Research Advances on a New System for Evaluating Metabolizable Nutrients in Swine: Postprint

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Abstract

In animal organisms, glucose serves important physiological functions. Glucose metabolism holds a pivotal central position in animal energy metabolism. Current nutritional evaluation indicator systems are largely established on the basis of energy indices, neglecting the central role of glucose metabolism in energy metabolism, severing the intimate connection between energy metabolism and material metabolism, and exhibiting pronounced superficiality and limitations, thus necessitating further development. This paper presents the theoretical framework of a material indicator system based on metabolic glucose (MG), metabolic protein (MP), and metabolic lipogenic substances (MLS), along with research progress in its application to nutritional evaluation in pigs, constituting a preliminary exploration toward constructing a new metabolizable nutritional assessment system for swine.

Full Text

Research Development of New Evaluating System of Metabolizable Nutrition in Swine

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Abstract: Glucose plays a crucial physiological role in animals, with carbohydrate metabolism occupying a central position in energy metabolism. Current nutrition evaluating systems are largely built upon energy indicators, which neglect the pivotal role of carbohydrate metabolism in energy metabolism and sever the close connection between energy and substance metabolism. These systems are thus highly apparent and limited, requiring further development.

This paper introduces the theoretical framework of a substance-based indicator system grounded in metabolizable glucose (MG), metabolizable protein (MP), and metabolizable lipogenic substances (MLS), along with research progress in swine nutrition evaluation, offering a preliminary exploration toward constructing a new evaluating system for metabolizable nutrition in pigs.

Keywords: swine; metabolizable nutrition; evaluating system

1.1 Physiological Roles of Glucose

Glucose ($C_6H_{12}O_6$) holds significant importance in biological research as both an energy source for living cells and an intermediate product of metabolism, participating in numerous vital metabolic processes. Glucose serves as a critical energy source for central nervous system cells, particularly brain cells [1]. Immunologically, glucose can significantly enhance immune function [2], while high glucose concentrations affect the secretion of immunosuppressive substances by colorectal cancer tumor cells [3]. In muscle tissue, glycogenolysis provides glucose to meet energy demands during exercise or oxygen deficiency, regulates amino acid (AA) transport, and acts as an important signaling molecule for protein synthesis in piglet skeletal muscle [4-5]. Regarding fat synthesis, glucose can synthesize the reduced coenzyme II (NADPH) essential for fat metabolism through the pentose phosphate pathway, and increased glucose uptake enhances fat synthesis in adipose tissue [6]. In the intestine and liver, small intestinal glucose absorption is indispensable for animal growth and represents a key factor influencing the digestion of starch and other feed nutrients [7-9]. Absorbed glucose can be synthesized into hepatic glycogen for storage, which influences the body' s defense and detoxification responses to toxins and other chemicals. Research indicates that higher hepatic glycogen levels correlate with stronger disease resistance [10]. In reproduction and lactation, adequate glucose supply is fundamental for oocyte metabolism and serves as an energy source for early embryonic development, with glucose metabolism also being essential during sperm-egg fusion [11]. For breeding females, blood glucose affects mammary gland development and is the sole precursor for lactose synthesis. Zhao et al. [12] demonstrated that increasing glucose supply promotes lactose synthesis by elevating substrate concentration, while glycolysis and pentose phosphate pathway metabolism also increase, thereby promoting cellular energy synthesis and ultimately enhancing milk fat synthesis in mammary glands.

1.2 Sources of Glucose in Animals

Animal glucose derives from two primary sources: exogenous and endogenous glucose. Exogenous glucose originates from digestion and absorption in the small intestine, primarily produced by hydrolysis of starch and fiber. Endogenous glucose is converted from non-carbohydrate substances (such as lactic acid, acetic acid, and propionic acid) in the liver through gluconeogenesis [13]. In ruminants, glucose mainly comes from endogenous glucose produced via ruminal propionate gluconeogenesis. In monogastric livestock like pigs and poultry, some nutrients (primarily carbohydrates) not digested and absorbed in the anterior intestine undergo microbial fermentation in the large intestine, producing volatile fatty acids, of which propionic and lactic acids can be converted to glucose via hepatic gluconeogenesis. Varel et al. [14] reported that soluble fiber fermented by microorganisms in the large intestine can produce substantial volatile fatty acids, which can provide up to 30% of the energy required for maintenance in pigs. Other studies have shown that higher proportions of resistant starch in diets increase volatile fatty acid production in the large intestine [15].

1.3 Glucose Metabolism in the Body

Dietary carbohydrates are digested by digestive enzymes in the gastrointestinal tract and absorbed predominantly as glucose. Those enzymatic products that are not glucose must first be converted to glucose by intestinal mucosal enzymes before absorption into the liver. This conversion represents the primary form of dietary carbohydrate transformation in monogastric animals. Upon entering the liver, glucose is phosphorylated to glucose-6-phosphate by glucokinase, which then converts to glucose-1-phosphate in preparation for glycogen synthesis. Glucose-1-phosphate reacts with uridine triphosphate (UTP) to form uridine diphosphate glucose (UDPG) and pyrophosphate. Since pyrophosphate is rapidly hydrolyzed by pyrophosphatase in the liver, the reaction proceeds toward glycogen synthesis, with UDPG serving as “active glucose” that acts as a glucose donor.

During starvation, gluconeogenesis becomes the liver’ s primary pathway for supplying blood glucose. In sheep fed large amounts of roughage or in fasting states, hepatically produced glucose accounts for 85-90% of whole-body glucose turnover [16]. The main precursor for hepatic gluconeogenesis is propionate entering the liver from the digestive tract, contributing nearly half of glucose synthesis. Among substances used for hepatic gluconeogenesis, lactate accounts for only 15%, with amino acids and glycerol comprising certain proportions. During fasting, the proportion of propionate and lactate used for gluconeogenesis decreases significantly, while glycerol becomes the main precursor (accounting for 40%) [17]. Propionic and lactic acids produced by large intestine fermentation in monogastric livestock can also be converted to glucose via hepatic gluconeogenesis, though the proportion of glucose produced relative to whole-body glucose turnover has not yet been reported.

Hepatic glycogenolysis refers to the breakdown of glycogen to glucose. Glucose-6-phosphate derived from glycogenolysis can either be hydrolyzed to free glucose or metabolized through glycolysis or the pentose phosphate pathway. When animals experience starvation, the latter two metabolic pathways are suppressed, and hepatic glycogen is largely broken down into glucose released into the bloodstream and transported out of the liver. In the fed state, abundant glucose entering the liver is synthesized into glycogen for storage. The primary form of glucose catabolism in the liver is aerobic oxidation to generate ATP for energy, though a small portion can be metabolized via the pentose phosphate pathway to produce ribose phosphate, NADPH, and CO_2. The main physiological significance of this pathway lies in providing ribose for nucleic acid biosynthesis and NADPH as a hydrogen donor for various metabolic reactions, rather than generating ATP.

1.4 Relationships Between Carbohydrate, Fat, and Protein Metabolism

In living organisms, the metabolism of carbohydrates, fats, and proteins occurs simultaneously, forming a coordinated and unified whole through interconnections and mutual constraints. Intermediate products from carbohydrate catabolism, such as pyruvate, can produce certain non-essential amino acids through transamination and can also synthesize glycerol and fatty acids to form fats. However, since carbohydrate catabolism cannot produce intermediates corresponding to essential amino acids, carbohydrates cannot be converted into essential amino acids. Conversely, nearly all natural amino acids composing proteins can be converted to carbohydrates, though only small amounts of fat can be transformed into carbohydrates because fatty acids derived from fat breakdown generally cannot be converted to carbohydrates.

The interconversion among carbohydrates, fats, and proteins is conditional. Only when carbohydrate supply is adequate can large amounts be converted to fat for storage. Under such conditions, the body primarily uses glucose for energy, reducing fat and protein catabolism for energy supply. When glucose supply is insufficient or during starvation, glycogen stores are depleted, prompting the mobilization of stored fat for energy. With prolonged starvation, accelerated fat breakdown produces excessive ketone bodies, causing ketonemia, while enhanced gluconeogenesis mobilizes body protein to maintain stable blood glucose, thereby increasing protein utilization. Thus, carbohydrate metabolism occupies a central position in energy metabolism, with fat and protein metabolism playing secondary, supplementary roles. Their relationships are illustrated in Figure 1 [Figure 1: see original paper]. Reports indicate that adding sucrose to cattle diets can reduce the glucogenic effect of amino acids and decrease urea breakdown [18]. Other studies show that increasing digestible protein in the small intestine can improve small intestinal starch digestibility and net portal glucose absorption [19]. Therefore, studying protein and fat metabolism in animals necessitates simultaneous attention to glucose metabolism and holistic optimization.

2. Proposal and Significance of Animal Metabolizable Nutrition Evaluating Systems

Currently, nearly all existing nutrition evaluating systems treat energy as a separate nutrient and use it as the basis for determining requirements of various nutrients including protein, fiber, calcium, and phosphorus (Figure 2 [Figure 2: see original paper]). In reality, whether digestible energy, metabolizable energy, or net energy, all are calculated as the sum of carbohydrate, crude protein, and crude fat quantities multiplied by their respective energy values. For example, the formula for estimating feed digestible energy from digestible nutrients is:

$$\text{Digestible Energy (kJ/kg)} = 19.31X_1 + 42.1X_2 + 18.5X_3 + 17.0X_4$$

Where X_1, X_2, X_3, and X_4 represent grams of digestible crude protein, digestible crude fat, digestible crude fiber, and digestible nitrogen-free extract per kilogram of feed, respectively; the numbers preceding X_1-X_4 are average energy values for each substance.

Feed energy represents the potential energy produced by oxidation of carbohydrates, crude protein, and crude fat. However, under normal conditions, animal energy requirements are primarily met by carbohydrate metabolism, while fats and proteins are more commonly deposited as substances. Liu [20] investigated the effects of diets with identical digestible energy but different carbohydrate-to-fat ratios on growth performance of weaned piglets, finding significant differences in diet utilization efficiency. This demonstrates that energy indicators are overly general and highly apparent. The current energy-based nutrition evaluating system lacks assessment of glucose supply status, potentially leading to insufficient glucose supply and increased protein catabolism for energy, thereby reducing feed utilization efficiency.

In animals, energy metabolism and substance metabolism represent two aspects of a single process. Substance metabolism refers to chemical processes related to physiology, including digestion, absorption, transport, and catabolism of materials in the body. These materials must be broken down by digestive enzymes into simpler organic compounds before small intestinal absorption. Therefore, substance metabolism encompasses the metabolism of carbohydrates, proteins, and fats—the three major nutrients. Energy metabolism primarily concerns the utilization and transformation of energy produced during the metabolism of these three nutrients. Thus, substance metabolism and energy metabolism are closely interconnected. Current nutrition evaluating systems convert carbohydrates, proteins, and fats into energy values, neglecting differences among these energy-yielding substances in their energy-supplying functions and artificially separating energy metabolism from substance metabolism. Since energy is converted from the energy values of three substances rather than being a single material, energy indicators can only describe nutrient utilization outcomes but cannot enable targeted regulation of energy metabolic processes. Additionally, current systems suffer from difficult measurement methods, inability to obtain real-time data, high measurement costs, and challenges in acquiring large datasets.

To address these apparent limitations and highlight the central role of carbohydrates in energy supply, Lu [21] integrated the C3+C6 energy from propionate produced in the rumen and glucose provided by the small intestine into a holistic technical indicator in 1996, proposing the concept of metabolizable glucose (MG): the total amount of utilizable glucose provided by feed or diets after digestion and absorption for animal metabolism. Sun et al. [22] demonstrated that at 1.1 times maintenance feeding level, the maximum daily MG level for 40 kg sheep was 131.16 g or 8.24 g/kg $W^{0 \cdot 75}$, with MG energy accounting for 32.83% of metabolizable energy. Wang [23] investigated the appropriate MG level for 23 kg Inner Mongolia white cashmere goats at 1.2 times maintenance feeding level (non-mohair production period), finding the suitable daily MG level to be 44.13 g or 4.39 g/kg $W^{0 \cdot 75}$, with MG energy comprising over 12.28% of metabolizable energy. These preliminary studies indicate that an appropriate ratio of MG energy to metabolizable energy exists in animal diets, and maintaining this ratio can significantly improve energy utilization efficiency. Subsequent research has preliminarily established the MG technical system, laying the foundation for glucose nutrition regulation measures in ruminants.

Building upon MG research, Su [24] applied both MG and metabolizable protein (MP) indicators to investigate protein (amino acid) distribution patterns in Inner Mongolia white cashmere goats under different dietary MG levels. The study revealed an appropriate ratio between MG and MP under ideal small intestinal amino acid models, with the optimal MG/MP ratio being 1.06 for mohair production and 1.64 for overall performance.

To reflect the role of fat in energy and substance metabolism, Lu [25] integrated the C2+C4 energy from acetic and butyric acids in ME in 2004, proposing the concept of metabolizable lipogenic substances (MLS): the total amount of utilizable lipogenic substances (converted to acetic acid) provided by feed or diets after digestion and absorption, including acetic acid, butyric acid, and fat. Subsequently, Du [26] determined the MLS of a basal sheep diet to be 135.69 g/d based on this new concept, with (C2+C4) energy accounting for 89.24% of dietary ME. Additionally, the basal diet's MG was calculated as 43.83 g/d, with (C3+C6) energy comprising 11.30% of dietary ME and an MLS/MG ratio of 3.10. These data provide technical support for regulating (C3+C6) and (C2+C4) energy in ruminant diets and for overall optimization of ruminant energy regulation.

To systematically elaborate this theory, Lu [27] proposed the concept of "energy-yielding substances," defined as substances in feed or animal bodies that can provide energy through metabolism. In animals, energy-yielding substances have two fates: serving as "fuel" to provide ATP for life activities or acting as precursors for anabolic processes. Energy-yielding substances primarily include glucogenic substances, amino acidogenic substances, and lipogenic substances (Figure 3 [Figure 3: see original paper]). Based on the "energy-yielding substances" indicator, a new metabolizable nutrition evaluating system composed of "MG," "MP," and "MLS" can be constructed (Figure 4 [Figure 4: see original paper]). When applying this new system to regulate animal nutritional balance, priority should be given to ensuring structural balance among MG, MP, and MLS within energy-yielding substances, followed by balance among internal components of MG, MP, and MLS, and finally consideration of mineral and vitamin balance.

This new energy-yielding substance-based nutrition evaluating system can organically integrate energy metabolism and substance metabolism, achieving complete integration of energy metabolism indicators with protein and fat metabolism indicators. This approach addresses the shortcomings of current nutrition evaluating systems, creates conditions for holistic regulation of energy and substance metabolism, and promises to generate major breakthroughs in nutrition theory and application.

3. Construction and Progress of Swine Metabolizable Nutrition Evaluating Systems

Current swine diet formulation technologies revolve around feeding standards (or nutrient requirements), which are similarly based on energy indicators and lack metrics for evaluating metabolizable glucose. Consequently, formulators can only calculate energy and protein balance, making it difficult to assess whether swine metabolizable glucose requirements are met. This often results in insufficient glucose supply, forcing the mobilization of fat and protein for gluconeogenesis and reducing feed utilization efficiency. In severe cases, it may cause metabolic disorders, ketonemia, and uric acid poisoning. Therefore, applying Lu' s "energy-yielding substances" indicator to improve the current energy-based nutrition evaluating system and construct a swine metabolizable nutrition evaluating system holds significant theoretical and practical importance.

Currently, construction of the swine metabolizable nutrition evaluating system remains in its infancy, focusing primarily on MG nutrition research. In 2014, based on Lu' s MG concept and swine carbohydrate digestion characteristics, we established a swine MG calculation formula [28]:

$$\mathrm{MG} = \mathrm{IDSG} + \mathrm{LFAG} = 0.9\mathrm{K}_1\mathrm{S} + 0.83\mathrm{K}_2\mathrm{Pr} + 0.87\mathrm{K}_3\mathrm{La}$$

Where IDSG is exogenous glucose provided by small intestinal starch; LFAG is endogenous glucose converted from propionic and lactic acids produced by large intestine fermentation; S is small intestinal starch quantity (g/d); Pr is propionic acid quantity from large intestine fermentation (mmol/d); La is lactic acid quantity from large intestine fermentation (mmol/d); K_1 is small intestinal starch digestibility; K_2 and K_3 are absorption rates of propionic and lactic acids, respectively; and 0.9, 0.83, and 0.87 are conversion coefficients for starch, propionic acid, and lactic acid to glucose, respectively.

Building upon this, Fang [28] established an in vivo method for determining exogenous MG in weaned piglets by installing ileal fistulas, measuring exogenous MG values of four diets as 254.52, 315.04, 451.21, and 490.27 g/kg. Additionally, using in vitro digestion to simulate porcine gastric-intestinal digestion of the four diets, an in vitro formula for estimating exogenous MG was developed.

Zhang [29] established an endogenous MG determination method using arteriovenous difference techniques in weaned piglets fitted with carotid artery, portal vein, and mesenteric vascular fistulas. Combined with Fang' s [28] exogenous MG method, MG levels of four weaned piglet diets were determined as 239.62, 280.68, 400.79, and 454.35 g/kg. Based on estimated dietary MG levels and dietary starch and crude fiber contents, a MG regression equation was established: $Y = -196.44 + 12.13X_1 + 23.18X_2$ (where Y represents MG level, X_1 and X_2 represent dietary starch and crude fiber contents, respectively; $R^2 = 0.9989$, $P = 0.033$). By comparing effects of different MG levels on weaned piglet growth performance, the appropriate MG requirement for weaned piglets was ultimately determined.

These studies have laid the foundation for practical swine glucose nutrition regulation technology and created a promising start for constructing a swine metabolizable nutrition evaluating system. Future work must investigate swine MP and MLS, then apply MG, MP, and MLS to study nutrient requirements and balance parameters across different physiological stages. Simultaneously, in vivo and in vitro evaluation methods for feed MG, MP, and MLS must be established. Finally, a swine metabolizable nutrition evaluating system should be constructed based on MG, MP, and MLS to establish new swine feeding standards and guide pork production practices. This research represents a major strategic initiative for China' s swine nutrition and production science, involving substantial workload and heavy tasks that cannot be completed by individuals or small research groups alone. It requires attention from relevant academic leaders and departments, with systematic research and promotion at the national level to effectively advance this work and position China' s swine nutrition research and application at the forefront globally.

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