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Review

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Review: The roles and functions of histidine on growth performance and intestinal health of weaning piglets

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Abstract

Histidine is an essential limiting amino acid in piglet diets and plays a crucial role in pig production. Supplementing piglet diets with adequate histidine can enhance growth performance, promote protein synthesis, regulate lipid metabolism, and improve immune function in piglets. A large body of evidence indicates that histidine may improve digestion, nutrient absorption, and intestinal microbiota balance, thereby enhancing intestinal health. This review covers histidine's physicochemical properties, metabolic pathways, its application in piglet diets, and the requirements and influencing factors of histidine in piglets. The aim is to provide a reference for the precise use of histidine in piglet production.

Introduction

Histidine (His), also known as α-amino–β-imidazole propionic acid, is the principal amino acid (AA) responsible for the buffering capacity in biological systems. It was first isolated from salmon sperm by the German physiologist Albrecht Kossel in 1886 (Brosnan and Brosnan 2020). Optimizing the supply of AAs in swine nutrition is crucial for maximizing growth performance and economic efficiency in piglets. But the essential AA, His, is often overlooked in piglet diet studies (Li et al. 2002). His serves as a constituent AA of body proteins and, upon incorporation into proteins, it can undergo post-translational methylation to form methyl His. His also functions as a precursor for histamine, a neurotransmitter involved in immune responses. Both His and histamine are components of several dipeptides, which serve as pH buffers, metal-chelating agents, and antioxidants, particularly in skeletal muscles and the brain. A significant proportion of His in organisms exists in the form of carnosine, a dipeptide composed of His and β-alanine. For example, in the longissimus dorsi muscle, approximately 40% of the total His content is found in the form of carnosine. The His within carnosine can be methylated to form anserine or β-alanine, and most species are incapable of synthesizing both substances simultaneously, except for pigs (van Milgen and Le Floc'h 2021).

His is essential for piglet development, supporting muscle growth and immune health through its roles as a precursor, buffer, and antioxidant. And pigs' unique ability to synthesize carnosine and β-alanine further highlights the importance of optimal dietary His levels.

The physicochemical properties of His

His has the molecular formula $C_6H_9N_3O_2$ and the structural formula NH_2-CH ($CH_2CH_2CHNH_2COOH$)-COOH, with a relative molecular mass of 155. Its chemical name is α-amino—β-imidazole propionic acid. His has four stereoisomers, among which only the L-form is biologically active and can be absorbed and utilized by living organisms (Brosnan and Brosnan 2020). L-His typically exists in a crystalline form, appearing as white crystals or crystalline powder, odorless, with a slightly sweet taste, highly soluble in water, and slightly soluble in ethanol. Its melting point is 287°C. The molecular structural formula is shown in Figure 1. The unique chemical properties of His, stemming from the imidazole ring, encompass proton buffering, metal ion chelation, and antioxidant activities. These cytoprotective interactions may involve free HIS, HIS-containing peptides, His-CD, and His residues in proteins (Holeček 2020). Overall, L-His is the only biologically active stereoisomer. Its imidazole side chain endows the molecule with proton buffering, metal chelation, and antioxidant capacities, while its crystalline form (white, odorless, water-soluble) makes it easy to handle in feed. These physicochemical traits underpin all subsequent nutritional, metabolic, and physiological roles discussed in the following sections.

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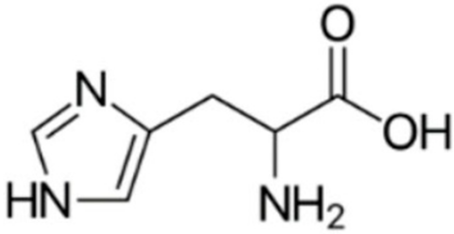

Figure 1. Chemical structure formula of L-histidine.

Overall L-His is an essential AA with a unique imidazole ring, which provides pH buffering, metal binding, and antioxidant protection, underpinning its key roles in piglet development.

The metabolic pathways of His in animal organisms

His is an essential limiting AA in piglet diets and may require supplementation (NRC 2012). It is one of the 20 AAs directly incorporated into polypeptide chains, and, during the rapid growth of piglets, must be supplied by feed to meet high protein-synthetic demand (Lopez and Mohiuddin 2025). Beyond protein synthesis, His fulfills unique physiological roles: it buffers protons, chelates metal ions, provides antioxidant defense, and suppresses advanced glycation and lipid-oxidation products (Boldyrev et al. 2013).

His can be obtained not only as free His or protein-bound His in feed, but also through the proteolysis of endogenous proteins and the hydrolysis of His-containing peptides (Brosnan and Brosnan 2020). In the body, it follows several metabolic routes (Fig. 2). Decarboxylation yields histamine (β-imidazolylethylamine), a key immune and neuro-endocrine mediator; conjugation with β-alanine produces the imidazole dipeptide carnosine (0.8–1.2 mmol $kg-^{1}$ muscle in 21-day-old piglets), which acts as an antioxidant and intracellular buffer and whose deficiency impairs skeletal-muscle protein turnover (Wu et al. 2022a). A separate catabolic branch converts His to cis- and trans-urocanate, and onward to Formiminoglutamic acid (FIGLU), ultimately feeding glutamate and one-carbon units into the TCA cycle and folate-dependent pathways (Holeček 2020). Excess His can be fully metabolized, whereas deficiency activates the NF-κB pathway, up-regulating pro-inflammatory cytokines (tumor necrosis factor-alpha [TNF-α], interleukin-6 [IL-6], cyclooxygenase-2 [COX-2]) and down-regulating anti-inflammatory mediators (interleukin-10 [IL-10], transforming growth factor-beta [TGF-β]) in the gut (Liang et al. 2022). Histamine itself exerts anti-inflammatory effects through H1 receptors (H1R)–H4 receptors (H4R) signaling: via H2 receptors (H2R), it elevates cAMP-PKA to suppress TNF-α and IL-6, while H4R modulates major histocompatibility complex class II (MHC-II) expression on dendritic cells, thereby regulating antigen presentation and T-cell differentiation (Branco et al. 2018; Jutel et al. 2002). Additionally, His residues in hemoglobin are critical for heme stabilization; substitutions at these sites lead to dysfunctional hemoglobin variants and congenital cyanosis (Shi et al. 2015). Together, His is indispensable for rapidly growing piglets: it must be supplied by the diet to sustain protein deposition, while its imidazole ring simultaneously buffers protons, chelates metals, and provides antioxidant defense. In vivo, His is channeled into three complementary fates: incorporation into peptides and heme, conversion to the anti-inflammatory mediator histamine via H1R–H4R, and catabolism to carnosine, urocanate, and FIGLU. Each contributes to redox balance, immune homeostasis, and energy metabolism. Optimal dietary provision therefore underpins not only muscle accretion but also gut health and systemic resilience in the post-weaning phase.

Overall, His is crucial for piglet growth and health, acting as a buffer, antioxidant, and precursor to key compounds. Adequate intake is essential for optimal development.

Research progress on the application of His and its derived mediators in piglet production

His enhances the growth performance of piglets

His is an essential limiting AA in piglet diets, and its appropriate supplementation can enhance piglet growth performance (NRC, 2012). Therefore, ensuring adequate His supplementation during the early stage of weaned piglet feeding is particularly important. Researchers found in their research that when the diet lacks His, weaned piglets exhibit reduced feed efficiency and growth performance (Wessels et al. 2016). Another study has fitted a broken-line linear regression model to their trial data, using the average daily gain (ADG) of 7–11 kg pigs as a function of increasing standardized ileal digestible (SID) His: Lys ratio. When the His: Lys ratio in the piglet diet was 24% and 28%, there was a trend of decreased growth performance in the piglets (Cemin et al. 2018). Increasing the His level in the diet within a certain range can effectively improve the piglets' growth performance. Research shows that 10–20 kg weaned piglets fed a His-deficient diet have significantly reduced growth performance. However, after adding adequate L-His · HCl · H_2O, their growth performance increases significantly (the optimum content is 0.31%) (Izquierdo et al. 1988). There is a study that has found the optimal His level in the ideal protein model for piglets (10–20 kg). Results showed that adding 0.12% crystalline His maximized ADG, with average daily feed intake showing a similar trend (Li et al. 2002). This indicates adequate crystalline His in the basal diet boosts piglets' feed consumption. Feed conversion efficiency significantly improved when dietary digestible His reached 0.32% or 0.35%, higher than in groups with 0.26% and 0.29% digestible His. In addition, researchers have studied the His requirements of weaned piglets on a low-protein diet. Results show that His supplementation doesn't affect the piglets' final body weight and weight gain, but significantly increases their feed intake in the sixth week, without influencing the relative organ weights and serum biochemical indices (Kang et al. 2020). Other researchers also studied the effects of the SID His-to-lysine ratio on the growth performance of 7–11 kg pigs. They found that increasing the SID His: Lys ratio above the NRC recommendation had no effect on growth performance or fecal scores. Therefore, appropriate levels of His can help improve the growth performance of piglets (Cheng et al. 2023). In practical production, we must ensure His requirements for piglets and avoid excessive addition that causes resource waste. In conclusion, His, as an essential limiting AA for piglets, plays a critical role in their growth. Adequate supplementation can enhance growth performance and feed efficiency, with optimal levels maximizing ADG and feed intake.

His and its derived mediators play an important role in regulating immune function in piglets

Histidine

Newborn piglets can acquire specific antibodies (passive immunity) from colostrum, which effectively prevents pathogen infection. Figure 3 illustrates how His exerts its immune functions in

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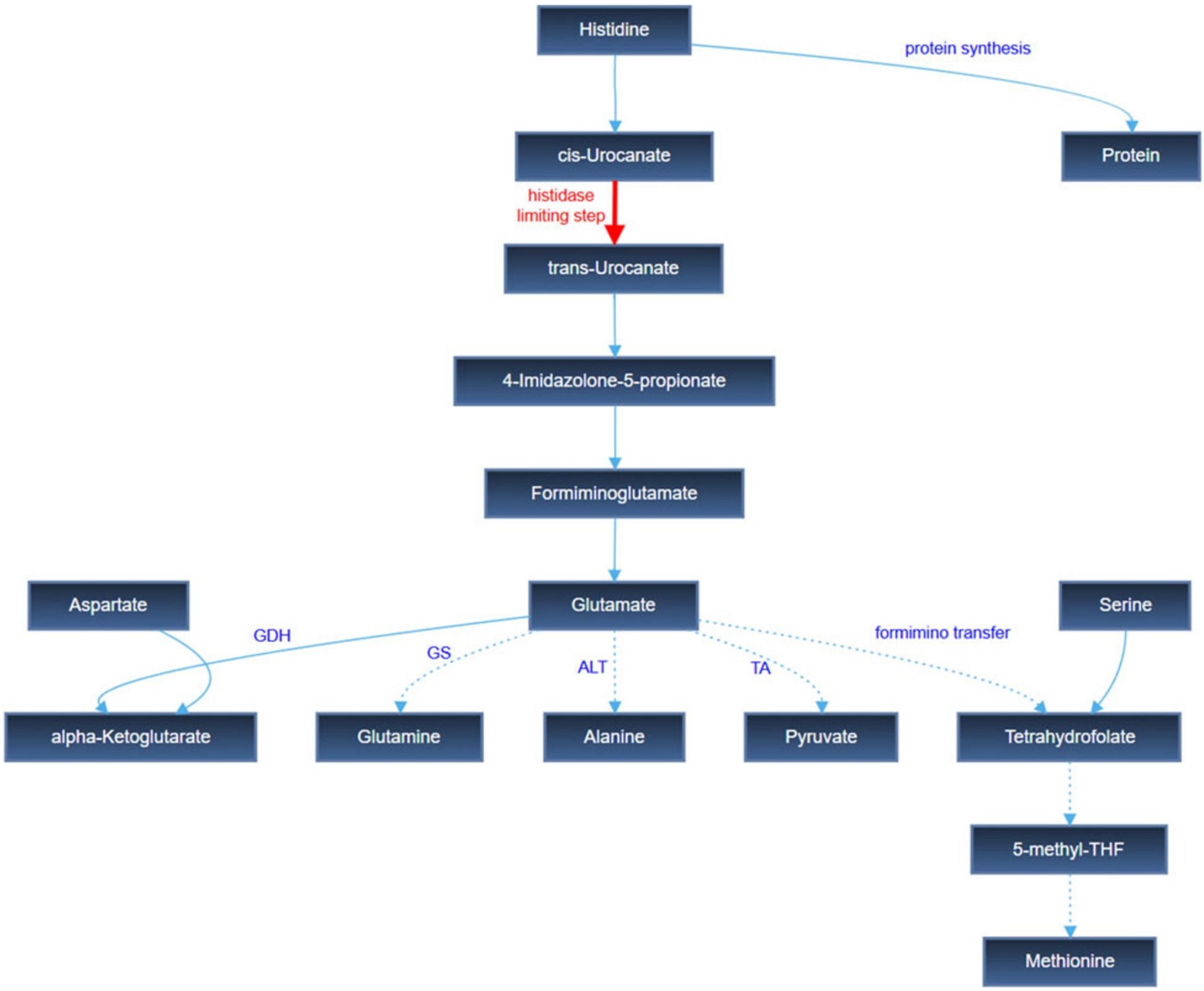

Figure 2. The metabolic pathways of histidine in piglets.
Note: Compared to rodents or humans, weaned piglets exhibit 30%–40% lower hepatic histidase activity, making the cis-urocanate → trans-urocanate conversion a rate-limiting step (indicated by a bold red arrow). GDH, glutamate dehydrogenase; GS, glutamine synthetase; ALT, alanine aminotransferase; TA, transaminase; THF, tetrahydrofolate.

piglets. Colostrum contains abundant immunoglobulins (Ig); His is an essential AA component of IgG (Inoue and Tsukahara 2021). Research has shown that high levels of His in piglet feed exhibit a positive effect on the content of IgG in the jejunal mucosa of weaned pigs (Cheng et al. 2023). Studies have confirmed a synergistic effect between L-His and hydrogen peroxide, with L-His potentiating the oxidative damage of hydrogen peroxide to Gram-negative bacteria. However, excessive His intake can exert adverse effects on immune function (Nagao et al. 2018). Another study found that His modulates cell–cell interactions, inhibiting immune cell infiltration and responses.

Histamine and other His-derived mediators

Histamine, a derivative of His known as β-imidazolyl ethylamine, serves as a pivotal mediator in numerous physiological and pathological processes. Notably, it plays a significant role in immune function, alongside its involvement in neurotransmission, cerebral activities, pituitary hormone release, and the regulation of gastrointestinal (GI) and circulatory functions (Liu et al. 2025). Importantly, histamine has been shown to effectively modulate immune responses (Leurs et al. 1995). Jutel et al. (2002) found that key immune cells (T lymphocytes, monocyte–macrophages, dendritic cells) express functional histamine receptors and can synthesize and release histamine. Recent experiments show histamine regulates monocyte–macrophage phagocytosis, dendritic cell antigen presentation, T lymphocyte proliferation/ differentiation, and antibody isotype switching via receptor-mediated signaling (Jutel et al. 2002). Current data indicate that histamine has a dual role in immune regulation. In a systematic review (Branco et al. 2018), it was detailed how histamine, via H1R-H4R-mediated signaling, modulates innate immunity (e.g., macrophage polarization, neutrophil chemotaxis) and adaptive immunity (e.g., Th1/Th2 balance, regulatory T-cell function). Thus, histamine significantly impacts piglet immune homeostasis by regulating cytokine profiles (e.g., IL-4, IL-10, IFN-γ) and immune cell activation. NF-κB serves as a key pathway in regulating inflammation within animal organisms and plays a crucial role in alleviating inflammatory responses (Tan et al. 2019). There is a study that shows that dietary His deficiency activates the NF-κB signaling pathway, inducing inflammatory responses. It upregulates pro-inflammatory factors (TNF-α, hepcidin 1, COX-2, CD80, CD83) and downregulates anti-inflammatory factors (TGF-β1, IκBα) at the mRNA level.

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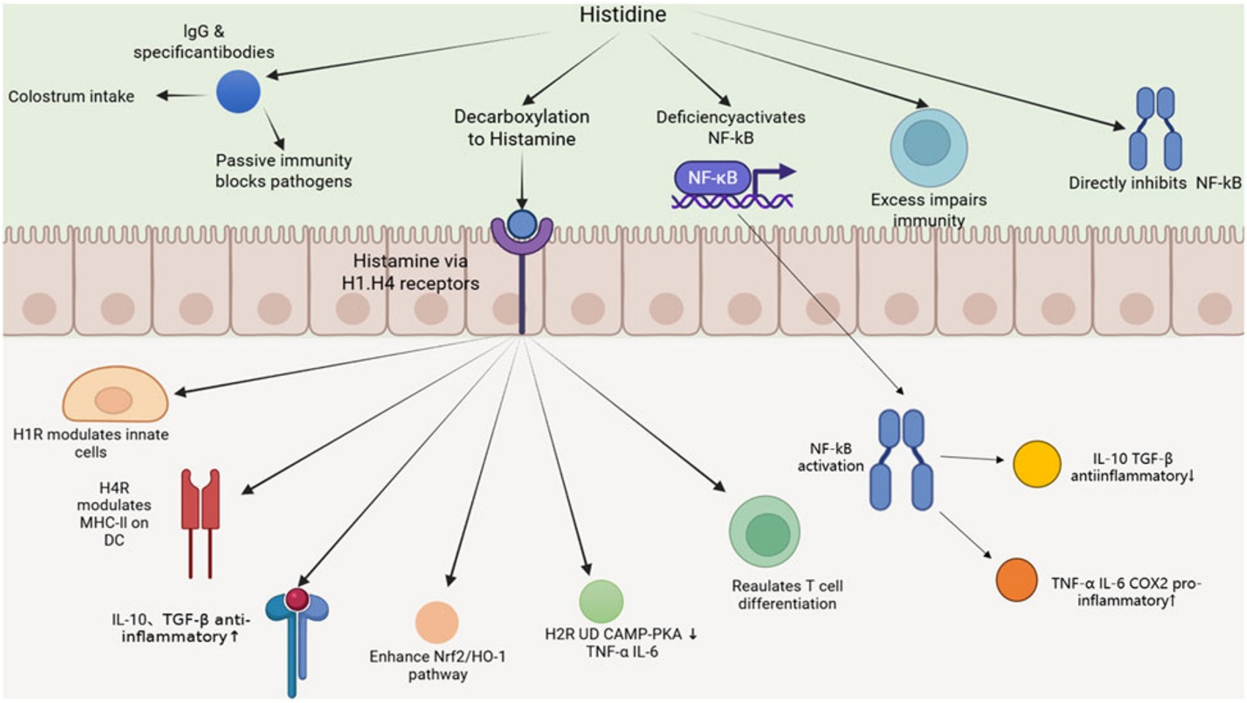

Figure 3. Histidine exerts its immune functions in piglets.

Note: IgG, immunoglobulin G; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; H1–H4R, histamine receptor 1–4; H2R, histamine receptor 2; H4R, histamine receptor 4; cAMP-PKA, cyclic adenosine monophosphate–protein kinase A; IL-10, interleukin-10; TGF-β, transforming growth factor-beta; TNF-α, tumor necrosis factor-alpha; COX-2, cyclooxygenase-2; Nrf2/HO-1, nuclear factor E2-related factor 2/heme oxygenase-1 (this figure is created in BioRender.com).

Additionally, His deficiency reduces anti-inflammatory cytokines (IL-10, TGF-β) and increases pro-inflammatory cytokines (TNF-α) in the gut, which mirrors the gene expression trends of inflammatory mediators (Liang et al. 2022). His deficiency can also activate this pathway, which may be the mechanism by which His regulates the NF-κB signaling pathway. Another way, His cannot only inhibit NF-κB activation in human coronary artery endothelial cells, but also the degradation of the anti-inflammatory protein IκBα, the expression of CD62E (a cell adhesion molecule), and the production of the pro-inflammatory cytokine IL-6. In doing so, His exerts anti-inflammatory effects during endothelial inflammation (Hasegawa et al. 2012). Histamine, a decarboxylation product of His, also exerts anti-inflammatory effects (Radermecker and Bury 1989). Histamine exerts significant anti-inflammatory effects by suppressing NF-κB activation and enhancing the Nrf2/HO-1 signaling pathway (Yang et al. 2020). Histamine mediates anti-inflammatory effects in the body through its H1R (Bhattacharya and Das 1985), H2R (Sirois et al. 2000), H3 receptors (H3R) (Honkisz-Orzechowska et al. 2023), and H4R (Lim et al. 2006; Sgambellone et al. 2023). Histamine acts via a G-protein-coupled signaling network through H1R–H4R. During weaning stress, it not only inhibits pro-inflammatory cytokines (e.g., TNF-α, IL-6) by activating the cAMP-PKA pathway through H2R but also modulates MHC-II molecule expression in dendritic cells via H4R, affecting antigen presentation (Hirasawa 2019; Jutel et al. 2002). Overall, His deficiency activates the NF-κB pathway, contributing to colitis-related inflammation. His and histamine can modulate the signaling pathway NF-κB to exert anti-inflammatory effects. Additionally, histamine modulates the immune and inflammatory responses of the organism through its H1R–H4R.

His's regulatory impact on lipid metabolism and its implications for metabolic disorders

Lipid metabolism, which primarily includes the metabolism of fatty acids, triglycerides, and cholesterol. Fatty acid metabolism serves as the foundation for the metabolism of other lipids, while the metabolism of triglycerides and cholesterol is closely associated with the lipid transport proteins High-Density Lipoprotein Cholesterol (HDL) and low-density lipoprotein (LDL) (Tanaka et al. 2003). His plays a vital role in the lipid metabolism of weaned piglets. Studies have shown that His, via its imidazole group, regulates in vitro lipid peroxidation systems. Their study confirmed that His's regulatory role is highly dependent on environmental conditions such as iron valence, ligand sequence, and concentration. Different functional groups in its molecule achieve precise regulation of lipid peroxidation by forming specific iron complexes or altering iron ion states (Erickson and Hultin 1992). This mechanism provides important evidence for understanding His's functions in physiological and pathological processes (Erickson and Hultin 1992). Recent evidence obtained with post-weaning piglets indicates that dietary His level can directly modulate lipid profiles: (Kang et al. 2020) fed 7–11 kg piglets diets containing 0.30% SID His and observed a 12% reduction in serum Non-Esterified Fatty Acids and a 9% decrease in hepatic triglycerides compared with the 0.21% SID control, while (Tang et al. 2023) reported that 0.35% SID His increased ω-3 PUFA proportion in the longissimus dorsi and lowered plasma total cholesterol in LPS-challenged piglets. Collectively, these data demonstrate that optimizing dietary His beneficially reshapes lipid metabolism in weaned piglets (Du et al. 2017). One study administered His supplementation to women with Metabolic Syndrome

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and observed significant reductions in cholesterol, triglycerides, fatty acids, unsaturated lipids, acetone, and α/β-glucose post-supplementation. This demonstrates that His can effectively regulate lipid metabolism and modulate carbohydrate metabolism. Furthermore, Krishnan et al. (2009) have unveiled that His influences lipid metabolism by modulating membrane fusion. The His residue in lipids accelerates membrane fusion, and a specific His "switch" in paramyxovirus hemagglutinin-neuraminidase (HN) is crucial for fusion-protein activation. His-containing peptides mimicking HN can promote membrane fusion and even restore fusion activity in HN His mutants. This underscores His's potential role in regulating membrane fusion events linked to lipid metabolism (Krishnan et al. 2009). However, excessive dietary His intake may lead to hypercholesterolemia. There is a study that found that in situations of His excess and copper deficiency, feeding rats a His-excess diet led to the accumulation of liver triacylglycerol, a decrease in serum triacylglycerol levels, and an increase in serum cholesterol levels. It also resulted in a significant decrease in copper content in both the liver and serum, along with an increase in urinary copper and zinc excretion. In contrast, a copper-deficient diet mainly caused a marked decrease in liver and serum copper content but had little effect on liver and serum zinc content (Aoyama et al. 1999). The results showed that His plays a complex role in lipid metabolism by influencing copper levels and lipid parameters. His can also react with other substances to form new compounds that play an important role in lipid metabolism. Research shows that acrolein from lipid peroxidation may mainly react with protein His residues to form Nτ-(3-propanal) His, which is likely one of the major adducts in oxidized LDL (Maeshima et al. 2012). Histamine, a decarboxylation product of His, can influence lipid metabolism by activating distinct receptors, including histamine H1R, histamine H2R, and H3R. There is a study that shows that histamine signaling via H1R and H2R plays a key role in regulating lipid metabolism and the development of Non-alcoholic steatohepatitis (NASH). H2R knockout mice displayed more severe metabolic issues and NASH phenotypes compared to H1R knockout mice (Wang et al. 2010). Similarly, He et al. (2009) have indicated that histamine can attenuate stress-induced lipid metabolic disorders. Under restraint stress, histamine levels in plasma and brain regions are significantly elevated. When administered at a dose of 50 mg/kg, histamine reduces the increase in plasma triglyceride levels caused by lipid emulsion injection. This effect is attributed to histamine's anti-stress properties and its enhancement of hepatic triglyceride lipase activity and mRNA expression (He et al. 2009). In addition to histamine, certain histamine polymers also regulate lipid metabolism (Mahadoo et al. 1981). In the intestine, increased permeability permits substantial lipid absorption via the lymphatic system. In major blood vessels, heightened endothelial permeability allows atherogenic lipids to penetrate into subendothelial tissues (Mahadoo et al. 1981). It has been shown that vascular lipid permeability is controlled by the histamine-heparan sulfate-histaminase system. Atherosclerosis and specific obesity types may stem from failures in this regulatory mechanism. In summary, His plays a crucial and multifaceted role in lipid metabolism. His influences lipid metabolism by modulating membrane fusion and can react with other substances to form new compounds that are important in lipid metabolism. However, excessive dietary His intake may lead to hypercholesterolemia. Additionally, His can be decarboxylated to form histamine, which also plays a role in lipid metabolism by activating distinct receptors.

His maintains piglet's GI barrier function

The intestine, vital for nutrient digestion/absorption and a key barrier against bacterial/endotoxin invasion, is crucial for piglets to combat stress (Tang et al. 2016; Tang et al. 2021; Tang et al. 2022). Reviews have shown that weaning stress, which alters intestinal morphology and function, disrupts digestion, absorption, and gut barrier function in piglets, leading to reduced feed intake, higher diarrhea rates, and growth retardation. Thus, safeguarding gut health in weaned piglets is crucial for production. Studies have confirmed that 35% SID His: Lys in piglet diets enhances intestinal health by reducing IgA and enterocyte proliferation while increasing jejunal villus height (Cheng et al. 2023). Research has shown that His plays a key role in repairing intestinal epithelial cells, His acting through transforming growth factor β1 (TGF-β1) mediated regulation, Supplementing the culture medium with 10 μM His under His-deficient conditions enhances intestinal epithelial cell repair and increases extracellular TGF-β1 concentration (Matsui et al. 2019). Furthermore, histidine's repair function is most prominent in intestinal epithelial cell 6 (IEC-6) cells; its uptake, studied in rainbow trout and potentially relevant to mammals, shows high specificity and efficiency, adapting to dietary His levels (Glover and Wood 2008). This AA supports gut barrier function, modulates microbiota balance, and exhibits anti-inflammatory effects, collectively enhancing GI health and resilience. There is a report showing that His maintains GI function via specific transport mechanisms in intestinal epithelial cells. Its uptake exhibits high specificity and efficiency, and adapts to dietary His levels (Glover and Wood 2008). Cholera, a severe disease caused by GI dysfunction (Cholera in the Americas 1991), which can be alleviated by 2.5 g/L L–His supplementation, highlighting His's significance in maintaining GI function (Rabbani et al. 2005). Histamine, a product of His decarboxylation, enhances gut function by activating H1R. This activation boosts tight junction proteins like occludin and claudin-1 in intestinal epithelial cells, reducing mucosal permeability and preventing pathogen/toxin translocation (Kim et al. 2012). Moreover, histamine promotes Intestinal barrier protein mucin 2 secretion, thickens the mucosal layer, and protects the gut from mechanical damage and pathogen invasion (Kim et al. 2012) (Lorenz et al. 1983). Studies have shown that histamine concentrations are higher in the gastric mucosa, and the enzymes involved in its metabolism are primarily located in the stomach. And to a certain extent, the enzymatic activities related to histamine synthesis and degradation are regulated by gastric acid secretion. Thus, histamine plays an important role in maintaining GI function. In summary, the intestine is vital for piglets to combat weaning stress, and His leads to protecting the intestine. Histamine, a derivative of His, also plays a role in maintaining GI barrier function through the regulation of gastric acid secretion.

Gut microbiota are essential for host health in mammals (Buffie and Pamer 2013). Weaning stress in piglets causes gut microbiota imbalance and usually induces GI infections, primarily involving Escherichia coli diarrhea (Schokker et al. 2015). There is a study that has found that His interacts with gut microbiota (Quesada-Vázquez et al. 2023). Inosine Monophosphate (IMP) is a metabolic product of intestinal microbiota using His as a substrate (Wu et al. 2022b), have found that the level of IMP in the feces of mice fed His is increased. Thus, it can be reasonably speculated that His has the effect of regulating the balance of gut microbiota. Additionally, His can significantly increase the abundance of gut beneficial bacteria, such as *Butyrivibrio* and *Bacteroides*, in weaned piglets (Kang

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Table 1. The recommended levels of SID histidine for different weight stage piglets are provided by official or authoritative bodies across various countries

Official or authoritative bodies	Weight stage/kg	SID His: Lys requirement/%	SID histidine requirement/%
NRC (2012)	7–11	34	0.32
NRC (2012)	11–25	34	0.28
CVB (2016)	5–25	30	0.32
INRA (2018)	5–15	31	0.33
China (2004)	5–10	30	0.32–0.34
EMBRAPA (2015)	5–15	29	0.30

Note: NRC, National Research Council; CVB, Centraal Veevoederbureau; INRA, National Institute for Agricultural Research; EMBRAPA, Brazilian Agricultural Research Corporation.

et al. 2020). Notably, studies have synthesized histidine-derived carbon dots (His-CDs) with antioxidant and multi-enzyme activities. These His-CDs can regulate gut microbiota by increasing beneficial bacteria in the gut, such as *Muribaculaceae, Dubosiella* and *Allobaculum*, additionally; the abundance of *Desulphurobacteria* and *Proteobacteria* was reduced (Wang et al. 2024). Overall, His regulates gut microbiota balance by interacting with gut microbes, and its derived carbon dots (His-CDs) can increase piglets gut beneficial bacteria.

His promotes piglets' digestion and nutrient absorption

In most organisms, nutrients enter the bloodstream via intestinal epithelial cells (Yin et al. 2014), and their digestion and absorption are critical for life processes. mTOR, which is a serine/threonine protein kinase, regulates translation via eukaryotic initiation factor 4E binding protein (eIF4EBP) and ribosomal protein S6 kinase B (RPS6KB) phosphorylation (Wang and Proud 2006). It drives intracellular protein synthesis and is crucial for cellular growth and function. Studies have shown that the small intestine has higher levels of mTOR, and His can enhance the mTOR pathway (Gao et al. 2015). This indicates its significance for the proliferation of intestinal epithelial cells. Notably, histamine stimulates gastric acid secretion, thereby enhancing GI digestion and absorption (Dyduch et al. 1996). A review also indicated that many gut microbial strains can synthesize histamine, which likewise confirmed histamine's positive role in GI absorption and digestion (Fiorani et al. 2023). As previously mentioned, histamine has four receptors, all of which are expressed in the GI tract, highlighting its importance in GI absorption and digestion (Poli et al. 2001). Further research has found that among these four receptors, H3R plays a positive role in regulating gut motility (Poli et al. 2001). In conclusion, His boosts intestinal cell growth via the mTOR pathway and aids digestion by promoting gastric acid secretion. Concurrently, histamine can affect intestinal motility and enhance nutrient absorption via its receptors.

In summary, His is a key driver of post-weaning success, optimizing growth, health, and performance when provided at 0.30%–0.36% SID levels. Its multifunctional role supports gut integrity, immune function, and metabolic balance, making it essential for efficient piglet development.

Research progress on the nutritional requirements of His for piglets

Current studies on His levels for weaned piglets generally differ from NRC (2012) recommendations, with few related reports available. The existing research only covers weaned piglets, and there are no studies on growing-finishing pigs. Official bodies or authoritative organizations in different countries have published varying nutritional requirement standards for piglets at different weight stages, as listed in Table 1. The NRC (2012) suggests that the standard ileal digestible (SID) His requirement for piglets weighing 7–11 kg and 11–25 kg is 0.39% and 0.35%, respectively.

The efficiency of dietary protein utilization is maximized in weaned piglets when the ratio of essential AAs to lysine in the feed matches that required for tissue growth in pigs, which is referred to as the ideal AA pattern. Conversely, an imbalance in the ratio of protein or AAs to energy in the diet of weaned piglets can negatively impact nutrient absorption and utilization efficiency, potentially leading to nutritional absorption disorders (Wu et al. 2018). His, as an essential AA in piglets, plays an important role in the AA balance of piglet diets (Stein et al. 2007). As piglets have a limited ability to synthesize His and a rapid growth rate, their requirement for His is high. Dietary supplementation can prevent His deficiency and avoid restricted synthesis of protein derivatives (Zhao et al. 2011). And adding His to the diet of weaned piglets significantly boosts the serum His concentration in low-protein-fed piglets and restores tryptophan levels (Kang et al. 2020). There is a study that has found that maintaining the SID His to Lys ratio between 35% and 41% in the nursery diet of pigs weighing 7–11 kg can optimize AA balance and enhance growth performance in piglets (Cheng et al. 2023). In contrast, researchers have found that the optimal SID His: Lys ratio for pigs weighing 7–11 kg is 31%, and they propose that low-protein diets can synergize with His in the diet to regulate AA balance. These studies substantiate the vital role of His in maintaining the balance of other AAs in piglet diets (Cemin et al. 2018). Excess His competes with lysine and branched-chain AAs for the common cationic transporter b^0+, reducing their ileal digestibility and lowering whole-body nitrogen retention. Conversely, an optimal SID His: Lys ratio enhances the efficiency of tryptophan-to-niacin conversion and increases arginine availability via the gut-liver axis, as evidenced by lower plasma urea nitrogen and higher NH_3 clearance (Bröer 2008; Cemin et al. 2019; Cheng et al. 2023; Harper et al. 1970). These data underline that dietary His not only fills its own requirement but also acts as a "ratio anchor" that modulates the utilization of other essential AAs in diets.

There is a study using pigs with an initial weight of 7–11 kg, and five gradients of SID His: Lys ratios were established, specifically 26%, 32%, 38%, 43%, and 49% found that the optimal SID His: Lys ratio for piglet growth was 31%, lower than the 34% recommended by NRC (2012) (Cemin et al. 2018). Similarly, a study involving 96 Landrace piglets weighing 10–20 kg, two sets of four SID His: Lys ratios were established. The first set included 18%, 25%, 30%, and 37%, while the second set comprised 20%, 22%, 24%,

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Table 2. The recommended levels of SID histidine for piglets

No.	Breed	BW/kg		Dietary protein level/%	SID His: Lys requirement/%	SID histidine requirement/%	Literature
		IBW/kg	IBW/kg				
1	–	7.10	11.40	14.60	35–41	0.43–0.49	Cheng et al. (2023)
2	(Large White × Landrace)	10.30	20.38	18.51	25	0.31	Li et al. (2002)
3	(Large White × Landrace)	10.20	22.59	17.74	27	0.35	Li et al. (2002)
4	[(German Landrace × Large White) × Piétrain]	8.30	21.70	14.00	30	0.30	Wessels et al. (2016)
5	DNA 241 × 600, Columbus, NE	7.10	19.30	17.60	31	0.43	Cemin et al. (2018)
6	DNA 241 × 600, Columbus, NE	7.10	18.70	17.30	34	0.39	Cemin et al. (2018)

Note: "–" indicates that it is not indicated in the reference. BW, body weight; IBW, initial body weight; FBW, final body weight; SID, standardized ileal digestibility.

and 27%. They found the optimal SID His: Lys requirement to be 25%, which is lower than the NRC (2012) recommendation of 34% (Li et al. 2002). In another study, 120 (German Landrace × Large White) × Piétrain piglets weighing 8.3 ± 0.6 kg were used, Five gradients of the SID His: Lys ratio were set, specifically at 22%, 26%, 30%, 34%, and 38%, results indicated the optimal dietary SID His: Lys ratio was 30%, also below the NRC (2012) recommendation 34% (Wessels et al. 2016). Notably, a study with 40 nursery pigs weighing 7.1 kg initially, two distinct sets of SID His: Lys ratios were established. The first group comprised six ratios: 24%, 28%, 32%, 36%, 40%, and 44%. The second group included seven ratios: 24%, 28%, 30%, 32%, 34%, 36%, and 42%. It was found that the optimal SID His: Lys ratio was found to be 35%–41%, slightly higher than the NRC (2012) recommendation 34% (Cheng et al. 2023).

Current research shows that optimal SID His: Lys ratios for weaned piglets are generally lower than NRC (2012) recommendations, with most studies reporting ranges of 25%-35%, though one suggests a higher range of 35%–41%. Data gaps persist for different breeds and weight stages. Current studies on His requirements for weaned piglets are summarized in Table 2.

Factors affecting the requirements of His for piglets

Dietary composition and nutritional level

Ensuring economic efficiency in swine production hinges on productive feed and efficiency. Piglets are often fed nutritionally and energy-dense diets to achieve these goals economically. Maximizing pigs' productive performance requires adequate dietary His. The His supply depends on diet protein levels, composition, intestinal AA digestibility, and free L-His availability. Dietary type and ingredient composition significantly impact His requirements. Current studies prioritize its standardized ileal digestibility (SID) or express it as a ratio of SID Lys levels (Cemin et al. 2018; Cheng et al. 2023; Li et al. 2002; Wessels et al. 2016). Both approaches align with the concept of the ideal dietary AA pattern for piglets, where the requirements for essential AAs are expressed relative to the requirement for the first limiting AA, Lys, such as SID His: Lys (Fuller et al. 1989; Wang and Fuller 1989). Among cereals, barley has the lowest His content (Li et al. 2002). Hence, low-crude protein (CP) diets based on barley need extra His supplementation in the feed.

The protein level and other essential AA content in diets influence the His requirements of piglets. Studies have shown that in pigs fed low-protein diets, AA metabolism undergoes significant changes, with a particular reduction in His. This highlights the importance of dietary components and nutrient levels as key factors influencing the His requirements of piglets (Yin et al. 2017). According to the NRC (2012), animal proteins (e.g., fish meal, blood meal) commonly used in diets for weaned piglets are rich in His (e.g., fish meal contains approximately 2.5%) and have a high bioavailability. Thus, they are suitable for high-protein diets and can meet the His requirements of piglets without additional L-His supplementation. Conversely, plant-based proteins (e.g., soybean meal, corn) contain low levels of His (soybean meal has about 1.2%, and corn has about 0.3%) and have a lower digestibility (SID His of approximately 80%–85%). When formulating low-protein diets, extra L-His must be added to these diets to prevent His deficiency. High-protein diets (>22% CP) based on fish meal or other animal proteins usually cover the His requirement without extra supplementation. Low-protein diets (<18% CP) based on corn-soybean meal must be corrected by adding crystalline L-His. Use the following formula from NRC (2012): Supplemental SID His (%) = Target SID His − Σ (Ingredient His (%) × SID His coefficient). Example for a 7-kg piglet (target SID His = 0.36%): 65% corn: 0.27% His × 0.85 SID = 0.149%; 25% soybean meal: 1.30% His × 0.82 SID = 0.267%; 5% fish meal: 2.45% His × 0.92 SID = 0.113%; Σ SID His supplied = 0.149 + 0.267 + 0.113 = 0.529% → 0.529% × 0.95 = 0.503%; Supplemental L-His needed = 0.36%–0.503% ≈ –0.14% → 0% (diet already adequate). Typical low-protein corn-soy diets require 0.05%–0.08% additional SID His. Formulators should also: keep Leu: Lys ≤ 1.5 to avoid antagonism (INRAE 2018); ensure adequate Met + Cys to prevent compensatory His oxidation; adjust absolute His intake when low-energy diets increase feed intake (CVB 2016).

Antibiotics

Instead of extrapolating from a single antibiotic study, we now report the *only* available piglet dataset together with its limitations (Yu et al. 2017)· showed that a 50 mg kg^{-1} cocktail of quinocetone, tylosin, and kitasamycin increased serum His (+18%) and upregulated jejunal ASCT2 and B^0AT1 mRNA in 21-day-old piglets. However, these effects disappeared when the same basal diet was fed antibiotic-free, and no follow-up work has examined whether withdrawal of antimicrobials changes the *quantitative* His requirement. Consequently, the data cannot yet be used to adjust dietary His recommendations for antibiotic-free production systems, and

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targeted dose–response trials under commercial, antibiotic-free conditions are warranted.

The international ban on antibiotics has spurred research into natural, green, and safe alternatives like antimicrobial peptides. Antimicrobial peptides, as the hottest candidates, are currently widely studied (Kim et al. 2023). However, compared to the well-studied antibiotics, there's a dearth of research on the impact of antibiotic-free feed on piglets' His requirements.

Breed, body weight, and gender of piglets

Differences exist in AA utilization and growth rates of weaned piglets of diverse breeds influenced by genetic background, dietary nutrients, and environment (Ma et al. 2022). Studies comparing Landrace, Yorkshire, and Duroc pigs have found that Duroc pigs have the most enriched ribosomal biogenesis, amino-acid-related enzymes, lysine biosynthesis, and glycine, serine, and threonine metabolism pathways. As these pathways are key for protein synthesis and AA utilization (Ma et al. 2022), it can be inferred that different pig breeds may also influence His requirements.

As piglets grow and their body weight increases, the digestibility of dietary His gradually improves, leading to a decrease in the requirement for dietary His. According to the NRC (2012), the SID His requirement for weaned piglets in the 7–11 kg phase is 0.39%, while for piglets in the 11–25 kg phase, the requirement is 0.35%. Most current studies on AA requirements for piglets haven't differentiated between genders, so there's almost no research on how gender affects His requirements for piglets. INRAE (2018) suggests that gender may influence nutritional requirements but doesn't specify details.

In conclusion, piglet His requirements are influenced by dietary composition, genetic background, and body weight, necessitating tailored feed formulations.

Summary

His contributes to protein synthesis in piglets, slightly boosting their growth and improving dietary AA balance. Along with its derivatives, His also enhances piglet gut health by maintaining GI barrier function, reducing inflammation, promoting digestion and nutrient absorption, and modulating gut microbiota balance. The specific mechanisms of how His regulates the dynamic balance between gut microbiota, immune function, and gut barrier, as well as its interactions with other AAs, require further research. This research is crucial for advancing precise nutrition strategies and improving the efficiency and cost-effectiveness of pig production. Looking ahead, future work should concentrate on defining dynamic His requirements for weaned piglets under antibiotic-free, low-protein diets by integrating breed, sex, and gut-microbiome data, while validating practical dose-response models that can be directly adopted in commercial feed formulation.

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