Regulatory Effects of -Ketoglutaric Acid on Animal Nutrient Metabolism and Some Functional Indicators and Its Mechanisms: Postprint

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Abstract

-ketoglutaric acid serves as both an important energy-yielding substance for animal organisms in the tricarboxylic acid cycle and a critical hub linking carbon and nitrogen metabolism. It can enhance immune function, influence calcium-phosphorus metabolism, increase bone mineral density and skeletal mineral element content, improve intestinal mucosal architecture, and positively affect certain amino acid metabolic pathways. Additionally, -ketoglutaric acid can augment skeletal muscle protein synthesis and deposition via activation of the mechanistic target of rapamycin (mTOR) signaling pathway, consequently improving animal growth performance. This review summarizes the regulatory roles of -ketoglutaric acid in animal nutrient metabolism and various functional indices, thereby providing a reference foundation for its promotion and application in animal production.

Full Text

The Regulatory Effects and Mechanisms of -Ketoglutaric Acid on Nutrient Metabolism and Functional Indicators in Animals

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Abstract

-ketoglutaric acid serves as both a critical energy-yielding substance in the tricarboxylic acid cycle and a pivotal hub connecting carbon and nitrogen metabolism in animals. It enhances immune function, modulates calcium and phosphorus metabolism, increases bone density and mineral content, improves intestinal mucosal architecture, and positively influences amino acid metabolism. Furthermore, -ketoglutaric acid improves animal growth performance by activating the mammalian target of rapamycin (mTOR) signaling pathway to promote skeletal muscle protein synthesis and deposition. This review synthesizes the regulatory effects and mechanisms of -ketoglutaric acid on nutrient metabolism and functional indicators in animals, providing a reference for its application in animal production.

Keywords: -ketoglutaric acid; animal; nutrient metabolism; regulation; mechanism

-ketoglutaric acid (AKG) is a multifunctional short-chain carboxylic acid that provides substantial energy through the tricarboxylic acid cycle in animals and can be converted into amino acids such as glutamine and glutamate, serving as an important intermediate linking carbon and nitrogen metabolism (Figure 1 [Figure 1: see original paper]) [1]. Glutamine is a crucial amino acid in animal blood and tissues with multiple physiological functions. As a conditionally essential amino acid, glutamine serves as a primary energy source for gastrointestinal cells and plays a vital role in maintaining intestinal structure and function in early-weaned piglets [2]. However, practical applications of glutamine are limited by its high cost and instability, as it is highly acid-sensitive and readily cyclized into toxic pyroglutamic acid and ammonia. AKG, possessing the glutamine carbon skeleton, can form glutamate via glutamate decarboxylase or transaminase, which then converts to glutamine through a rapid, stable, and safe process. Consequently, AKG has attracted considerable attention as a precursor for glutamate and glutamine. Research demonstrates that AKG promotes animal growth and improves growth performance [3-6], and may substitute for glutamine in regulating intestinal nutrient metabolism [2].

AKG: -ketoglutaric acid; NADH, NADH+: reduced form of nicotinamide-adenine dinucleotide; NAD+: oxidized form of nicotinamide adenine dinucleotide; CO : carbon dioxide; NH : ammonia.

Figure 1 Tricarboxylic acid cycle and transamination

1. Regulatory Effects of AKG on Oxidative Stress and Immunity

Dietary supplementation with 1% AKG in lipopolysaccharide-challenged weaned piglets alleviated the increase in serum malondialdehyde content and decrease in superoxide dismutase activity, indicating that AKG mitigates oxidative stress associated with weaning and enhances antioxidant capacity.

Additionally, reduced plasma globulin content suggests that AKG improves immune function in weaned piglets [7]. Xia et al. [8] reported that combined supplementation of modified Chinese herbal medicine 921 mixture and AKG in weaned rats increased intestinal epithelial lymph node surface area, promoted mucosal cell secretion of immunoglobulin A (IgA), and improved intestinal immune function, with synergistic effects superior to herbal medicine alone in both efficacy and onset time. In grass carp, dietary AKG significantly increased serum superoxide dismutase and lysozyme activities while reducing serum urea nitrogen and malondialdehyde content, demonstrating enhanced non-specific immunity [3].

2. Regulatory Effects of AKG on Calcium and Phosphorus Metabolism

AKG modulates calcium and phosphorus metabolism, which are essential mineral elements for bone and tooth formation, participate in multiple metabolic processes, and influence hormone secretion [9]. Supplementing lamb diets with 3 g/kg AKG significantly increased trabecular and cortical bone density [10], while 12 g/kg AKG in piglet diets significantly enhanced bone mineral density [11]. These effects occur through two primary mechanisms: first, AKG converts to glutamate, a key component of osteocalcin whose biological activity depends on glutamate and vitamin K; second, AKG metabolizes to proline, which hydroxylates to hydroxyproline—an essential substance for connective tissue and bone collagen synthesis, with bone collagen being a major bone matrix component [12]. Administration of 0.1 g/kg AKG solution to newborn sheep for 14 days significantly increased blood proline content and bone density [13], and 0.1 g/kg AKG in piglet diets significantly increased femur mineral density [14], further confirming AKG' s positive regulation of bone mineral deposition. Moreover, supplementing 2% AKG in low-protein diets for growing pigs significantly reduced fecal calcium and phosphorus content while increasing their apparent digestibility, and decreased urinary calcium and phosphorus excretion, though the latter effect was not significant [12].

3. Regulatory Effects of AKG on Intestinal Function and Health

As a glutamate family metabolite, AKG can be completely oxidized to carbon dioxide and water through the tricarboxylic acid cycle, providing energy for small intestinal epithelial cells. While glutamine serves as an energy source for the intestine and portal system, AKG acts as a selective metabolic fuel that maintains small intestinal mucosal integrity [15-16]. Dietary AKG supplementation improved intestinal structure and functional integrity in carp [17-18]. The intestine is both the primary site for nutrient absorption and the main absorption site for AKG. Glutamine positively influences intestinal morphological development and nutrient absorption [19-22], and AKG can convert to glutamine to promote intestinal development. AKG increased villus height across all in-

testinal segments in weaned piglets, enhancing absorptive capacity [23], and increased duodenal length in 2-week-old broilers [24]. Combined use of Chinese herbal medicine and AKG has also been investigated, with studies demonstrating synergistic effects on intestinal absorption superior to either component alone [25].

4. Regulatory Effects of AKG on Amino Acid Balance and Protein Deposition

AKG transports and stores nitrogen in animals, binding with ammonia to reduce endogenous nitrogen toxicity [26]. It decreases blood free ammonia by reducing glutamate and glutamine oxidation [27], improves post-surgical negative nitrogen balance, and increases muscle protein synthesis [28]. AKG and related products (glutamine, glutamate, and ornithine- -ketoglutarate) benefit recovery in elderly, post-surgical, and burn patients, with long-term oral AKG reducing plasma urea and arginine in hemodialysis patients and positively affecting protein metabolism [29-30]. In rats fed nitrogen-free diets, AKG reduced blood amino acid content by 22% while increasing small intestinal epithelial cell number and reducing weight loss [31]. Compared with glycine, ornithine- -ketoglutarate significantly increased plasma and muscle glutamine in burned rats [32]. In immune-stressed piglets, AKG increased liver free alanine and glutamine, elevated lysine and tyrosine, and increased plasma glutamate [33-34]. AKG promotes epithelial cell protein synthesis while inhibiting protein degradation [35], and significantly increased muscle crude protein content and serum amino acid levels in Songpu mirror carp fed different protein sources, with elevated serum amino acids enhancing protein synthesis [36].

The mTOR signaling pathway plays a crucial role in skeletal muscle protein translation as a central regulator of growth. Two upstream pathways—phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt)/mTOR and liver kinase B1 (LKB1)/AMP-activated protein kinase (AMPK)/mTOR—activate mTOR, which then stimulates protein synthesis through downstream effectors ribosomal protein S6 kinase (S6K) and eukaryotic initiation factor 4E-binding protein 1 (4EBP1). Activation is regulated by growth factors, amino acids, and ATP [37]. In lipopolysaccharide-challenged piglets, dietary AKG significantly increased the phosphorylated mTOR to total mTOR ratio by 47.93% and phosphorylated p70S6K to total p70S6K ratio by 23.77% compared to controls, demonstrating AKG' s action on the mTOR pathway to enhance protein synthesis and deposition [34]. In vitro studies show direct AKG stimulation of C2C12 cells significantly increases intracellular total protein content, suggesting AKG may directly activate mTOR to increase protein synthesis rate [38-39]. Since AKG synthesizes amino acids that can activate mTOR [40], it may regulate this pathway through amino acid synthesis.

5. Current Challenges and Future Prospects

AKG absorption and utilization vary across different gastrointestinal segments, with highest absorption in the small intestine, followed by the stomach, and lowest in the colon [41]. Overall absorption efficiency in animals is relatively low. Junghans et al. [42] found duodenal infusion had greater effects on whole-body energy and nutrient metabolism. Unlike glutamate and glutamine, a portion of AKG always remains in the body. In growing pigs, only 5% of enterally administered 5% AKG entered portal blood compared to 86% with parenteral injection [43]. Studies using ^{13}C-AKG revealed minimal oxidation to ^{13}CO [44], indicating low utilization rates that require alternative solutions such as rumen-protected coating or synthesis of compounds like dimethyl -ketoglutarate and ornithine- -ketoglutarate. Whether these compounds exhibit equivalent effects and efficiencies as AKG monomers warrants further investigation.

AKG holds significant promise in animal production and feed applications, including recovery from castration or parturition and mitigation of stress from vaccination or group transfer. Developing superior feed additives using AKG could positively impact immune function, bone growth, amino acid balance, and protein synthesis and deposition. Investigating AKG' s regulatory effects on nutrient metabolism is crucial for improving animal growth performance and feed resource utilization.

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