Research Progress on Cysteamine in Swine Nutrition: Postprint

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Abstract

As the demand for meat products continues to increase, maximizing animal growth performance has become a research hotspot for animal husbandry researchers. Cysteamine (CS) is a non-hormonal physiological regulator that exerts growth-promoting effects by modulating the animal's endocrine system, and possesses multiple physiological functions including antioxidant activity, promotion of intestinal health, and immunomodulation. It has already been applied as a feed additive in practical production. This article reviews the application of cysteamine in pig nutrition and its potential mechanisms of action, aiming to provide references for future scientific research.

Full Text

Research Progress of Cysteamine in Swine Nutrition

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Abstract

With the growing demand for meat products, maximizing animal growth performance has become a research focus in animal husbandry. Cysteamine (CS) is a non-hormonal physiological regulator that promotes growth by modulating the endocrine system and exhibits multiple physiological functions including antioxidant activity, promotion of intestinal health, and immunomodulation. It has been used as a feed additive in practical production. This review summarizes

the application of cysteamine in swine nutrition and its potential mechanisms of action, aiming to provide references for future research.

Keywords: cysteamine; pigs; growth performance; meat quality; gut health; stress; immunoregulation

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One of the primary goals of livestock production is to provide more high-quality animal products for human consumption. Under similar nutritional and management conditions, pig growth rate is mainly regulated by endocrine hormones [1]. Cysteamine (cysteamine, CS) can specifically bind to the disulfide bonds of somatostatin (SS), destroying its biological activity and thereby enhancing animal growth rate through endocrine modulation. Additionally, CS participates in the synthesis and metabolism of important bioactive substances such as cysteine, glutathione (GSH), hypotaurine, and taurine, and is involved in maintaining the body' s antioxidant defense system. Therefore, CS holds significant importance as a novel feed additive in animal production.

1 Physical and Chemical Properties of CS

CS, also known as 2-mercaptoethylamine, has a melting point of 99°C and is highly soluble in water and ethanol. CS is a natural product of coenzyme A degradation in animals. During degradation, coenzyme A produces pantetheine, which is hydrolyzed by pantetheinase to generate CS and pantothenic acid [2-3] (Figure 1 [Figure 1: see original paper]).

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CS can be extracted from animals or chemically synthesized. It is easily oxidized to cystamine in air, alkaline environments, and in the presence of metal ions. In animals, exogenous CS readily binds to plasma proteins or is oxidatively degraded by free radicals [4]. Therefore, CS is typically formulated as cysteamine hydrochloride or coated in production to better exert its physiological effects in vivo. Studies have shown that coated CS can resist gastric juice effects while providing sustained release, avoiding damage to the gastric mucosa [5].

Figure 1 The metabolic process of cysteamine in vivo

2.1 Effects of CS on Growth Performance

CS has been used as a feed additive in pig production to improve growth performance, feed conversion rate, body protein deposition, muscle growth in piglets and finishing pigs, and reproductive performance in sows. The European Agency for the Evaluation of Medicinal Products (EMEA) has classified it as an "organic substance for which no maximum residue limit needs to be established" for use in mammals producing food products [6].

In piglet studies, Du et al. [7] demonstrated that dietary supplementation with 36 mg/kg CS (effective dose) fed to 15-35 day-old piglets significantly increased feed intake and body weight gain. In growing-finishing pigs, application doses vary. Liu et al. [8] found that dietary supplementation with 70 mg/kg CS fed to finishing pigs for 47 days significantly improved growth performance; however, some studies indicate that CS only exhibits growth-promoting effects when the effective dose reaches 200 mg/kg [9-10]. These discrepancies may be related to dietary composition and management levels used during production. Additionally, the instability of free sulfhydryl groups in CS may cause partial oxidation and inactivation, reducing the effective dose; some crude CS products may contain off-odors that affect animal feed intake, resulting in different feeding effects. Research suggests that the optimal dose of CS should be appropriately increased with pig body weight during different finishing stages [11].

The growth-promoting mechanism of CS in animals is primarily achieved by inhibiting somatostatin activity. Somatostatin is a brain-gut peptide hormone synthesized and released by the hypothalamus, widely distributed in the gastrointestinal tract, central nervous system, and lymphoid tissues. Somatostatin can inhibit growth hormone (GH) secretion, digestive enzyme secretion in the gastrointestinal tract, peptide hormone release, and smooth muscle contraction, thereby hindering animal growth and development and affecting nutrient digestion and absorption [12-14]. CS can specifically bind to somatostatin in vivo, disrupting its disulfide bonds and thus destroying its biological activity, relieving the inhibitory effects of somatostatin on growth hormone and digestive enzyme secretion, thereby promoting nutrient absorption and body growth [15-19]. Additionally, CS' s metabolite—taurine—can enhance the activities of digestive enzymes such as amylase (AMY) and trypsin, thus CS can also indirectly promote nutrient absorption through its metabolites [20]. However, studies indicate that CS' s growth-promoting effects are dose- and time-dependent, with effects gradually diminishing over time. Whether administered orally or via rumen or duodenal fistula infusion, CS' s inhibitory effect on somatostatin activity decreases over time, with somatostatin activity returning to pre-treatment levels within approximately one week [21]. Therefore, some scholars recommend feeding CS to growing-finishing pigs once every 5-7 days, though this method is cumbersome in practical production [22]. Some researchers have compared the effects of continuous versus intermittent CS supplementation.

Regarding growth performance studies, reports indicate that continuous supple-

mentation of low-dose CS at an effective dose of 18.22 mg/kg throughout the 56-day finishing stage of commercial pigs produced better growth performance improvement than incremental supplementation in two stages (effective dose of 21.87 mg/kg for days 1-28 and 29.16 mg/kg for days 29-56), with higher input-output ratios and economic benefits, making it more practical and promotable [23]. Another report studying CS effects on late-finishing pigs found that with a 20-day feeding period, daily administration of CS at an effective dose of 20 mg/kg improved daily weight gain better than administration of the same dose once every 5 days [24].

In sow studies, reports show that dietary CS supplementation during late gestation promotes fetal growth and development in sows, increases litter size, birth uniformity, and piglet birth weight, and reduces weak piglet rate [25-26]. The mechanism may involve CS regulating sex hormone secretion through the gonadal axis, improving metabolic status in sows, thereby affecting nutrient supply to fetuses. Additionally, CS supplementation during lactation can improve sow nutrient utilization, reduce body weight loss caused by lactation, shorten weaning-to-estrus interval, and improve piglet survival rates by increasing immunoglobulin content in colostrum [27].

2.2 Effects of CS on Carcass and Meat Quality

Current research on CS effects on pig carcass and meat quality primarily focuses on growing-finishing pigs. Studies show that dietary supplementation with 70 mg/kg CS fed to finishing pigs for 47 days significantly improved protein deposition [8]. Additionally, feeding a diet containing 180 mg/kg cysteamine hydrochloride (effective dose) for 35 days during the late finishing stage significantly increased carcass lean percentage and bone percentage, reduced fat percentage, and improved meat color [28]. Dietary supplementation with 70 mg/kg cysteamine hydrochloride fed to growing-finishing pigs for 21 days significantly reduced backfat thickness at the P2 point (last rib) [29]. Dietary supplementation with 9.45 mg/kg CS (effective dose) for 29 days also significantly increased deoxymyoglobin content in pork, significantly decreased metmyoglobin content, and delayed post-slaughter oxidative discoloration of pork [30].

The reasons for CS improving carcass quality and reducing body fat deposition may include several aspects. First, CS can regulate secretion of growth hormone, thyroid hormone, and glucagon [31-32,43], promoting nutrient redistribution in the body, reducing lipid synthesis in adipocytes, and promoting protein synthesis and lipolysis in muscle cells [33]. Second, it is also related to its regulation of thyroid hormone and glucagon secretion, thereby promoting muscle tissue growth and development and fat tissue decomposition [33]. Additionally, CS can reduce body fat deposition by increasing hormone-sensitive lipase activity and decreasing expression of malate dehydrogenase, glucose-6-phosphate dehydrogenase, and isocitrate dehydrogenase [34-35].

2.3 Effects of CS on Nutrient Metabolism

Dietary CS supplementation can improve nutrient metabolism in the body. Studies show that CS supplementation can increase total protein (TP) content and decrease urea nitrogen (UN) content in pig serum [34,36]. Serum total protein content is an important indicator reflecting protein metabolism status in the body, playing crucial roles in maintaining plasma osmotic pressure, buffering blood pH, and nutrient supply [37], while also reflecting immune status. Serum urea nitrogen is a metabolite formed through the arginine cycle from proteins and amino acids in the body, and its content shows a significant negative correlation with nitrogen deposition rate and protein (or amino acid) utilization [38]. When serum total protein content is high and urea nitrogen content is low, it indicates stable amino acid metabolism, strong protein anabolism, and high dietary nitrogen utilization efficiency. Therefore, CS can promote protein metabolism and improve nitrogen utilization.

Regarding lipid and glucose metabolism indicators, CS has the effect of reducing serum total cholesterol (TC), triglycerides (TG), and glucose (GLU) content [39-40]. Since carbohydrate, protein, and lipid metabolism are all regulated by endocrine hormones, CS can promote glucose utilization by tissues through increasing insulin activity. CS also accelerates adipose tissue decomposition, transporting blood cholesterol and triglycerides back to the liver for catabolism to conserve glucose, thereby reducing blood total cholesterol and triglyceride content. The related mechanism is that CS can bind to sulfur-containing amino acids in liver enzymes involved in cholesterol and triglyceride synthesis, inhibiting their activity, thereby inhibiting cholesterol and triglyceride synthesis and promoting their catabolism [41].

Additionally, different feeding modes have varying effects on pig nutrient metabolism. Studies show that continuous feeding of CS at 37.5 mg/kg (effective dose) to finishing pigs resulted in higher serum activities of glutamic-pyruvic transaminase (GPT), glutamic-oxaloacetic transaminase (GOT), alkaline phosphatase (AKP), and amylase compared to feeding the same dose every 6 days. Glutamic-pyruvic transaminase and glutamic-oxaloacetic transaminase reflect protein anabolism, alkaline phosphatase participates in lipid metabolism, and amylase participates in carbohydrate metabolism—all of which are positively correlated with nutrient digestion and absorption. The results suggest that continuous CS feeding is more effective in improving nutrient metabolism in pigs [42].

2.4 Effects of CS on Intestinal Health and Nutrient Absorption

The small intestine is the primary site for nutrient digestion and absorption; therefore, studying CS effects on the intestine is significant for guiding pig production. Studies show that dietary CS supplementation can improve apparent digestibility of dietary dry matter, nitrogen-free extract, crude protein, crude

fat, crude fiber, calcium, and total phosphorus in growing pigs [43]. CS can also significantly increase activities of protease, lipase, and amylase in small intestinal contents and pancreatic trypsin activity [44]. The mechanism may involve CS relieving somatostatin' s inhibitory effects on secretin and cholecystokinin, thereby promoting pancreatic enzyme synthesis and secretion [45]. Additionally, CS can increase expression of sodium-glucose cotransporter 1 (SGLT1) in piglet small intestine, promoting glucose absorption and utilization [46].

The intestinal antioxidant defense system and immune system play important roles in maintaining intestinal health. Glutathione, glutathione peroxidase (GSH-Px), and superoxide dismutase (SOD) in intestinal mucosa are important components of the intestinal antioxidant defense system, while secreted immunoglobulin A (IgA), immunoglobulin M (IgM), and immunoglobulin G (IgG) content reflect intestinal immune defense capacity. Studies show that dietary CS supplementation in finishing pigs can increase glutathione content, enhance glutathione peroxidase activity, and reduce superoxide dismutase activity in jejunal mucosa; secreted immunoglobulin A, immunoglobulin M, and immunoglobulin G content in jejunal mucosa also significantly increase [47]. These results indicate that CS can maintain intestinal antioxidant defense and immune systems, promoting intestinal health.

Furthermore, CS can significantly enhance expression of tight junction proteins Occludin, Claudin-1, and ZO-1 in jejunal mucosa [47]. Therefore, CS plays an important role in improving tight junction proteins to maintain intestinal barrier integrity and promote intestinal epithelial tissue development.

2.5 Role of CS in Alleviating Piglet Stress

In modern pig production, early weaning of piglets often induces severe weaning stress, leading to diarrhea and growth retardation. Insufficient gastric acid secretion is an important cause of growth retardation and diarrhea in weaned piglets [48]. Studies show that CS can increase endogenous gastric acid secretion in piglets by depleting somatostatin and promoting secretion of gastrin and growth hormone-releasing peptide in gastric mucosa [7,49]. Shi et al. [50] found that CS can increase mRNA expression of H+-K+-ATPase in gastric tissue, promoting gastric acid secretion in weaned piglets. Additionally, weaning stress causes significant increases in serum cortisol, triiodothyronine (T3), and thyroxine (T4) content [51]. CS supplementation can significantly decrease serum cortisol content and maintain stable triiodothyronine and thyroxine levels in weaned piglets, reducing energy mobilization for stress response and alleviating weaning stress [52].

Beyond regulating gastric acid and hormone secretion to alleviate stress, CS can also relieve stress responses through antioxidant effects. Superoxide dismutase and glutathione peroxidase are important components of the body' s antioxidant defense system. Studies show that feeding CS to piglets can significantly increase serum superoxide dismutase and glutathione peroxidase activities [53].

Therefore, CS supplementation improves piglets' antioxidant defense capacity against external stress. The antioxidant mechanism of CS may involve several aspects: First, CS' s active sulfhydryl groups can convert excessive cystine in lysosomes to cysteine [54], which then synthesizes glutathione, indirectly exerting antioxidant effects by increasing glutathione content [30]; other reports indicate that CS has protective effects against various liver oxidative damages induced by galactosamine, carbon tetrachloride (CCl4), and acetaminophen, being a more effective oxygen free radical scavenger than glutathione in the liver [55]; additionally, CS can be converted to taurine, enhancing catalase and glutathione metabolism-related antioxidant enzyme activities [56-57].

2.6 Immunomodulatory Function of CS

CS can modulate pig immune function to a certain extent. Liu et al. [58] reported that CS can significantly increase serum immunoglobulin A and immunoglobulin G content, leukocyte phagocytic rate, and T-lymphocyte transformation rate in weaned piglets, enhancing immunity. Liu et al. [59] reported that the interaction between CS and N-carbamylglutamate benefits the recovery of foot-and-mouth disease antibody levels in weaned piglets, effectively avoiding interference from maternal antibodies and improving piglet immunity. Additionally, dietary CS supplementation during late gestation in sows can increase immunoglobulin G content in colostrum, indirectly improving piglet immune function [27]. Chang et al. [60] reported that piglets fed cysteamine hydrochloride preparation had significantly higher classical swine fever virus antibody blocking rates than the control group, suggesting that cysteamine hydrochloride preparation also has certain effects on enhancing swine fever vaccine efficacy. Furthermore, CS can increase complement 3 levels in finishing pig blood [61], and the complement system is a component of non-specific immunity that assists antibodies in phagocytosing pathogenic microorganisms [62].

The immunomodulatory mechanism of CS is related to inhibiting somatostatin activity. Somatostatin can inhibit immunoglobulin and cytokine synthesis [63], with inhibitory effects on immunoglobulin A synthesis reaching 20-50% [58]. CS can deplete somatostatin levels in the body, promoting release of growth hormone and insulin-like growth factor-1, whose elevated levels facilitate glucose and amino acid uptake into lymphocytes, thereby promoting immunoglobulin synthesis [64].

3 Problems in CS Application

Although CS has growth-promoting functions, inappropriate dosage and usage methods can also cause negative effects. Studies show that high doses of CS can cause duodenal ulcers and perforation in rats [65-66]. Additionally, CS can reduce blood flow in rat duodenal mucosa by promoting endothelin release, causing local tissue ischemia and hypoxia, and decreasing body defense function [67]. Furthermore, high-dose CS can cause oxidative stress, resulting in direct

and necrotic cytotoxicity [68].

4 Summary

Appropriate dietary CS supplementation can effectively improve pig growth performance, carcass quality, meat quality, nutrient metabolism, intestinal health, stress response, and immunomodulatory function. However, current application effects of CS in animal production are inconsistent, as different studies vary in CS purity, effective dose, feeding duration, and pig growth stage, environment, and breed. Therefore, further research is needed on optimal dosage and supplementation methods for each growth stage. Additionally, although promoting growth performance through growth hormone secretion is effective, the safety of this direct approach has not been accepted by some countries, and its effects and potential toxic side effects in livestock production require further evaluation. Most current experiments also have shortcomings of short duration and small animal populations, requiring more long-term, large-scale feeding trials to evaluate CS' s sustained effects. Furthermore, improving CS processing technology to reduce off-odors, enhance chemical stability for better physiological effects in vivo, and further research on CS' s mechanisms of action in the body are also needed.

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Note: Figure translations are in progress. See original paper for figures.