Physiological Functions and Mechanisms of Guanidinoacetic Acid and Its Applications in Broiler and Pig Production: A Postprint

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Abstract

Guanidinoacetic acid, as a novel nutritional feed additive, has demonstrated certain effects on improving production performance, promoting energy metabolism, accelerating protein deposition, enhancing antioxidant capacity, and improving meat quality in broilers and pigs. This paper reviews the metabolic pathways, physiological functions and underlying mechanisms of guanidinoacetic acid, as well as the latest research progress on its application in production performance and meat quality of broilers and pigs, aiming to provide references for further research and exploration.

Full Text

Physiological Action and Mechanism of Guanidinoacetic Acid and Its Application in Broiler Chicken and Pig Production

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Abstract: Guanidinoacetic acid (GAA), a novel nutritional feed additive, demonstrates significant effects on improving production performance, promoting energy metabolism, accelerating protein deposition, enhancing antioxidant capacity, and improving meat quality in broiler chickens and pigs. This review synthesizes current research on GAA' s metabolic pathways, physiological functions, and underlying mechanisms, while summarizing recent advances in

its effects on production performance and meat quality in broiler chickens and pigs, providing a reference for future research and exploration of GAA.

Keywords: guanidinoacetic acid; metabolism; production performance; meat quality; broiler chickens; pigs

Guanidinoacetic acid (GAA), also known as guanidine acetic acid or N-amidinoglycine, has a molecular formula of C H N O and a molar mass of 117.11 g/mol. It appears as a white or off-white powder or crystalline substance, odorless, soluble in water, and sparingly soluble in ethanol and ether [1-2]. Weber first discovered and isolated GAA from urine, proposing it as a precursor for creatine synthesis, though without conducting in-depth research [1]. Bloch et al. [3] subsequently identified that GAA is synthesized from arginine and glycine in vivo, establishing it as a glycine derivative. GAA is ultimately converted to creatine through methylation in the liver [4], and dietary GAA supplementation aims to increase creatine content in animals. The European Union approved GAA as a feed additive in October 2009 [5]. The widespread use of plant-based feed ingredients lacking creatine [6] has increased animal requirements for arginine and glycine, potentially leading to creatine deficiency. Since direct dietary creatine supplementation is costly and creatine is unstable, adding GAA to plant-based diets has become the preferred solution [7]. While the endogenous synthesis of GAA and its conversion to creatine are well understood, GAA' s metabolic pathways and antioxidant mechanisms in animals require further investigation. As a novel feed additive, GAA has attracted increasing attention from researchers in livestock production, prompting this comprehensive review of its effects in broiler chickens and pigs.

1 GAA Metabolic Pathways

Animals possess endogenous GAA synthesis pathways. L-arginine glycine amidinotransferase (AGAT) cleaves the amidine group from L-arginine, which then combines with glycine to form GAA [3]. The resulting L-ornithine can be reconverted to L-arginine via the urea cycle. Although GAA synthesis was first discovered in the kidneys, subsequent research confirmed its occurrence in the liver and pancreas, with the kidneys remaining the primary site of synthesis. Both endogenously synthesized and dietary GAA are transported via circulation to the liver for further methylation to creatine. In the liver, S-adenosylmethionine (SAM) provides the methyl group for GAA methylation under the catalysis of S-adenosylmethionine:guanidinoacetate N-methyltransferase (GAMT), producing creatine and S-adenosyl-L-homocysteine (SAH). SAH can be hydrolyzed by adenosylhomocysteinase to form adenosine and homocysteine, establishing a close link between homocysteine production and GAA methylation [1]. Stead et al. [4] demonstrated that SAM provides the methyl groups required for creatine synthesis, with over 85% of SAM-dependent methylation reactions occurring in the liver [8]. Consequently, excessive dietary GAA increases methyl demand and elevates homocysteine levels, potentially causing hyperhomocysteinemia, as observed by Setoue et al. [9] and Ohuchi

et al. [10]. However, betaine can remethylate homocysteine to methionine via betaine-homocysteine methyltransferase (BHMT), with choline enhancing BHMT activity. Therefore, simultaneous supplementation of choline and betaine with GAA effectively prevents GAA-induced hyperhomocysteinemia [11]. Additionally, high-casein diets and lentinacin have shown efficacy in suppressing GAA-induced hyperhomocysteinemia in rats [12].

Creatine is phosphorylated to phosphocreatine by creatine kinase (CK). In cells, creatine and phosphocreatine spontaneously cyclize to form creatinine, the sole known end product of creatine metabolism. Creatinine diffuses passively across cell membranes and is excreted in urine [13]. A young 70 kg male loses approximately 1.7% of total body creatine daily (about 2 g/d) as creatinine [14], necessitating dietary intake or de novo synthesis to compensate for these losses.

2 Creatine Synthesis and Transport

In vertebrates, GAA serves as the precursor for creatine synthesis, which occurs primarily in the liver through methylation [4]. AGAT catalyzes the conversion of L-arginine and glycine to GAA [3], after which kidney-synthesized GAA is transported to the liver. In hepatocytes, SAM and GAA react under GAMT catalysis to produce creatine and SAH [4,16]. SAH strongly inhibits most SAM-dependent methyltransferases, including GAMT, which catalyzes the final step of creatine synthesis. Notably, 75% of SAM is utilized for creatine biosynthesis in humans [9], making GAMT the primary enzyme converting SAM to SAH in vertebrates [17]. High GAMT mRNA levels in human and mouse livers confirm the liver as the main organ for creatine biosynthesis [18]. Feedback regulation exists in endogenous creatine synthesis, where GAMT expression is modulated but AGAT expression is not [19], indicating that GAA synthesis is the rate-limiting step. This provides the theoretical basis for dietary GAA supplementation to increase creatine levels.

Hepatocytes cannot synthesize creatine directly from arginine and glycine but readily convert GAA to creatine [11]. GAA delivery to hepatocytes is mediated by the creatine transporter (CRT) [20], taurine transporter (TauT) [21], and potentially other transporters. Research indicates that -aminobutyric acid transporter II (GAT2) contributes at least 64.4% to hepatic GAA uptake [23]. GAT2 localizes primarily to the sinusoidal membrane of hepatocytes in the periportal region, showing distribution patterns consistent with GAMT. This functional coupling between GAT2 and GAMT regulates GAA supply and creatine synthesis in periportal hepatocytes [23].

3.1 Enhancement of Energy Metabolism

GAA promotes catabolism and increases ATP levels by modulating key enzymes in glycolysis and the respiratory chain, thereby enhancing energy storage compound synthesis. Additionally, GAA improves energy metabolism through creatine synthesis. Creatine derived from GAA plays a crucial role in storing

and transporting phosphate groups in tissues with high energy demands [23]. When energy is abundant, creatine accepts phosphate groups to form phosphocreatine, serving as a temporary energy reserve. Phosphocreatine functions as a high-energy phosphate buffer, rapidly releasing ATP through CK during energy deficits [27-29]. The phosphocreatine-creatine system represents the primary regulator of intracellular energy utilization, controlling cellular ATP levels and providing immediately available energy [30].

3.2 Mechanism of Enhanced Energy Metabolism

Pyruvate kinase (PK), a rate-limiting enzyme in glycolysis, catalyzes the final dephosphorylation reaction with ATP generation, regulating cellular ATP, ADP, and glycolytic intermediate levels. Its activity directly reflects glycolytic capacity [31]. During glycolysis, hexokinase (HK) and phosphofructokinase (PFK) catalyze phosphorylation reactions that consume ATP. In the tricarboxylic acid cycle, isocitrate dehydrogenase (IDH) and malate dehydrogenase (MDH) generate NADH, which enters the respiratory chain. NADH generates 2.5 mol ATP per mole through NADH-coenzyme Q reductase (NADH-CoQ) and ATP synthase (ATPase) [31]. CK directly catalyzes the interconversion of phosphocreatine and ATP, with its activity reflecting muscle energy storage and conversion status. Li et al. [32] reported that supplementing nursery pig diets with 600 mg/kg GAA increased plasma PK, IDH, MDH, NADH-CoQ, and ATPase activities by 253%, 312%, 151%, 492%, and 183%, respectively, while PFK and CK activities increased by 252% and 202%. These results indicate that ATP synthesis increased far more than consumption.

Dietary GAA supplementation significantly elevates muscle creatine content [33], which correlates positively with phosphocreatine levels. When phosphocreatine is available, it provides phosphate groups for ADP phosphorylation until depleted, after which glycogenolysis resumes to supply phosphate groups for ATP generation [34]. Furthermore, phosphocreatine enhances mitochondrial respiratory chain complex I, II, III, and IV activities in lipopolysaccharide-induced human venous cells, promoting mitochondrial ATP production and energy metabolism [35]. In summary, GAA enhances energy metabolism both directly by increasing glycolytic and respiratory chain enzyme activities to boost ATP synthesis, and indirectly by elevating phosphocreatine content to promote mitochondrial ATP production.

3.3 Antioxidant Effects

Reactive oxygen species accumulate in animals through respiration and exposure to pollutants, radiation, and toxic gases. Excessive free radicals damage cellular membranes, inactivate proteases, and injure DNA. The loose chemical structure of cell membranes makes them particularly susceptible to free radical attack, with membrane lipids undergoing peroxidation to form malondialdehyde (MDA). Serum MDA concentration serves as a key indicator of peroxidation severity.

Dietary GAA supplementation increases total antioxidant capacity (T-AOC) and activities of superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px) while reducing serum MDA content [36].

3.4 Antioxidant Mechanism

The enhanced antioxidant capacity following GAA supplementation occurs through two primary mechanisms. First, increased creatine and phosphocreatine levels provide direct antioxidant effects. Creatine scavenges reactive oxygen species, particularly carboxyl groups and reactive nitrogen species, while activating CK to consume free radicals through ADP recycling mechanisms [37]. Lawler et al. [38] demonstrated radical scavenging by creatine in vitro, and Guidi et al. [39] showed creatine' s protective effect against oxidative stress-induced mitochondrial DNA damage. Zhao et al. [40] reported that phosphocreatine supplementation increased SOD and CAT activities while decreasing MDA in rats with doxorubicin-induced myocardial injury, confirming its antioxidant enzyme-enhancing properties.

Second, dietary GAA reduces endogenous synthesis, conserving arginine with its inherent antioxidant functions. Arginine quenches free radicals such as superoxide anion (O) [41], prevents copper-induced lipoprotein oxidation, and protects against oxidative stress from oxidized low-density lipoprotein (LDL) in endothelial cells [36]. By increasing creatine and phosphocreatine while conserving arginine, GAA exerts its antioxidant effects through dual pathways.

4.1 Effects of GAA on Production Performance in Broilers and Pigs

Dietary GAA supplementation enhances creatine synthesis, improves feed conversion, and promotes growth in broilers and pigs [42-43]. Jiang [44] reported that supplementing Arbor Acres broiler diets with 200, 400, 600, or 800 mg/kg GAA significantly increased average daily gain and reduced feed conversion ratio, with optimal effects at 600-800 mg/kg. Similarly, 300-600 mg/kg GAA in finishing pig diets significantly improved average daily gain and feed conversion without affecting feed intake [45-47]. The growth-promoting effects likely stem from reduced endogenous GAA synthesis, sparing glycine and arginine for protein synthesis [48-49]. As arginine is essential for growing pigs and broilers, GAA supplementation effectively alleviates deficiencies. Additionally, GAA reduces ascites-related mortality in broilers [50].

Increased muscle creatine and phosphocreatine reduce reliance on carbohydrate, fat, and protein catabolism for energy. Creatine enhances cellular hydration, increasing muscle cell volume through osmotic water influx, which inhibits protein degradation while promoting protein and glycogen synthesis [51]. GAA also stimulates growth hormone secretion by influencing -aminobutyric acid release in the hypothalamus and promotes insulin-like growth factor-I (IGF-I) secretion [33].

Qin et al. [52] observed that 500 and 1000 mg/kg GAA in finishing pig diets increased dressing percentage by 3.19% and 5.57%, lean meat percentage by 10.38% and 18.55%, and loin eye area by 2.57% and 4.83%, respectively, with 1000 mg/kg significantly improving lean meat percentage. Jiang [44] reported that 200, 400, 600, and 800 mg/kg GAA in broiler diets increased dressing percentage by 2.74%, 3.36%, 4.99%, and 5.03%; breast muscle percentage by 3.33%, 14.84%, 21.98%, and 23.00%; and leg muscle percentage by 12.02%, 15.40%, 21.55%, and 22.23%, respectively. Pan et al. [47] found that 500 mg/kg GAA in finishing pig diets increased dressing percentage by 3.82% and loin eye area by 8.48%. These improvements in dressing percentage and lean meat percentage reflect GAA' s promotion of protein deposition in muscle rather than fat storage. Since phosphocreatine is abundant in muscle and nerve tissues but scarce in adipose tissue, GAA directs energy storage and distribution toward muscle tissue, improving carcass composition.

4.2 Effects of GAA on Meat Quality

Dietary GAA supplementation effectively increases muscle pH, reduces shear force and drip loss, and improves meat quality. Wang et al. [36] reported that 800, 1200, and 2000 mg/kg GAA in finishing pig diets increased post-mortem muscle pH by 0.44, 0.03, and 0.21; reduced drip loss by 38.84%, 26.03%, and 9.09%; and decreased shear force by 13.69%, 11.43%, and 6.38%, respectively. Liu et al. [53] observed that 1000 mg/kg GAA increased pH at 45 min and 24 h post-mortem by 0.2 and 0.21, reduced drip loss by 2.45%, and decreased shear force by 15.66%. Pan et al. [47] found that 500 mg/kg GAA increased pH and pH by 0.14 and 0.10, respectively, while Chen et al. [54] reported that 500 mg/kg GAA increased pH and pH by 0.15 and 0.25, reduced drip loss by 21.93%, and decreased shear force by 17.24%.

Post-mortem circulation cessation interrupts oxygen supply, reducing ATP levels and promoting anaerobic glycolysis with lactic acid production, which decreases muscle pH. However, GAA supplementation increases creatine and phosphocreatine reserves, elevating ATP levels and delaying post-mortem glycolysis, thereby increasing pH. Improved water-holding capacity reduces meat hardness [55], as higher pH decreases protein denaturation, shifting myofibrillar proteins away from their isoelectric point and increasing negative charges that enhance water-protein interactions. During the period before pH reaches its minimum post-mortem, calcium ions release from the sarcoplasmic reticulum [56], causing muscle contraction. Maximum hardness occurs at 40% shortening, beyond which meat becomes tender due to Z-line disruption from excessive thin filament insertion [33]. GAA-induced ATP elevation enables super-contraction under sufficient energy conditions, thereby improving tenderness.

5 Conclusion

Dietary GAA supplementation improves feed conversion, regulates energy metabolism, and enhances meat quality in livestock. As a novel feed additive, GAA application in Chinese animal production remains in its early stages. Future research should focus on determining optimal supplementation stages and dosages for different species, evaluating tolerance levels, and elucidating underlying mechanisms to maximize its potential in animal agriculture.

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