



## REVIEW ARTICLE

## METABOLIC AND DIGESTIVE FUNCTIONS OF GLUCAGON-LIKE PEPTIDE-1 IN PIGS

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**Ethical considerations:** When reporting experiments on animals Observation of the ARRIVE guidelines 2.0: Updated guidelines for reporting animal research, published on July 14, 2020 (DOI: 10.1371/journal.pbio.3000410), is applied. The authors ensure that all procedures were performed in compliance with the guidelines for animal care of their institutions or with national/international guidelines.

## ABSTRACT

**Glucagon-like peptide-1 (GLP-1) is a hormone with multiple biological effects that plays a key role in glucose metabolism, digestion, and energy homeostasis. In pigs, GLP-1 serves as an important metabolic regulator with relevance for both production efficiency and translational research. This review summarizes current knowledge on GLP-1 physiology in pigs, including synthesis, secretion, metabolism, and biological actions. Particular emphasis is placed on the role of GLP-1 in insulin secretion, digestive function, including gastric mucosal protection and ulcer prevention, appetite regulation, and lipid metabolism. Understanding GLP-1 mechanisms in pigs has practical implications for optimizing feeding strategies in swine production and provides insights relevant to human metabolic disease research.**

**Keywords:** digestion; GLP-1; glucose homeostasis; incretin; insulin; metabolism; pigs; stomach ulcers

## INTRODUCTION

Glucagon-like peptide-1 (GLP-1) is a 30-amino acid incretin hormone originating in intestinal enteroendocrine L-cells where proglucagon undergoes tissue-specific enzymatic processing [1]. It is an incretin hormone that enhances glucose-dependent insulin secretion following nutrient intake. Since its discovery in the 1980s, GLP-1 has become the focus of intensive research due to its therapeutic potential for treating type 2 diabetes and obesity in humans together with other emerging therapeutic areas [2, 3].

Although most GLP-1 research has been conducted in humans and laboratory rodents, pigs also represent a valuable model for studying GLP-1 physiology. Due to their

comparable anatomical and physiological features to humans, pigs provide relevant biomedical models for metabolic disease research [4]. Additionally, understanding GLP-1's role in pig metabolism has practical significance for improving feed efficiency and growth performance in commercial pig production [5]. Research on GLP-1 in various animal models, including pigs, has greatly contributed to the development of GLP-1-based therapeutics now widely used in clinical practice, especially for treating type 2 diabetes and obesity [2, 6].

In pigs, proglucagon is processed to GLP-1 and other bioactive peptides through prohormone convertase (PC) 1/3 in intestinal L-cells [1]. The bioactive forms include GLP-1(7-36) amide and GLP-1(7-37), with the amidated form pre-

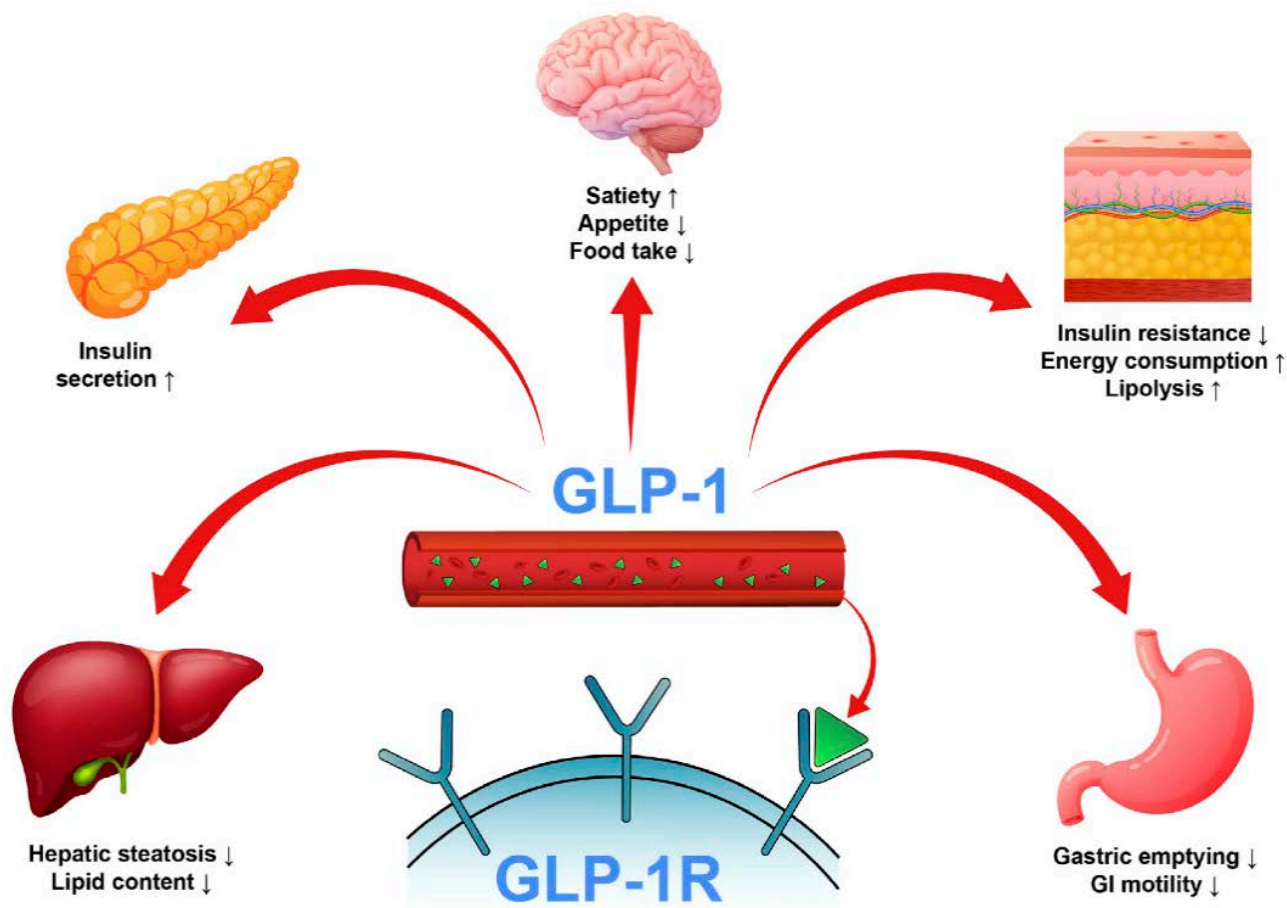


Fig. 1. Schematic representation of GLP-1 biological multi-organ effects mediated through the GLP-1 receptor (GLP-1R). GLP-1 regulates multiple physiological processes, including insulin secretion from pancreatic  $\beta$ -cells, appetite control in the brain, gastric emptying and GI motility, hepatic lipid metabolism, and adipose tissue energy consumption. Adapted from Alturki et al. (2025) [46] (CC BY 4.0 license)

dominating in pigs as in humans [7]. Eissele et al. [8] demonstrated a distribution of L-cells (GLP-1-releasing cells) along the gastrointestinal tract, with the highest accumulation in the distal part of the small intestine and colon (Figure 1). Like other mammals, pigs exhibit rapid GLP-1 degradation by dipeptidyl peptidase-4 (DPP-4), resulting in a plasma half-life of approximately 1–2 minutes [9, 10, 11].

## LITERATURE SEARCH STRATEGY

Relevant scientific literature was identified through systematic searches of the PubMed, Web of Science, Scopus, and Google Scholar databases. The search strategy employed combinations of the following keywords and their variants: *GLP-1*, *glucagon-like peptide-1*, *pigs*, *porcine*, *incretin*, *glucose metabolism*, *insulin secretion*, *digestive function*, *gastric emptying*, *gastric ulcers*, *gastroprotection*, *gut hormones*, and *intestinal microbiota*.

Publications published primarily between 1990 and 2025 were considered, with emphasis placed on peer-reviewed original research articles and review papers written in English. Additional relevant references were identified through manual screening of the reference lists of selected articles. Studies focusing on GLP-1 physiology, secretion, metabolism, and biological effects in pigs were prioritized, while key comparative studies in humans and other animal models were included where they provided important mechanistic or translational insights. Only publications directly relevant to metabolic, digestive, or gastrointestinal aspects of GLP-1 were included in the final synthesis.

## GLP-1 SECRETION AND REGULATION

### Nutrient and Neural Regulation

Nutrient intake, particularly carbohydrates and lipids, has been shown to stimulate GLP-1 secretion in pigs [12].

Perfused porcine ileum studies demonstrate dose-dependent GLP-1 release in response to glucose [13]. Long-chain fatty acids are especially potent secretagogues, acting through G-protein-coupled receptors (GPCRs) on L-cells [14]. Also, fermentable dietary fibers promote GLP-1 secretion through short-chain fatty acid production by gut microbiota [14, 15].

Glucagon-like peptide-1 secretion in pigs is also modulated by neural mechanisms. Sympathetic innervation inhibits secretion via  $\alpha$ -adrenergic receptors, while  $\beta$ -adrenergic receptor activation and cholinergic stimulation enhance GLP-1 release [16]. However, vagal nerve stimulation shows minimal effect in anesthetized pigs, suggesting intrinsic cholinergic nerves play a more important role than extrinsic vagal pathways [16]. These findings indicate complex local and systemic regulation of GLP-1 secretion.

Glucagon-like peptide-1 secretion exhibits both nutrient-stimulated and basal autonomous patterns. While acute secretory responses to nutrients represent the primary regulatory mechanism, recent evidence indicates that in

humans, GLP-1 also follows an intrinsic circadian rhythm. L-cells have been demonstrated to possess autonomous molecular clocks regulated by identified core circadian genes (BMAL1 and CLOCK) modulating time-dependent GLP-1 secretion patterns independently of immediate nutrient stimuli [17]. The basal autonomous pattern as described in humans may be disrupted by various factors, including high-fat diets, irregular sleep patterns, and gut microbiota dysbiosis, potentially contributing to metabolic dysfunction [17]. Characterizing these temporal secretion patterns should be considered when developing guide evidence-based feeding strategies in pig production and providing comparative insights into circadian metabolic regulation across mammals.

### Metabolism and Clearance

Glucagon-like peptide-1 metabolism in pigs exhibits tissue-specific patterns. Studies in anesthetized pigs reveal substantial renal extraction of endogenous GLP-1 (approximately 33%), indicating the kidneys play a ma-

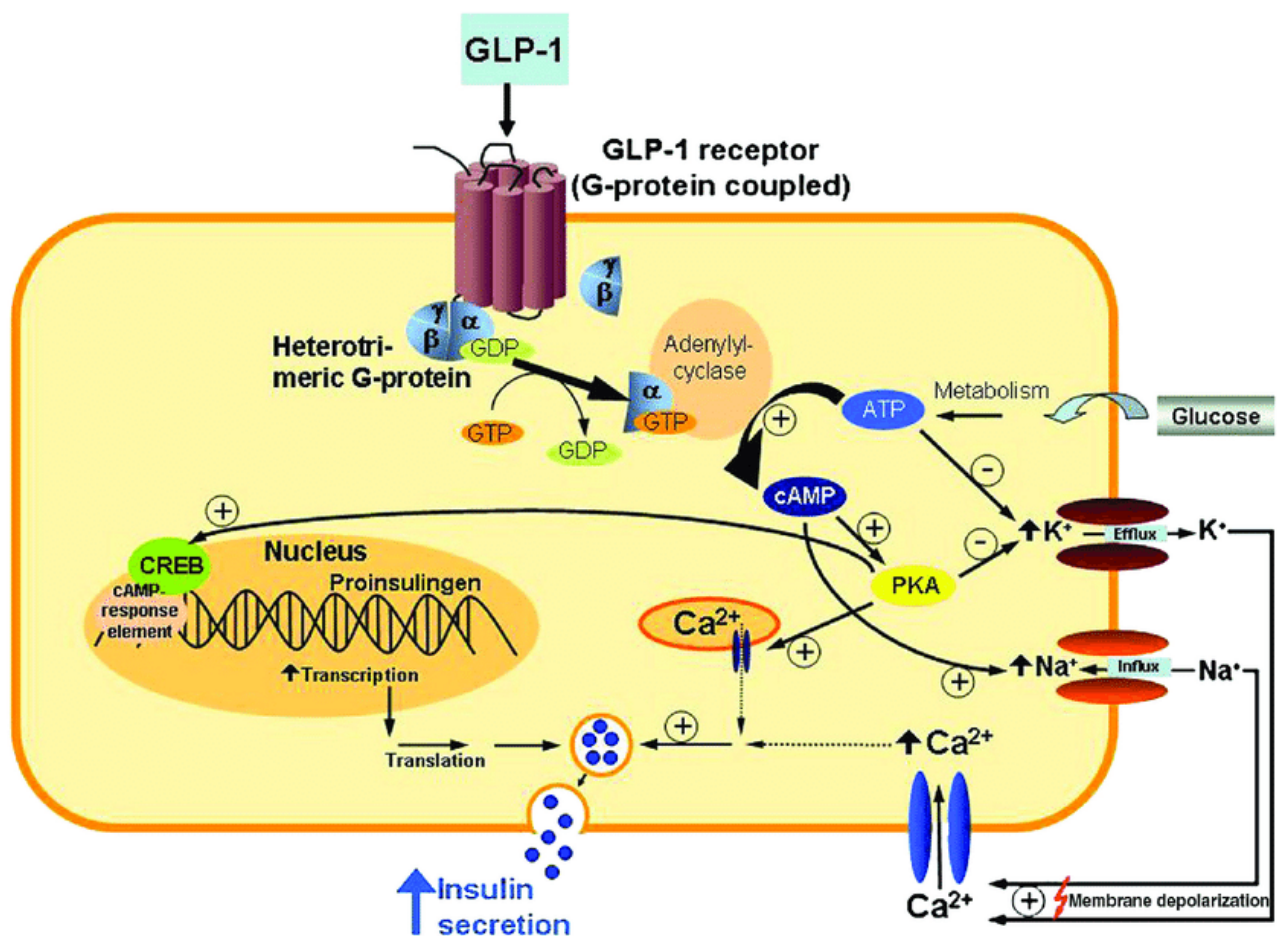


Fig. 2. Molecular mechanism of GLP-1 receptor signalling in pancreatic  $\beta$ -cells. Adapted from Sheikh (2013) [34] (CC by 2.0 license).

major role in GLP-1 clearance, as confirmed by subsequent studies in the same model [9, 18]. The liver and lungs also contribute to elimination through N-terminal cleavage by DPP-4 [9, 10]. Peripheral tissues including skeletal muscle show significant GLP-1 extraction, suggesting widespread hormone metabolism [9]. This rapid degradation necessitates continuous secretion to maintain physiological effects [1].

## GLUCOSE METABOLISM AND INSULIN SECRETION

### The Incretin Effect

The incretin effect has attracted growing interest since the identification of GLP-1 as a physiological incretin in humans by Kreyman et al. [19]. In pigs, glucagon-like peptide-1 contributes significantly to the incretin effect, whereby oral glucose results in greater insulin secretion than intravenous glucose at equivalent blood glucose levels [20]. This effect is comparable in magnitude to the one observed in humans, supporting the pig's validity as a translational model [4, 21]. Both GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) cooperate to increase insulin secretion [20].

The glucagon-like peptide-1 receptor on pancreatic  $\beta$ -cells activates adenylyl cyclase via Gs proteins, increasing intracellular cAMP and activating protein kinase A (PKA) [2, 22]. This signalling pathway is shared across mammals (Figure 2). Importantly, the insulinotropic action of GLP-1 is glucose-dependent, stimulating insulin secretion only at elevated glucose levels and thereby minimizing the risk of hypoglycemia [20]. This safety feature differentiates GLP-1 from conventional insulin secretagogues [23].

### $\beta$ -Cell Effects

Beyond acute insulin secretion, GLP-1 exerts long-term trophic effects on pancreatic  $\beta$ -cells. Studies using porcine islets demonstrate that GLP-1 promotes  $\beta$ -cell proliferation, inhibits apoptosis, and increases insulin gene expression [24]. These protective effects involve PKA and EPAC (exchange protein directly activated by cAMP) pathways. Such trophic actions may be particularly relevant during metabolic challenges and developmental transitions in pigs, such as weaning [12, 25]. The capacity to

maintain  $\beta$ -cell mass and function suggests GLP-1 plays a role beyond immediate glucose regulation.

## DIGESTIVE FUNCTION

### Gastric Emptying and Motility

Glucagon-like peptide-1 significantly slows gastric emptying in pigs [26]. This effect contributes to postprandial glucose control by moderating nutrient delivery to the small intestine, thereby influencing the rate of glucose absorption. The mechanism involves both direct effects on gastric smooth muscle as well as indirect neural pathways [27, 28]. Delayed gastric emptying also enhances satiety and reduces food intake. Additionally, GLP-1 inhibits gastric acid secretion, complementing its effects on gastric emptying [26].

Glucagon-like peptide-1 also influences intestinal function beyond the stomach. It modulates intestinal motility and may affect pancreatic enzyme secretion, though these effects vary with physiological conditions [29]. Recent evidence suggests GLP-1 supports intestinal barrier integrity and reduces intestinal permeability [2, 4]. This is particularly relevant during weaning stress and dietary transitions in commercial pig production, where maintaining gut health is crucial for animal welfare and performance [30].

### Nutrient Absorption

Emerging evidence indicates GLP-1 may influence intestinal nutrient absorption, though the specific mechanisms in pigs remain incompletely understood. Results from postnatal preterm pig studies indicate that intestinal maturation is associated with changes in hexose absorptive capacity and brush-border enzyme activities, processes in which gut hormone signalling from intestinal L-cells plays an important role in postnatal intestinal development [12]. Furthermore, GLP-1's effects on intestinal blood flow may indirectly support nutrient uptake [25]. These actions have important implications for feed efficiency in swine production, though practical applications require further investigation.

### Gastric Ulcers

Gastric ulcers are a frequent finding in pigs, especially in those raised in large-scale farms, significantly affecting productivity. Development of gastric ulcers in pigs has been extensively studied. Key contributing factors include

infectious agents (*Helicobacter suis*), feeding strategies, environmental factors inducing stress, and non-steroidal anti-inflammatory drugs (NSAIDs) administration [31].

Despite commonly reported gastrointestinal adverse effects associated with GLP-1 receptor agonist therapy in patients with type 2 diabetes, several beneficial actions beyond glycaemic control have been documented [32, 33, 34].

Glucagon-like peptide-1 may exert gastroprotective properties via several mechanisms, including delayed gastric emptying [35], inhibition of gastric acid secretion [36, 37], enhanced mucosal barrier function [38, 39], and anti-inflammatory effects [32, 33], as demonstrated in multiple species, including humans and pigs. Understanding the relationship between GLP-1 and gastric ulcers may be of particular relevance in swine production, where gastric ulceration is highly prevalent [31].

## APPETITE REGULATION AND FOOD INTAKE

Glucagon-like peptide-1 functions as a satiety signal in pigs, reducing voluntary feed intake when administered exogenously [40]. This effect involves peripheral mechanisms like delayed gastric emptying and central mechanisms mediated through GLP-1 receptors in the hypothalamus and brainstem [25, 28]. GLP-1 receptors are present in brain regions that control food intake and energy homeostasis, including the *nucleus tractus solitarius* and *area postrema* [25, 28].

From a production perspective, modulating the GLP-1 system could theoretically optimize feed efficiency by improving the growth-to-feed ratio. Dietary strategies promoting endogenous GLP-1 secretion, such as fermentable fiber supplementation, may influence food intake and metabolic efficiency [14, 15]. The gut microbiota plays a key role, producing short-chain fatty acids that stimulate GLP-1 release [14, 15].

## LIPID METABOLISM

Glucagon-like peptide-1 influences lipid metabolism through multiple pathways. In porcine models of metabolic syndrome [4], GLP-1 receptor activation associates with reduced hepatic lipid accumulation and improved hepatic lipid metabolism (including increased fatty acid oxidation

and decreased lipogenesis), consistent with effects observed across diverse mammalian models [41]. These effects may result from direct hepatocyte actions or indirect mechanisms involving insulin secretion and food intake changes [41].

Glucagon-like peptide-1 may also affect adipose tissue metabolism by modulating lipolysis and lipogenesis [42]. However, results across studies show some inconsistency, possibly reflecting differences in experimental protocols, pig breeds, or metabolic states. Understanding GLP-1's role in lipid metabolism is important for optimizing meat quality and metabolic health in pig production, as well as for developing pig models of lipid disorders relevant to human health [4].

## DEVELOPMENTAL AND GENETIC ASPECTS

Glucagon-like peptide-1 physiology changes throughout pig development. Studies examining blood plasma and intestinal GLP-1 concentrations during suckling and post-weaning reveal significant developmental changes [43]. Neonatal and weaned piglets exhibit different GLP-1 secretory patterns and receptor sensitivity compared to adult pigs [43]. These changes reflect enteroendocrine system maturation and adaptation to dietary transitions that occur across key production stages in pigs.

Genetic variability in the GLP-1 system exists among pig breeds. Evidence from human and animal studies suggests that differences in body composition and metabolic status may influence incretin responses and GLP-1 sensitivity [27, 44]. Understanding this genetic variation could inform breeding strategies aimed at improving metabolic efficiency and production traits. The interaction between genotype and nutrition in modulating the GLP-1 system represents an important area for future investigation, potentially enabling precision feeding strategies tailored to genetic background.

## TRANSLATIONAL SIGNIFICANCE AND FUTURE PERSPECTIVES

Pigs serve as excellent translational models for GLP-1 research due to anatomical, physiological, and metabolic similarities to humans [4]. Porcine GLP-1 research has

contributed to understanding incretin physiology and developing GLP-1-based therapeutics for type 2 diabetes and obesity [2]. In past years, GLP-1-based therapy and DPP-4 inhibitors have become a standard clinical treatment, and porcine models have played important roles in their development [45, 3]. Conversely, insights from human clinical studies can inform strategies to optimize metabolic health and production efficiency in swine [5, 10].

Future research directions include investigating interactions between GLP-1 and other gut hormones, exploring the gut microbiota's role in GLP-1 modulation, and developing dietary strategies to enhance endogenous GLP-1 secretion [2, 14, 15]. Understanding how early-life nutrition influences GLP-1 system development could have implications for programming metabolic health [12, 22]. Additionally, exploring GLP-1 modulation for improving feed efficiency and reducing environmental impacts of pig production represents an important sustainability consideration. The potential for GLP-1-based approaches to enhance both animal welfare and production efficiency warrants continued investigation.

## CONCLUSION

Glucagon-like peptide-1 is a hormone with diverse biological actions, playing a key role in glucose metabolism, digestive function, and appetite regulation in pigs. The physiological importance of GLP-1 in pigs largely parallels its role in other mammals, including humans, supporting the pig's utility as both an agricultural species and a translational model for metabolic diseases. Understanding GLP-1 mechanisms has practical implications for optimizing nutrition and management in pig farming. Continued research on GLP-1 physiology in pigs promises to gain insights relevant to both animal production and biomedical research, contributing to improved production efficiency and understanding of metabolic regulation across species.

## Ethical Statement

No ethical approval was necessary for this study.

## Conflict of Interest

The authors declare no conflicts of interest.

## Generative AI Statement

The authors declare that no generative AI or AI-assisted technologies were used in the writing of this manuscript.

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## Authors' Contributions

**EČ** – Conceptualization, Methodology, Literature review, Writing—original draft, Writing—review and editing

**ZK** – Methodology, Literature review, Writing—review and editing, Supervision.

**KB** – Literature review, Writing—original draft, Visualization.

**JN** – Conceptualization, Investigation, Writing—review and editing, Supervision, Funding acquisition.

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