutic effects of GLP-2 [45–47], and synthetic GLP-2 analogs that are resistant to DPP-IV degradation have been used to prolong and increase its biological activity. Modifications include replacing the Ala (2) residue with Gly [40,42], which increases the half-life of GLP-2 to approximately 3 h in humans [48], or conjugating the peptide to various polymers, which extends the half-life in humans to as great as 10 d, based on theoretical projections from animal models [49–51]. Further advances in our understanding of factors that increase GLP-2 synthesis and means to enhance its biological activity will support its potential use as an enhancer of animal productivity, health, and well-being.

2.2. Regulation of GLP-2 release

Both nutrient ingestion and intestinal injury stimulate release of GLP-2 from enteroendocrine L cells whereby its actions facilitate nutrient uptake, and mucosal growth, protection, and healing [28,52]. The signaling pathway responsible for the GLP-2 response to intestinal injury remains unknown [28]. The postprandial increase in circulating GLP-2 concentration occurs in 2 phases, the first of which is within 30 min of nutrient intake and is neuronally mediated [53,54]. Although the neuronal signals have not been completely characterized for most species, rodent models indicate that nutrients entering the duodenum activate endocrine K cells to release gastric inhibitory peptide, which stimulates vagal afferent nerves. Vagal efferent nerves and enteric neurons then induce GLP-2 release from L cells located in the distal small intestine and colon via acetylcholine and gastrin-releasing peptide. The second peak in GLP-2 release occurs 60 to 120 min after a meal through direct nutrient stimulation of L cells [53] by activation of specialized G-protein–coupled receptors present on their apical surfaces, which act as luminal chemosensors or "taste" receptors [55,56]. The L cells express multiple types of chemosensors that are specifically activated by nutrients and sensory factors that stimulate GLP-2 secretion, including amino acids and peptones (via receptors T1R1-T1R3, CaSR, and LPAR5), bile acids (via receptor TGR5), simple sugars and non-nutritive sweeteners (via receptor T1R2-T1R3), free fatty acids and their metabolites (via receptors GPR40, GPR41, GPR43, GPR119, and GPR120), and bitter substances (via numerous taste receptor type 2 receptors; [52,57]). Through the activation of these receptors, many benefits of stimulating GLP-2 release particularly on gut function and health of production animals through dietary intervention may be possible and are discussed in the following.

2.3. Physiological effects of GLP-2 on intestinal tissues

The effects of GLP-2 on the intestinal tract are quite extensive and diverse because GLP-2 has both direct and indirect effects (via intermediate factors) on target cells, including enterocytes, goblet cells, Paneth cells, stem and/or progenitor cells, sensory and enteric neurons, subepithelial myofibroblasts, endothelial cells of blood vessels, and various enteroendocrine cells [30,52,58,59]; Figure 1. The effects of GLP-2 most commonly reported include increased intestinal weight and mucosal development (eg, increased enterocyte volume, microvillus and villus heights, and crypt depth), increased mesenteric blood flow, enhanced glucose and peptide transporter expression, or activity and digestive enzyme activity in the intestinal brush border, reduced gut motility, increased barrier function and/or reduced intestinal permeability, reduced intestinal inflammation and apoptosis of intestinal epithelial cells, and improved intestinal healing after injury (reviewed by [28,30]). The detailed cellular and signaling