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Betaine, Taurine and α -Ketoglutarate in Broiler Nutrition: Linking Metabolic Homeostasis, Nutrient Utilization and Growth Efficiency

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ABSTRACT

Modern broiler chickens are selected for rapid growth, high breast-muscle accretion and low feed conversion ratio, a phenotype that requires continuous coordination among intestinal nutrient acquisition, hepatic intermediary metabolism, mitochondrial energy production, redox control and skeletal-muscle protein deposition. Functional nutrients that regulate metabolic pathways rather than merely supply substrate have therefore attracted increasing attention in poultry nutrition. Betaine, taurine and α -ketoglutarate (AKG) are chemically distinct metabolites that enter broiler metabolism at different but interconnected nodes. Betaine (trimethylglycine) is a zwitterionic quaternary ammonium compound that acts as a compatible osmolyte and a methyl donor for betaine-homocysteine methyltransferase, thereby supporting methionine regeneration and S-adenosylmethionine-dependent methyl transfer. Taurine (2-aminoethanesulfonic acid) is a non-proteinogenic sulfur-containing metabolite produced downstream of cysteine; it contributes to bile-acid conjugation, membrane stability, mitochondrial function and antioxidant signaling, and recent broiler work has linked it to Nrf2, AMPK/SIRT1/CPT1, lipid metabolism and tissue-specific responses to methionine replacement. AKG (2-oxoglutarate) is a five-carbon keto-dicarboxylate positioned at the junction of the tricarboxylic-acid cycle and amino-group transfer; recent poultry studies have connected AKG with intestinal morphology, antioxidant defense, Nrf2 signaling, microbiota, growth and UCP2-associated control of intestinal oxidative phosphorylation. This review integrates the three nutrients through a methyl-sulfur-carbon metabolic framework rather than treating them as independent feed additives. We trace each compound from chemical structure and gastrointestinal handling to cellular signaling, organ physiology, nutrient partitioning and growth efficiency, while clearly distinguishing direct broiler evidence from avian support and cross-species mechanistic inference. Particular attention is paid to one-carbon metabolism, transsulfuration, bile-acid physiology, Nrf2-Keap1 redox signaling, AMPK/SIRT1 lipid sensing, UCP2-mediated mitochondrial regulation, gut-liver-muscle communication, nitrogen efficiency and context-dependent dose responses. The synthesis identifies major gaps in head-to-head comparison, combination studies, tissue-resolved metabolomics, phosphoproteomics, mitochondrial phenotyping and stable-isotope tracing. A future precision-nutrition framework is proposed in which betaine, taurine or AKG is selected according to the metabolic node that limits nutrient retention and biological efficiency rather than according to generic feed-additive claims.

Introduction

Genetic selection has produced broilers that grow faster and deposit considerably more breast muscle than historical strains, but this productive phenotype has also increased the requirement for coordinated intestinal, hepatic, mitochondrial and muscular metabolism (Hoque, 2026; Oke, 2024). Rapid-growing birds must acquire large quantities of amino acids, glucose precursors and lipid-derived energy within a short production cycle, and these nutrients must be directed toward lean-tissue accretion rather than being lost through inefficient oxidation, excessive lipogenesis, oxidative damage or inflammatory maintenance costs (Alabi, 2025). Contemporary evidence therefore supports viewing feed efficiency as a systems phenotype rather than a simple ratio of feed intake to weight gain, because the observed FCR reflects digestion, absorptive surface function, hepatic substrate routing, mitochondrial ATP generation, nitrogen retention, endocrine signaling and muscle protein synthesis simultaneously.

Traditional requirement-based poultry nutrition remains indispensable, but the concept of a nutrient requirement does not fully describe compounds whose main contribution is regulatory rather than structural (Alabi, 2025; Uyanga, 2022). Methyl donors can change one-carbon flux, osmolytes can stabilize intracellular water activity, sulfur metabolites can influence bile and redox physiology, and TCA-cycle intermediates can alter carbon–nitrogen exchange and mitochondrial metabolism. These compounds are often called functional nutrients because they may modify the efficiency with which absorbed nutrients are processed even when they make a relatively small direct contribution to dietary energy or protein (Olayiwola, 2025; Kim, 2025). The practical implication is important: a functional nutrient should be judged by the metabolic constraint it corrects, not only by whether it produces a statistically significant increase in body weight under every dietary condition (Wang, 2025; Gupta, 2022).

Betaine, taurine and AKG provide a particularly informative trio for this purpose because their structural chemistry predicts different metabolic entry points. Betaine is a methylated glycine derivative whose permanently charged quaternary ammonium group and carboxylate allow the molecule to function as both a methyl-group donor and a highly compatible osmolyte. Taurine is an amino sulfonic acid rather than a conventional amino carboxylic acid, is not incorporated into proteins, and remains available for bile-acid conjugation, osmoregulation, membrane interactions and redox-related functions (Wang et al., 2026; Ghashghaei et al., 2025). AKG contains two carboxyl groups and a keto group and is positioned simultaneously within the mitochondrial TCA cycle and the transamination network that interconverts AKG and glutamate.

The biological significance of considering these compounds together becomes clearer when metabolic branch points are examined. Betaine-dependent remethylation converts homocysteine back to methionine, whereas homocysteine can alternatively enter transsulfuration to generate cysteine and ultimately taurine. Methionine therefore links betaine and taurine through competition between methyl recycling and sulfur metabolism, while AKG links the same network to cellular energy and nitrogen handling because amino groups from numerous amino acids are transferred to AKG to generate glutamate. The three compounds are therefore not simply unrelated additives with similar performance claims; they represent methyl, sulfur/redox and carbon–nitrogen nodes whose output converges on cellular homeostasis and nutrient partitioning (Wang et al., 2025; Buonaiuto et al., 2025).

Recent broiler research has made this integrated view more timely. Current studies show that betaine can modify one-carbon metabolism under methionine limitation, taurine can support selected downstream sulfur-amino-acid and redox functions, and α -ketoglutarate can influence intestinal mitochondrial and redox regulation (Wang et al., 2025; Yang et al., 2026). These findings justify a pathway-based synthesis rather than a descriptive comparison of supplementation trials; representative study designs and outcomes are summarized later in Table 2.

The objective of this review is therefore to evaluate betaine, taurine and AKG as metabolically active nutrients that influence broiler efficiency through different but interacting mechanisms. The review first establishes their chemistry and gastrointestinal handling, then examines one-carbon metabolism, transsulfuration, bile-acid physiology, mitochondrial carbon–nitrogen metabolism and key nutrient-sensing pathways. It subsequently integrates these mechanisms across the gut–liver–muscle axis, evaluates implications for nutrient retention and growth, explains context-dependent variation among studies, and proposes experiments needed to test the methyl–sulfur–carbon network directly. The central argument is that improved biological efficiency should be interpreted as a consequence of restored metabolic homeostasis and productive nutrient partitioning, rather than as an isolated FCR response. This is a mechanistic critical review rather than a formal systematic review; recent broiler studies through August 2026 are prioritized, while older studies are used only when needed to establish conserved biochemical pathways (Wang et al., 2025; Buonaiuto et al., 2025).

Chemical Identity and Nutritional Relevance

Betaine, taurine and α -ketoglutarate (AKG) are considered here from a nutritional rather than a purely chemical perspective. Their structures are useful because they explain why each compound enters metabolism differently. Betaine, written as

$(\text{CH}_3)_3\text{N}^+-\text{CH}_2-\text{COO}^-$, is a trimethylated glycine derivative whose methyl groups support betaine-homocysteine methyltransferase-mediated remethylation of homocysteine, while its zwitterionic character allows it to act as a compatible osmolyte. In broilers, these properties link betaine with methionine economy, one-carbon metabolism and cellular water balance, particularly when methyl supply or osmotic homeostasis is challenged (Wang et al., 2025; Abd El-Ghany, 2022).

Taurine, written as $\text{H}_3\text{N}^+-\text{CH}_2-\text{CH}_2-\text{SO}_3^-$, is an amino sulfonate that remains largely free in tissues rather than being incorporated into protein. This distinction is central to its nutritional role: taurine can support bile-acid conjugation, membrane and mitochondrial stability, and redox regulation, but it cannot replace methionine needed for protein synthesis or S-adenosylmethionine formation. Recent broiler studies therefore support viewing taurine as a regulator of downstream sulfur-amino-acid physiology rather than simply as an antioxidant feed additive (Ghashghaei et al., 2025; Mierzejewska et al., 2024).

AKG, written as $^- \text{OOC}-\text{CO}-\text{CH}_2-\text{CH}_2-\text{COO}^-$, is a five-carbon organic acid positioned within the tricarboxylic-acid cycle and reversibly linked with glutamate through transamination. Its nutritional significance in broilers lies in connecting mitochondrial energy metabolism with amino-acid nitrogen handling, intestinal metabolism and redox control. Recent evidence involving intestinal UCP2 further suggests that AKG may influence how mitochondrial oxidative phosphorylation is balanced against reactive oxygen species generation, making it a useful metabolic link between carbon utilization and cellular homeostasis rather than a conventional energy supplement (Yang et al., 2026; Gupta et al., 2024).

Table 1. Structural and physiological comparison of the three metabolic nutrients

Compound	Primary nutritional context	Principal tissue focus	Most informative biomarker(s)	Current evidence status
Betaine	Methyl insufficiency or osmotic/intestinal challenge	Liver and intestine	SAM/SAH, homocysteine, BHMT; nutrient digestibility	Established for one-carbon metabolism; growth effects are context dependent
Taurine	Sulfur-amino-acid, bile/lipid or oxidative challenge	Liver, intestine and muscle	Taurine/bile-acid profile; Nrf2 and lipid-regulatory markers	Moderate-to-strong for redox and lipid pathways; bile signaling remains emerging
α -Ketoglutarate	Carbon-nitrogen imbalance or intestinal mitochondrial stress	Intestine and mitochondria; liver	AKG/glutamate/succinate; UCP2 and mitochondrial redox markers	Emerging but rapidly expanding, particularly for intestinal mitochondrial regulation

Avian Gastrointestinal Physiology and First-Pass Metabolism

The physiological effect of a functional nutrient is determined not only by its chemistry but also by where it is released, absorbed and first metabolized. Broiler feed passes through the crop, proventriculus and gizzard before reaching the duodenum, jejunum and ileum, where most enzymatic digestion and nutrient absorption occur; the paired ceca provide an additional site for microbial metabolism of material escaping the small intestine. Portal blood delivers absorbed solutes directly to the liver, making hepatic first-pass metabolism central to the fate of methyl donors, amino acids and organic acids. The avian liver also synthesizes and secretes bile, thereby creating an anatomical connection between hepatic lipid handling and intestinal digestion (Wang et al., 2025; Buonaiuto et al., 2025).

Betaine is sufficiently water soluble to be absorbed in the small intestine and transported to tissues, with the liver acting as a major site of BHMT-dependent metabolism. A portion of intracellular betaine can remain available for osmotic regulation, so absorption does not imply immediate methyl donation. Taurine is absorbed as a small polar solute and participates in enterohepatic physiology through conjugated bile acids; hepatic taurine conjugation increases bile-acid hydrophilicity and supports lipid emulsification and micelle formation in the intestinal lumen (Wang et al., 2026; Ghashghaei et al., 2025). AKG can be utilized locally by metabolically active intestinal epithelial cells, converted into glutamate-related metabolites or transported through portal blood, which explains why dietary, in-ovo, gavage and hindgut-targeted routes can produce different physiological effects (Gupta, 2024; Gupta, 2022).

Site of delivery is especially important for AKG because enterocytes have high ATP demand and active mitochondrial metabolism (Gupta, 2024; Gupta, 2022). The 2026 hindgut-targeted AKG study is mechanistically notable because it did not merely report an increase in growth; it linked local AKG exposure to UCP2-associated changes in intestinal oxidative phosphorylation and redox balance (Yang, 2026). This finding supports a broader principle: the metabolic effect of a compound may depend on the tissue that encounters it before systemic dilution, and formulation strategies can therefore alter mechanism as well as dose.

Betaine: One-Carbon Metabolism, Osmoregulation and Nutrient Partitioning

BHMT-dependent remethylation and the methionine cycle

Betaine's defining biochemical reaction is catalyzed by BHMT, which transfers a methyl group from betaine to homocysteine to generate methionine and dimethylglycine. Methionine is then activated by methionine adenosyltransferase to form SAM, and SAM-dependent methyltransferases transfer methyl groups to numerous acceptors, producing SAH. SAH is subsequently converted toward homocysteine, closing the cycle. Because SAM is a methyl donor and SAH inhibits many methyltransferases, the relative abundance of these metabolites is often interpreted as a marker of methylation potential, although direct epigenetic effects require separate measurement of DNA, RNA or protein methylation (Wang et al., 2025; Buonaiuto et al., 2025). Recent broiler studies directly support a betaine effect on one-carbon metabolism under methionine limitation. The main mechanistic implication is that changes in methyl-cycle status can occur without a proportional growth response, so biochemical correction should be interpreted separately from final performance. This distinction is important when evaluating betaine as a metabolic regulator rather than only as a growth-promoting additive. The methionine-sparing concept must nevertheless be defined precisely. Betaine can spare methionine that would otherwise be consumed for methyl donation by facilitating homocysteine remethylation, but it cannot replace methionine incorporated into body proteins and cannot replicate all choline functions in phospholipid membranes (Alabi, 2025). The magnitude of 'sparing' therefore depends on whether methyl-group availability, structural methionine or choline-derived phospholipid synthesis is the limiting process. This explains why betaine responses differ among low-methionine, low-choline, thermally challenged and nutritionally adequate diets (Wang, 2025; Jaman, 2023).

Osmoregulation and intestinal cell stability

Cells exposed to osmotic stress must preserve volume and hydration while avoiding excessive accumulation of inorganic ions that destabilize proteins. Compatible osmolytes such as betaine can accumulate at relatively high intracellular concentrations without interfering strongly with enzymatic reactions, thereby stabilizing the hydration shell surrounding proteins and membranes. In the intestine, this property is relevant to transporter function, epithelial barrier integrity and enzyme activity; in muscle and other tissues it can support cell-volume homeostasis during thermal or water-balance challenges (Jaman, 2023). Evidence from coccidial challenge illustrates why this property can affect nutrient utilization. Recent challenge studies indicate that betaine can improve nutrient digestibility and intestinal resilience when gut function is compromised. More recent broiler experiments have also associated betaine with improved nutrient digestibility and intestinal outcomes under coccidial or production stress (Suliman, 2023; Won, 2023). The mechanistic interpretation should remain cautious: improved digestibility may reflect osmoregulation, epithelial preservation, altered digestive enzyme activity or indirect changes in feed intake, and most studies do not quantify all of these processes simultaneously (Hafeez et al., 2026; Suliman et al., 2023).

Hepatic lipid metabolism and phospholipid economy

One-carbon metabolism intersects lipid metabolism because methyl groups are required for pathways that influence phosphatidylcholine synthesis and lipoprotein handling, while hepatic energy sensors regulate whether carbon is directed toward oxidation or storage. Betaine has been associated with altered hepatic lipid metabolism, carcass fat and transcriptional networks in poultry, including changes under cyclic heat stress (Kim, 2023; Suliman, 2023). The 2023 liver-transcriptome study showed that dietary betaine modified networks related to energy, amino-acid and immune metabolism in heat-stressed broilers, supporting a broad metabolic effect rather than a single endpoint. Transcriptomic changes, however, should not be equated with metabolic flux. A decrease in SREBP-related lipogenic transcription can be biologically different from increased fatty-acid oxidation, improved VLDL export or altered dietary fat absorption, even though each mechanism can lower hepatic lipid accumulation (Algothmi et al., 2024; Kouvedaki et al., 2024). For a rigorous broiler interpretation, betaine studies should ideally combine one-carbon metabolites, phosphatidylcholine species, hepatic triglycerides, acylcarnitines, β -oxidation markers and tissue-level lipid deposition rather than relying on serum triglycerides alone.

Context-dependent betaine responses

Betaine is one of the best examples of context-dependent efficacy in poultry nutrition. Studies report benefits under methionine restriction, coccidial challenge, heat stress and selected practical diets, whereas other experiments show biochemical or antioxidant effects without substantial growth improvement (Wang, 2025; Kim, 2023). This pattern is not evidence that the molecule has an inconsistent mechanism; it suggests that the mechanism becomes performance-limiting only under particular nutritional or physiological conditions. Once methyl-group availability and osmotic stability are adequate, increasing betaine does not necessarily increase productive nutrient flux (Abd, 2022). Accordingly, the most informative betaine studies are those that measure the state of the target pathway before and after supplementation. Basal dietary methionine, choline, crude protein, electrolyte balance, water availability, intestinal challenge and age should be treated as mechanistic moderators rather than merely as experimental details (Alabi, 2025). This perspective can also explain non-linear dose responses, including the finding

that 1,500 mg/kg produced a more favorable methyl-metabolic response than the higher dose in the 2025 low-methionine experiment.

Taurine: Transsulfuration, Bile Physiology, Redox Signaling and Lipid Partitioning

Connection with sulfur-amino-acid metabolism

Taurine is metabolically connected to methionine through transsulfuration. Homocysteine generated from the methionine cycle can be condensed with serine to form cystathionine and subsequently cysteine; cysteine is then oxidized through cysteine dioxygenase and cysteine-sulfinate decarboxylase toward hypotaurine and taurine (Wang et al., 2026; Ghashghaei et al., 2025). This branch competes conceptually with remethylation because the same homocysteine pool can be recycled to methionine or committed to sulfur-metabolite synthesis. Thus, betaine and taurine are connected at a true biochemical branch point rather than only because both are described as stress-protective nutrients. The distinction also clarifies why taurine cannot be regarded as a full methionine substitute. Methionine contributes to body protein, initiates translation and supplies SAM, whereas taurine contributes to terminal sulfur physiology but cannot be re-incorporated into the methionine cycle. Ghashghaei et al. tested partial replacement of crystalline methionine with taurine in broilers and found tissue-specific antioxidant responses that were not accompanied by a simple universal improvement in growth (Ghashghaei, 2025). Such findings are mechanistically informative because they reveal which consequences of sulfur-amino-acid nutrition can be supported by taurine and which still require methionine itself.

Bile-acid conjugation and intestinal lipid acquisition

Bile acids are synthesized from cholesterol in the liver and are conjugated before secretion into bile; taurine conjugation increases the hydrophilicity and physicochemical behavior of the bile-acid pool (Wang et al., 2026; Ghashghaei et al., 2025). Once released into the small intestine, bile acids facilitate emulsification and formation of mixed micelles containing fatty acids, monoacylglycerols, cholesterol and fat-soluble vitamins (Bao et al., 2025; Yu et al., 2025). These micelles increase the effective aqueous solubility of hydrophobic digestion products and enhance their movement across the unstirred water layer toward the enterocyte surface. This physiology is particularly relevant to broilers because dietary fats are commonly used to increase energy density and because immature birds have limited digestive capacity relative to older birds. Taurine supplementation has been examined alone and in combination with bile acids, with studies reporting changes in fat digestibility, lipid metabolism and growth-related outcomes. The key mechanistic point is that a taurine effect on growth can arise before any intracellular antioxidant signaling occurs: an altered bile-acid pool can change the quantity and form of lipid-derived energy entering enterocytes (Mierzejewska et al., 2024). Bile acids also function as signaling molecules through receptors such as FXR and TGR5 in mammalian systems, linking the bile-acid pool to hepatic lipid, glucose and energy metabolism. Avian bile-acid signaling is increasingly investigated, but direct evidence that dietary taurine changes broiler performance specifically through FXR or TGR5 remains incomplete. A rigorous review should therefore distinguish taurine's established biochemical role in conjugation from the more emerging hypothesis that taurine-induced changes in bile-acid species subsequently alter receptor signaling.

Nrf2-Keap1 antioxidant signaling

Nrf2 is a central transcriptional regulator of cellular antioxidant and cytoprotective responses (Algothmi et al., 2024; Kouvedaki et al., 2024). Under basal conditions, Keap1 promotes Nrf2 degradation; oxidative or electrophilic changes reduce this restraint, allowing Nrf2 to accumulate, translocate to the nucleus and regulate antioxidant-response-element-associated genes, including heme oxygenase-1 and glutathione-related enzymes. In poultry, Nrf2 is repeatedly implicated in nutritional protection against oxidative and heat-related stress, making it one of the best-supported molecular bridges between redox biology and feed intervention (Oke, 2024; Mierzejewska, 2024). Broiler evidence supports taurine-sensitive redox regulation, but the mechanistic value lies in the coordinated change across lipid peroxidation, antioxidant signaling and tissue function rather than in any single marker. Exact study designs and dose-specific outcomes are summarized in Table 2. These results should not be simplified into the statement that taurine is a 'direct antioxidant'. Taurine may affect oxidant production, membrane susceptibility, mitochondrial function and transcriptional antioxidant defenses simultaneously (Wang et al., 2026; Ghashghaei et al., 2025). A reduction in MDA can therefore reflect lower generation of lipid radicals, better enzymatic removal of oxidants or preservation of mitochondrial electron transport, and these routes have different implications for energetic efficiency. The strongest future experiments should measure mitochondrial respiration and ROS generation alongside Nrf2-pathway activation rather than relying on antioxidant enzyme activity alone.

AMPK-SIRT1-CPT1 regulation of lipid metabolism

AMPK senses cellular energy status and generally promotes ATP-generating pathways while restraining energy-consuming biosynthesis (Algothmi et al., 2024; Kouvedaki et al., 2024). SIRT1 is an NAD⁺-dependent deacetylase that interacts with energy-sensitive transcriptional networks, CPT1 controls mitochondrial entry of long-chain fatty acids for β -oxidation, and

SREBP-1 promotes lipogenic transcription. Together these regulators describe a shift between lipid storage and lipid oxidation, a distinction that is directly relevant to abdominal fat deposition, hepatic steatosis and feed-energy efficiency in broilers. Recent taurine studies support coordinated effects on redox control, lipid handling and cellular stress responses, although direct flux-level confirmation remains limited. Heat-stress studies similarly link taurine with altered lipid accumulation and carcass characteristics. These findings are consistent with a shift away from lipogenesis and toward fatty-acid oxidation, but mRNA expression alone does not establish the magnitude of lipid flux. Confirmation requires measures such as acylcarnitine profiles, β -oxidation rates, respiratory quotient or stable-isotope tracing.

Mitochondrial and skeletal-muscle effects

Broiler skeletal muscle has unusually high demands for ATP, protein synthesis and redox control because breast-muscle accretion is a major component of the selected phenotype (Hoque, 2026; Hubert, 2022). Mitochondrial dysfunction increases electron leakage, oxidative damage and the energetic cost of repair, potentially reducing the fraction of dietary nutrients retained as muscle (Macelline, 2025). Taurine-associated mitochondrial protection reported under chronic heat stress is therefore relevant to growth efficiency even when heat stress itself is not the central topic. Muscle should also be treated as a tissue-specific target rather than merely the source of meat-quality measurements. Taurine can accumulate intracellularly, influence membrane and osmotic properties and interact with redox signaling; consequently, changes in pH decline, lipid oxidation, shear force or water-holding capacity can be interpreted as outcomes of muscle cellular physiology rather than isolated postmortem traits (Mierzejewska, 2024; Xing, 2021). The recent methionine-replacement work further indicates that liver, breast and thigh tissues can respond differently to taurine, arguing against the assumption that a single serum antioxidant marker adequately represents whole-body taurine biology (Ghashghaei, 2025).

α -Ketoglutarate: Carbon–Nitrogen Coupling, Intestinal Energetics and Mitochondrial Redox Control

TCA-cycle position and transamination

AKG is generated from isocitrate by isocitrate dehydrogenase and converted to succinyl-CoA by the AKG dehydrogenase complex, reactions that couple carbon oxidation to the production of reducing equivalents for oxidative phosphorylation. The TCA cycle is not simply an energy-producing circle; intermediates are continuously withdrawn for biosynthesis and replenished by anaplerotic reactions. AKG therefore participates in the balance between energy generation and biosynthetic demand, a balance that is particularly active in tissues supporting rapid growth (Yang et al., 2026; Gupta et al., 2024). The same molecule accepts amino groups in transamination reactions to generate glutamate. Glutamate can be converted to glutamine, donate nitrogen for synthesis of other amino acids or undergo oxidative deamination to regenerate AKG. This network makes AKG a biochemical bridge between dietary amino-acid nitrogen and carbon oxidation. When amino acids are catabolized rather than retained in muscle, their nitrogen must be processed for excretion while the remaining carbon skeleton enters energy or lipid metabolism; AKG participates directly in that routing (Alabi, 2025).

Intestinal metabolism and epithelial function

Broiler AKG research now spans developmental, dietary and targeted-delivery models. These models are most useful when interpreted by route and tissue exposure rather than pooled as equivalent supplementation studies. Exact experimental designs and outcomes are summarized in Table 2. Enterocytes are metabolically active cells that continuously support ion pumping, nutrient transport, tight-junction maintenance and epithelial turnover. AKG can provide carbon for mitochondrial metabolism and can also enter glutamate-related pathways within the intestine. Dietary AKG studies reporting improved villus morphology, intestinal health or microbiota therefore have a plausible energetic basis, but morphology alone does not demonstrate improved metabolic efficiency. To establish mechanism, intestinal ATP production, oxygen consumption, redox state and transporter function need to be measured alongside histology (Kherde, 2024; Talpur, 2022).

UCP2 and oxidative phosphorylation

UCP2 is an inner-mitochondrial-membrane protein associated with regulation of proton conductance, mitochondrial membrane potential and ROS production (Algothmi et al., 2024; Kouvedaki et al., 2024). Strong coupling of the proton gradient to ATP synthesis improves ATP yield per substrate molecule, but very high membrane potential can increase conditions favoring electron leakage and superoxide generation. Mild uncoupling can lower mitochondrial ROS at the cost of some proton motive force, making the biological effect dependent on the balance between energy efficiency and oxidative damage. Recent targeted-delivery work links AKG with intestinal UCP2 and redox control. This finding is important because it shifts the interpretation of AKG from a generic antioxidant effect toward a defined mitochondrial mechanism.

Nrf2-mediated redox responses and developmental effects

In-ovo AKG studies have reported improvements in plasma antioxidant balance and hepatic Nrf2-related expression at selected doses (Gupta, 2024; Gupta, 2022). Under cyclic heat stress, AKG reduced rectal temperature and improved antioxidant gene expression but did not completely prevent heat-associated growth depression. This pattern resembles the betaine example in which a metabolic pathway can improve without an immediate full correction of growth, reinforcing the value of separating molecular resilience from production phenotype. The developmental route of administration is also important. In-ovo exposure can alter embryonic tissue maturation before the gastrointestinal tract is exposed to post-hatch feed, whereas neonatal gavage delivers AKG directly to an immature intestine. Dietary supplementation later in life addresses a different physiological system in which gut microbiota, digestive enzymes and metabolic tissues are more developed (Kherde, 2024; Talpur, 2022). Future synthesis should therefore avoid pooling these studies as simple 'AKG supplementation' and instead interpret them by developmental stage and site of exposure.

AKG-dependent dioxygenases: an emerging hypothesis

AKG is also a required co-substrate for a large family of dioxygenases, including enzymes involved in HIF regulation and DNA or histone demethylation. This chemistry creates an attractive connection between nutrient metabolism, oxygen sensing and epigenetic regulation. However, most direct evidence for these mechanisms comes from mammalian or cellular systems rather than broiler feeding experiments. In a poultry review, these mechanisms should therefore be presented as biologically plausible future directions rather than as established explanations for growth or gut responses (Wang et al., 2025; Buonaio et al., 2025). Testing the hypothesis would require measurement of tissue AKG and succinate, HIF hydroxylation or target genes, and locus-specific or genome-wide methylation endpoints in the same birds. Without such data, a change in AKG availability cannot be assumed to produce an epigenetic effect. This distinction exemplifies the critical approach required throughout the review: conserved biochemistry can identify a candidate mechanism, but only avian experiments can establish its production relevance.

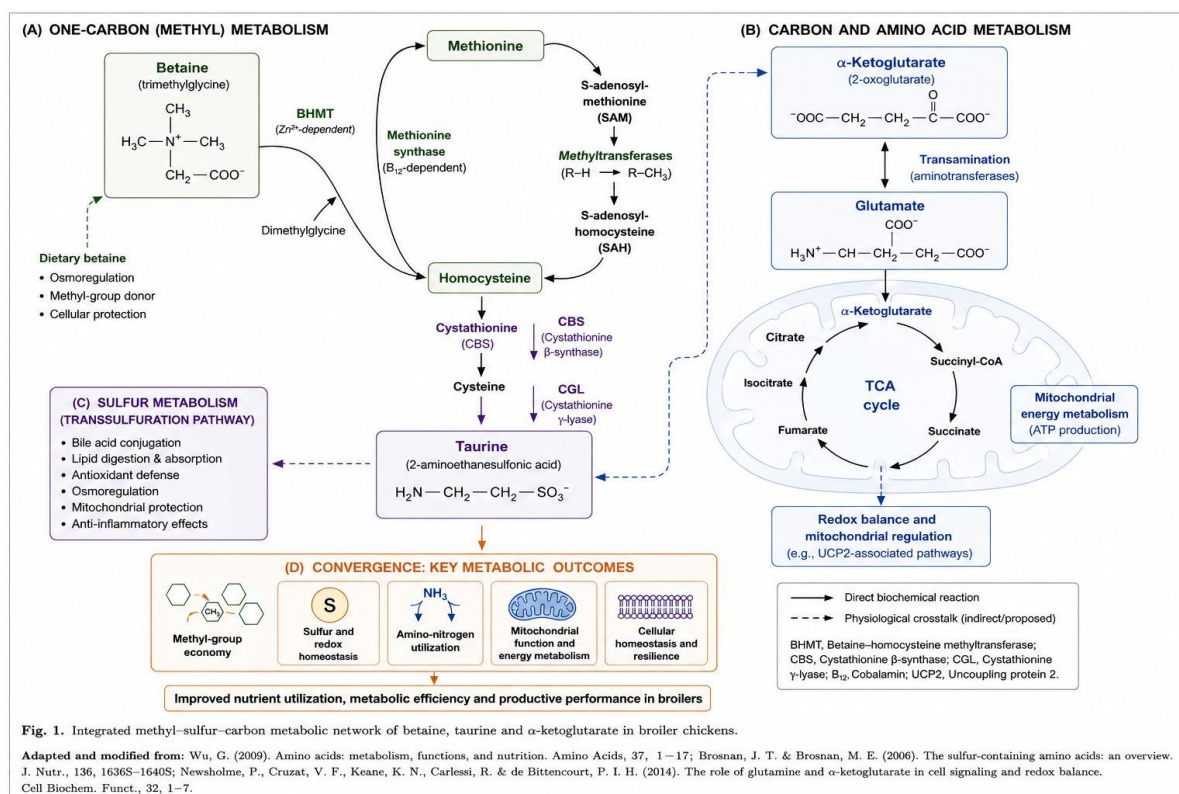


Fig. 1. Integrated methyl-sulfur-carbon metabolic network of betaine, taurine and α-ketoglutarate in broiler chickens.

Adapted and modified from: Wu, G. (2009). Amino acids: metabolism, functions, and nutrition. *Amino Acids*, 37, 1–17; Brosnan, J. T. & Brosnan, M. E. (2006). The sulfur-containing amino acids: an overview. *J. Nutr.*, 136, 1636S–1640S; Newsholme, P., Cruzat, V. F., Keane, K. N., Carlessi, R. & de Bittencourt, P. I. H. (2014). The role of glutamine and α-ketoglutarate in cell signaling and redox balance. *Cell Biochem. Funct.*, 32, 1–7.

Figure 1. Integrated methyl-sulfur-carbon metabolic network of betaine, taurine and α-ketoglutarate in broiler chickens.

The figure illustrates the interconnected metabolic routes through which betaine regulates one-carbon metabolism and methionine regeneration, taurine contributes to sulfur metabolism, bile acid physiology and redox regulation, while α-

ketoglutarate links carbon–nitrogen metabolism with mitochondrial energy production. The convergence of these pathways supports nutrient partitioning, metabolic homeostasis and productive efficiency.

Metabolic Crosstalk: The Methyl–Sulfur–Carbon Network

The strongest rationale for combining betaine, taurine and AKG is that the three nutrients regulate different sections of a connected metabolic system. Betaine modifies homocysteine remethylation and methionine/SAM economy. Taurine lies downstream of the competing transsulfuration route and contributes to bile, membrane and redox physiology (Wang et al., 2026; Ghashghaei et al., 2025). AKG regulates the carbon and nitrogen economy needed to oxidize nutrients and redistribute amino groups. The three nodes therefore converge on the same fundamental question: whether absorbed carbon and nitrogen are retained productively or consumed by maintenance, stress responses and inefficient metabolism.

Betaine–taurine crosstalk occurs most clearly at homocysteine. Increasing BHMT-dependent remethylation can alter the amount of homocysteine available for transsulfuration, whereas exogenous taurine could theoretically reduce endogenous demand for terminal taurine synthesis. This does not imply that betaine necessarily decreases taurine synthesis or that taurine necessarily spares methionine in all diets; the direction of flux depends on dietary methionine, cysteine, choline, methyl demand and tissue requirements (Alabi, 2025). Direct broiler flux studies are currently lacking, which makes the interaction a high-priority hypothesis rather than a settled fact.

Betaine–AKG crosstalk is more systems-level. SAM formation and methyl transfer require ATP and interact with hepatic phospholipid and amino-acid metabolism, whereas AKG participates in mitochondrial ATP generation and transamination. A bird with adequate amino-acid supply but impaired mitochondrial carbon handling may not retain those amino acids efficiently, while a bird with adequate energy but inadequate methyl recycling may divert methionine away from structural protein synthesis (Alabi, 2025; Wang, 2025). Factorial betaine × AKG studies under reduced-protein or marginal-methionine diets would therefore be biologically more informative than testing each compound only in a nutritionally complete control diet.

Taurine–AKG convergence is most evident at mitochondria and redox regulation. Taurine is associated with Nrf2 activation, membrane preservation and protection against mitochondrial oxidative injury, whereas AKG is associated with Nrf2 responses and UCP2-mediated modulation of oxidative phosphorylation. The two nutrients may therefore act at different points in the same oxidative cascade: taurine may reduce propagation of oxidative damage and support antioxidant defenses, while AKG may alter substrate flow and mitochondrial ROS generation. Whether these actions are additive, synergistic or redundant in broilers is unknown (Wang et al., 2025; Buonaiuto et al., 2025).

The proposed methyl–sulfur–carbon network is a mechanistic framework, not an argument that all three nutrients should always be supplemented together. Betaine represents methyl economy, taurine represents sulfur/bile/redox economy and AKG represents carbon–nitrogen/energy economy. Their common output is metabolic homeostasis across intestine, liver and muscle. Supplementation should improve growth only when the targeted node constrains productive nutrient partitioning, a principle that explains why biochemical responses can be stronger and more reproducible than growth responses (Wang et al., 2025; Buonaiuto et al., 2025).

Molecular Signaling Nodes Shared Across the Network

Nrf2–Keap1 and redox defense

Nrf2-mediated antioxidant defense is relevant to production because oxidative damage has an energetic and nutrient cost: oxidized lipids and proteins must be repaired or replaced, mitochondrial dysfunction reduces ATP efficiency, and inflammatory signaling can redirect amino acids away from growth (Macelline, 2025; Oke, 2024). Taurine has the strongest direct broiler evidence for Nrf2-associated protection, whereas AKG has growing evidence from in-ovo and intestinal studies. Betaine can also reduce oxidative damage in selected broiler models, although its best-established primary mechanism remains methyl donation and osmoprotection. The three compounds should not be presented as equivalent Nrf2 activators because the strength and primacy of this mechanism differ among them. For taurine, Nrf2 is part of a recurring direct experimental signature. For AKG, Nrf2 and UCP2 are emerging mechanistic nodes (Yang, 2026; Gupta, 2024). For betaine, redox improvements may arise secondarily from improved methyl metabolism, membrane hydration or reduced metabolic stress.

AMPK–SIRT1 and energy-sensitive lipid regulation

AMPK and SIRT1 form an energy-sensitive network that can increase fatty-acid oxidation, improve mitochondrial adaptation and restrain anabolic lipid synthesis when cellular energy is limited (Algothmi et al., 2024; Kouvedaki et al., 2024). Taurine has direct broiler evidence involving increased AMPK α , SIRT1 and CPT1 expression with reduced SREBP-1 at an effective dose. Betaine transcriptomic and lipid-metabolic studies support possible interaction with similar hepatic pathways, although direct phosphorylation-level validation is less consistent (Kim, 2023; Abd, 2022). AKG may influence AMPK indirectly through TCA-

cycle energy state, but a specific AKG-AMPK mechanism should not be claimed without direct avian evidence. From a nutritional perspective, the value of this pathway is that it links cellular energy status with the decision to oxidize or store absorbed lipid. Accordingly, AMPK/SIRT1-related responses should be interpreted together with CPT1, lipogenic markers, hepatic lipid deposition and, where possible, direct measures of fatty-acid oxidation rather than as isolated transcriptional changes.

mTOR and muscle protein accretion

mTORC1 integrates amino-acid availability, cellular energy and growth-factor signals to control translational initiation and protein synthesis (Algothmi et al., 2024; Kouvedaki et al., 2024). This pathway is conceptually central to broiler growth because improved digestibility or metabolic health cannot increase breast-muscle deposition unless amino acids ultimately enter protein synthesis. However, direct studies linking dietary betaine, taurine or AKG to mTOR signaling in broiler muscle are much less developed than studies of redox and lipid metabolism. The absence of direct evidence is itself important: future supplementation experiments should measure muscle mTORC1 phosphorylation, downstream translation markers and fractional protein-synthesis rate rather than assuming that a higher breast yield demonstrates mTOR activation.

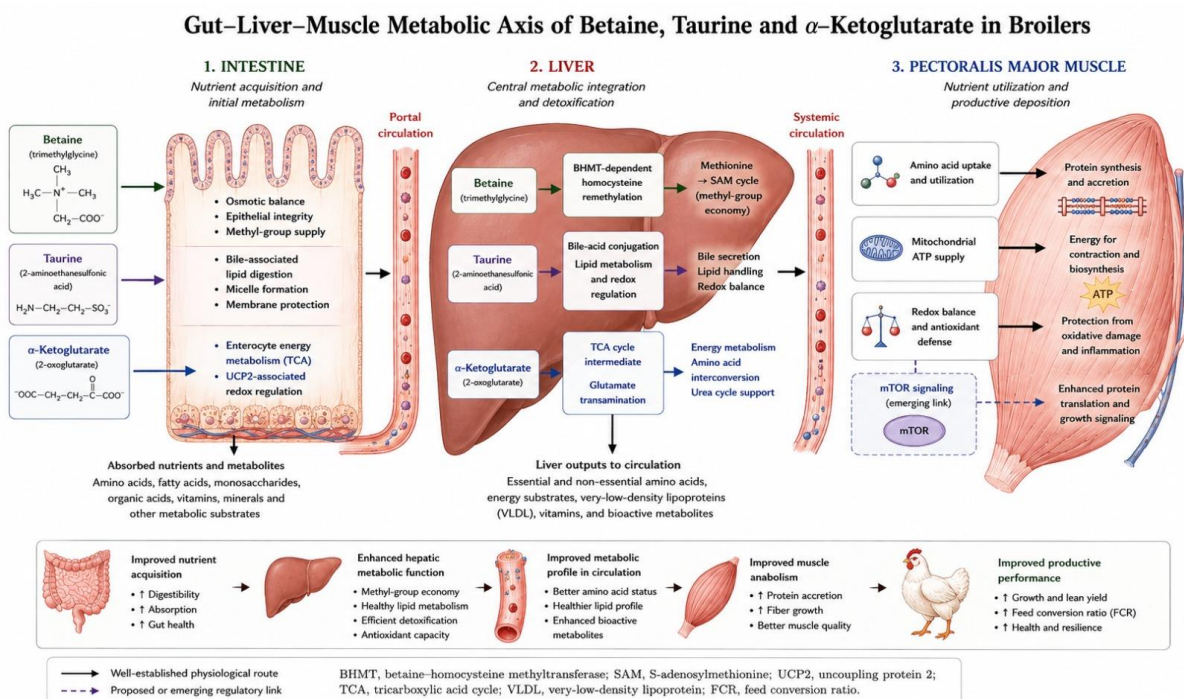


Figure 2. Gut–liver–muscle metabolic axis illustrating the physiological roles of betaine, taurine and α -ketoglutarate in broilers.

The schematic represents the interaction among intestinal nutrient acquisition, hepatic metabolic integration and skeletal muscle nutrient utilization. Betaine, taurine and α -ketoglutarate influence intestinal integrity, hepatic methyl and lipid metabolism, mitochondrial function, amino acid utilization and muscle protein deposition, collectively contributing to improved growth efficiency and metabolic resilience.

The Gut–Liver–Muscle Axis: Translating Mechanism into Nutrient Partitioning

Intestine: nutrient acquisition and maintenance cost

The intestine determines how much dietary nutrient enters metabolism, but absorptive capacity has an energetic cost because enterocytes must maintain ion gradients, tight junctions, transporter turnover and epithelial renewal. Betaine can stabilize epithelial hydration and may improve digestibility under challenge (Jaman, 2023; Suliman, 2023). Taurine can influence lipid acquisition through bile physiology and support membrane/redox stability. AKG can act as an intestinal carbon substrate and may alter mitochondrial redox control through UCP2 (Kherde, 2024; Talpur, 2022). These are distinct mechanisms that converge on a common outcome: the amount of absorbed nutrient obtained per unit of intestinal maintenance cost. Histological improvements should therefore be interpreted carefully. Greater villus height or villus:crypt ratio can suggest expanded absorptive surface, but it does not directly quantify nutrient transport, ATP cost or epithelial oxygen consumption. High-quality future work should combine histology with transporter abundance, barrier permeability, mitochondrial respiration and

nutrient flux. This is especially relevant to AKG, for which gut morphology and redox effects are often reported together but the causal sequence remains incompletely resolved.

Liver: metabolic integration

The liver is the central organ in the proposed network because it receives portal nutrients and contains the pathways needed to integrate them. Betaine enters BHMT-dependent remethylation; taurine participates in bile-acid conjugation and lipid/redox physiology; AKG participates in the TCA cycle and amino-group transfer. The liver simultaneously decides whether carbon is oxidized, stored as lipid, exported in lipoproteins or used for biosynthesis, while also controlling the fate of amino-acid nitrogen. A change in hepatic metabolism can therefore alter carcass composition even when intestinal digestibility is unchanged (Wang et al., 2025; Buonaiuto et al., 2025). A truly integrative experiment should measure these pathways in the same liver rather than comparing unrelated studies. The most informative targeted metabolite panel would include betaine, dimethylglycine, methionine, SAM, SAH, homocysteine, cysteine, taurine, major conjugated bile acids, AKG, glutamate, glutamine, succinate and selected acylcarnitines. These data should be paired with BHMT, AMPK/SIRT1/CPT1, SREBP-1, Nrf2 and mitochondrial functional measurements. Such a design would determine whether the three nutrients converge metabolically or merely produce parallel phenotypes.

Skeletal muscle: productive nutrient retention

Skeletal muscle, especially pectoralis major, is the major productive sink for amino acids in modern broilers (Hoque, 2026; Hubert, 2022). Increasing body weight is not equivalent to increasing metabolically efficient muscle deposition because weight gain can include gut contents, water and adipose tissue. Productive nutrient partitioning requires absorbed amino acids to reach muscle, enter intracellular pools and be incorporated into protein using ATP-dependent translation (Alabi, 2025). Betaine may contribute by preserving methionine methyl economy and modifying lipid partitioning; taurine may protect muscle membranes and mitochondria and reduce oxidative damage; AKG may influence amino-acid carbon skeletons and energy supply (Wang, 2025; Kim, 2023). These mechanisms should be tested using breast-muscle protein synthesis, muscle amino-acid uptake, mitochondrial respiration, fiber hypertrophy and intramuscular lipid rather than relying solely on final breast weight. Stable-isotope incorporation into muscle protein would provide the clearest measure of whether supplementation truly redirects dietary nitrogen toward productive tissue.

From Metabolic Homeostasis to Nutrient Utilization

Amino-acid and nitrogen efficiency

Low-protein feeding has renewed interest in the metabolic cost of amino-acid catabolism because absorbed amino acids that are not retained in protein must be deaminated, their nitrogen excreted and their carbon skeletons oxidized or converted into lipid (Alabi, 2025; Macelline, 2025). Betaine may preserve methionine for structural use when methyl demand is limiting, taurine may modify sulfur-amino-acid partitioning, and AKG directly accepts amino groups to form glutamate. These mechanisms are complementary and suggest that the three nutrients could be especially informative in reduced-protein diets in which nitrogen economy is a major performance constraint. Apparent ileal digestibility alone cannot establish nitrogen efficiency. A diet can increase amino-acid absorption while still causing substantial post-absorptive catabolism (Liu et al., 2021). Mechanistic trials should therefore combine standardized ileal amino-acid digestibility with plasma amino-acid kinetics, uric-acid output, whole-body nitrogen balance and isotope-based muscle incorporation. Such measurements would reveal whether improved FCR reflects better digestion, lower catabolic loss or greater anabolic retention.

Lipid digestion, oxidation and carcass partitioning

Taurine has the most direct structural connection to lipid digestion because of bile-acid conjugation (Wang et al., 2026; Ghashghaei et al., 2025). Betaine can influence hepatic lipid handling through methyl and energy-sensitive pathways (Kim, 2023; Abd, 2022), while AKG can influence lipid metabolism indirectly through TCA flux and mitochondrial redox state. Lower abdominal fat or hepatic triglyceride therefore cannot be assigned to a single mechanism without measuring fat digestibility, lipogenesis, oxidation and export. The most informative phenotype is the fate of absorbed fatty acids. If taurine improves micellar lipid absorption but the additional energy is stored as fat, FCR may improve without a desirable carcass change. If betaine or AKG shifts hepatic metabolism toward oxidation or away from lipogenesis, the same absorbed energy may be used differently. Integrating bile-acid profiling, digestibility, hepatic lipidomics, acylcarnitines and carcass composition is therefore necessary to distinguish digestive efficiency from metabolic partitioning (Wang et al., 2025; Buonaiuto et al., 2025).

Metabolic resilience across nutritional and environmental challenges

Heat stress remains a useful mechanistic model because it simultaneously disrupts feed intake, water balance, gut permeability, mitochondrial function, redox status and endocrine signaling (Olayiwola, 2025; Kim, 2025). Betaine, taurine and AKG have

each been investigated under thermal challenge, but restricting their relevance to heat stress would overlook their roles in methionine economy, bile physiology, nitrogen metabolism and intestinal energetics (Wang, 2025; Ghashghaei, 2025). The more general concept is metabolic resilience: the capacity to maintain coordinated nutrient processing when one or more physiological systems are challenged. Other useful challenge models include methionine/choline limitation for the methyl node, reduced-protein diets for carbon-nitrogen efficiency, coccidiosis or intestinal inflammation for gut maintenance, and high-energy or lipid-rich diets for hepatic partitioning. Comparing responses across these challenges would help identify whether a nutrient has a broad homeostatic action or a narrow effect that becomes visible only under a specific limitation.

Table 2. Representative mechanistic broiler studies of betaine, taurine and α -ketoglutarate

Compound	Representative study and model	Exposure / context	Mechanistic endpoints	Main finding	Critical interpretation
Betaine	Wang et al. (2025); 960 male broilers, 1-21 d	Methionine-deficient diet + 1,500 or 3,000 mg/kg	SAM, SAH, total homocysteine and hepatic one-carbon enzymes	1,500 mg/kg produced clear methyl-metabolic stabilization despite limited growth response	Direct evidence that betaine can correct one-carbon metabolism before a proportional growth response becomes apparent
Betaine	Kim et al. (2023); cyclic heat-stress model	0.2% dietary betaine	Liver transcriptome: energy, amino-acid and immune pathways	Broad hepatic transcriptomic response	Supports systems-level hepatic action, although transcript abundance should not be treated as metabolic flux
Betaine	Wen et al. (2021); broilers fed mold-contaminated corn	Dietary betaine	Growth, liver health, antioxidant status and carcass traits	Improved growth, liver health, antioxidant status and breast-meat yield/quality	Provides recent evidence that betaine can support metabolic and hepatic resilience under a feed-quality challenge
Taurine	Xing et al. (2021); oxidative-challenge broilers	Dietary taurine under H ₂ O ₂ challenge	Redox status, cell-death signaling, growth and meat quality	Attenuated oxidative damage and improved performance/meat quality under challenge	Recent mechanistic evidence linking taurine to redox regulation and cell-survival pathways
Taurine	Ghashghaei et al. (2025); methionine-replacement model	15-45% methionine replacement with taurine	Tissue-specific antioxidant indices	No simple universal growth benefit	Shows that taurine can support selected downstream sulfur-amino-acid functions without replacing all methionine functions
Taurine	Gupta et al. (2026); in-ovo taurine + cyclic heat stress	Graded in-ovo taurine	Growth, antioxidant capacity and hepatic gene expression	Mostly modest effects with selected molecular responses	Useful recent evidence that route and developmental timing strongly influence taurine efficacy
α -Ketoglutarate	Gupta et al. (2024); in-ovo exposure followed by cyclic heat stress	Graded in-ovo AKG	Hepatic NRF2, antioxidant indices and rectal temperature	Improved redox/thermal physiology without full rescue of growth	Demonstrates that molecular resilience and growth response can diverge
α -Ketoglutarate	Talpur et al. (2022); 288 broilers	1 or 2 kg/t dietary AKG	Growth, intestinal immunity and microbiota	Evidence of post-hatch gut-related responses	Useful dietary evidence, but metabolic flux was not measured

Compound	Representative study and model	Exposure / context	Mechanistic endpoints	Main finding	Critical interpretation
α -Ketoglutarate	Elashry et al. (2026); dietary AKG study	Dietary AKG supplementation	Performance, gut health, gene expression, antioxidant capacity and hematology	Broad improvements in performance and physiological indices	Confirms current dietary relevance of AKG while highlighting the need for direct flux-level validation
α -Ketoglutarate	Yang et al. (2026); hindgut-targeted delivery	Targeted AKG pellets	UCP2, oxidative phosphorylation and intestinal redox status	Improved intestinal redox status and growth	Strong current evidence for a defined mitochondrial effector; replication and dose-window work remain important

Why Supplementation Studies Disagree

Variation in response among studies can often be explained by differences in basal diet, dose, age, genotype, challenge and route of administration rather than by assuming that the nutrient lacks biological activity (Wang, 2025; Ghashghaei, 2025). Betaine depends strongly on methionine and choline status because its methyl-sparing potential is greatest when methyl demand is limiting. Taurine responses depend on basal sulfur-amino-acid supply, lipid level, oxidative challenge and tissue examined. AKG studies differ dramatically in route—dietary, in-ovo, gavage or targeted intestinal delivery—and therefore expose different tissues at different developmental stages (Gupta, 2024; Gupta, 2022).

Dose is equally important. The 2025 betaine study did not support a simple 'higher is better' relationship because 1,500 mg/kg produced a more favorable methyl-metabolic pattern than 3,000 mg/kg (Wang, 2025). Taurine dose-response work similarly identified 5 g/kg as a biologically favorable concentration even though 7.5 g/kg was tested. These patterns are consistent with pathway saturation and homeostatic feedback: once a limiting biochemical step is corrected, additional substrate can produce diminishing returns or shift other pathways.

A critical review should therefore compare studies using mechanistic moderators rather than simply label results as positive or negative. Basal methionine, choline, crude protein, dietary fat, energy density, age, sex, strain, environmental temperature, pathogen challenge, route, duration and tissue sampling point should be extracted systematically. This approach reduces repetition because a conflicting result is discussed once within the context that explains it, rather than being repeated separately in each compound section (Wang et al., 2025; Buonaiuto et al., 2025).

Comparative Evidence Strength and What Is Still Hypothetical

The evidence base is uneven across pathways and should therefore be interpreted according to the type of endpoint measured rather than by counting positive studies. Direct broiler evidence is strongest when a supplementation study demonstrates a pathway-specific biochemical or molecular response in the relevant tissue, whereas mechanisms inferred mainly from conserved biochemistry should remain explicitly provisional. Table 3 summarizes this evidence hierarchy without repeating the mechanistic explanations developed in Sections 4–10.

Table 3. Comparative strength of mechanistic evidence for betaine, taurine and α -ketoglutarate

Mechanistic domain	Betaine	Taurine	α -Ketoglutarate	Direct support	broiler	Critical caveat
One-carbon/methyl metabolism	Strong	Indirect	Indirect	Wang et al. (2025)		Do not infer epigenetic changes from SAM/SAH alone
Transsulfuration/sulfur metabolism	Indirect	Moderate	Indirect	Ghashghaei et al. (2025)		Flux through transsulfuration not directly quantified
Bile-acid/lipid digestion	Moderate	Strong	Low	Recent taurine and bile-acid studies		FXR/TGR5 signaling remains emerging in broilers

Mechanistic domain	Betaine	Taurine	α -Ketoglutarate	Direct support	broiler	Critical caveat
TCA/carbon metabolism	Low-direct	Low-direct	Strong biochemical; emerging in broilers	Talpur et al. (2022); Yang et al. (2026)		Static AKG does not equal TCA flux
Nrf2/redox	Moderate	Strong	Moderate-strong	Gupta et al. (2024); Yang et al. (2026)		Marker induction does not establish reduced ROS production
Mitochondrial regulation	Emerging	Moderate-strong	Strong-emerging	Recent taurine studies; Yang et al. (2026)		Respiration data remain limited
Osmoregulation	Strong	Moderate	Limited	Betaine osmolyte biology + challenge studies		Cellular osmolyte pools are rarely measured directly
Nutrient partitioning	Moderate	Moderate	Emerging	Carcass/lipid/growth outcomes across studies		Requires isotope or flux confirmation
mTOR/protein synthesis	Hypothesis	Hypothesis/emerging	Hypothesis/emerging	Mechanistically plausible		Direct broiler muscle signaling evidence insufficient

Multi-Omics and Flux Measurements Needed to Move Beyond Descriptive Nutrition

Targeted metabolomics offers the most direct first step toward testing the integrated network because the key metabolites are chemically defined. A single liver and plasma panel could quantify betaine, dimethylglycine, methionine, SAM, SAH, homocysteine, cysteine, taurine, major conjugated bile acids, AKG, glutamate, glutamine, succinate and selected acylcarnitines. Measuring these compounds in the same birds would reveal whether manipulating one node alters adjacent pathways, something that cannot be inferred by comparing separate experiments (Wang et al., 2025; Buonaiuto et al., 2025).

Transcriptomics is useful for pathway discovery but should be paired with proteomics or phosphoproteomics when the pathway is controlled post-translationally (Kim, 2023). AMPK and mTOR are activated largely through phosphorylation, mitochondrial respiratory complexes are regulated beyond transcription, and Nrf2 activity depends on protein stabilization and nuclear translocation (Algothmi et al., 2024; Kouvedaki et al., 2024). A transcript-only claim that a nutrient 'activated AMPK' or 'increased mitochondrial function' therefore overstates the evidence unless phosphorylation, enzyme activity or respiration is also measured.

Mitochondrial phenotyping is especially important for taurine and AKG. High-resolution respirometry can separate basal respiration, ATP-linked respiration, maximal respiratory capacity and proton leak, while mitochondrial ROS assays can determine whether improved redox status arises from lower ROS generation rather than merely increased antioxidant enzymes (Yang, 2026; Xing, 2021). These measurements could test the UCP2 hypothesis directly and determine whether taurine protects mitochondria through improved electron transport, membrane stabilization or secondary antioxidant effects.

Stable-isotope tracing is ultimately required to establish nutrient partitioning. ^{13}C -labeled carbon sources can follow entry into TCA intermediates, lipid or amino-acid carbon skeletons; ^{15}N -labeled amino acids can quantify transamination and nitrogen retention; sulfur-labeled methionine can reveal partitioning between protein, methyl metabolism and sulfur products (Macelline, 2025; Lalande, 2025). Compound-specific isotope analysis has already been demonstrated in broiler methionine research, indicating that technically sophisticated flux studies are feasible in poultry. Applying isotopes to betaine, taurine and AKG would transform the proposed network from a conceptual model into a measured metabolic system.

Future Experimental Designs

Future research should test the proposed methyl-sulfur-carbon network with experiments designed around specific metabolic questions rather than additional additive-versus-control performance trials. Direct comparisons, factorial interactions and context-specific challenge models should combine pathway-specific biomarkers with nutrient-retention endpoints so that any improvement in FCR can be traced to a defined change in metabolic flux. Table 4 therefore focuses on unresolved questions, decisive biomarkers and experimental designs rather than repeating the mechanistic discussion presented earlier.

Table 4. Research gaps and experiments required to resolve them

Unresolved question	Recommended experiment	Core biomarkers	Target tissues	What would constitute convincing evidence?
Does betaine alter taurine synthesis through the homocysteine branch point?	2×2 betaine × taurine factorial study under marginal methionine supply	SAM, SAH, homocysteine, cysteine, taurine, BHMT and transsulfuration enzymes	Liver and plasma	A measured shift in remethylation versus sulfur-metabolite flux
Does methyl economy interact with AKG-dependent carbon-nitrogen metabolism?	2×2 betaine × AKG study in a reduced-protein diet	Methyl-cycle panel, AKG, glutamate, ATP, uric acid and nitrogen retention	Liver and skeletal muscle	Greater protein retention at the same digestible amino-acid supply
Are taurine and AKG complementary at mitochondria?	2×2 taurine × AKG study with direct mitochondrial phenotyping	Respiration, proton leak, UCP2, ROS, Nrf2 and ATP	Intestine and muscle	Lower ROS and preserved tissue function without an excessive ATP penalty
Does taurine alter bile signaling or only bile chemistry?	Taurine dose-response with bile-acid metabolomics	Conjugated bile-acid species, fat digestibility and receptor targets	Liver and ileum	A dose-linked change in bile composition that predicts lipid absorption and signaling
Does AKG affect avian epigenetic or HIF biology?	AKG dose-response with metabolomics and epigenomics	AKG:succinate, HIF targets and DNA/histone methylation	Intestine and liver	Direct association between AKG status and a validated epigenetic/HIF endpoint
Do improved FCR values reflect true nutrient repartitioning?	Stable-isotope feeding study	¹³ C/ ¹⁵ N incorporation, nitrogen retention and heat production	Whole bird and breast muscle	More dietary carbon/nitrogen retained as lean tissue rather than maintenance or fat

Conclusion

Betaine, taurine and AKG are best understood as three metabolically active nutrients whose chemical structures determine different primary functions. Betaine's trimethylated zwitterionic structure supports methyl transfer and osmoprotection; taurine's sulfonic, non-proteinogenic structure supports free intracellular, bile-conjugation, membrane and redox functions; AKG's keto-dicarboxylate structure supports TCA-cycle metabolism and reversible amino-group transfer. These distinctions provide the mechanistic basis for interpreting supplementation effects rather than treating all three compounds as generic growth promoters (Wang et al., 2025; Buonaiuto et al., 2025).

The strongest integrative connection is the methyl-sulfur-carbon network. Betaine regulates homocysteine remethylation and methionine/SAM economy, taurine lies downstream of transsulfuration and links sulfur metabolism to bile and redox physiology, and AKG links mitochondrial carbon oxidation with glutamate-dependent nitrogen metabolism. Direct broiler evidence now supports betaine-dependent changes in methionine metabolism, taurine-dependent changes in Nrf2 and AMPK/SIRT1/CPT1-related physiology, and AKG-dependent changes in Nrf2 and UCP2-associated intestinal redox control (Wang et al., 2025; Buonaiuto et al., 2025).

The key limitation is that these pathways have almost always been studied separately. Consequently, the proposed crosstalk remains a mechanistic synthesis rather than a demonstrated three-nutrient interaction. The next generation of research should therefore emphasize factorial designs, tissue-resolved metabolomics, mitochondrial respiration, phosphoproteomics and isotope tracing. These methods can determine whether supplementation changes actual metabolic flux and whether the resulting nutrient partitioning favors lean tissue rather than maintenance or fat deposition.

For practical broiler nutrition, the most useful conceptual shift is from additive-based to pathway-based feeding. The relevant question is not whether betaine, taurine or AKG is 'best', but which metabolic node is limiting in a given diet, growth phase or challenge. A functional nutrient becomes valuable when its chemistry corrects that limitation and when the correction can be traced from molecular pathway to tissue physiology, nutrient retention and productive growth (Wang et al., 2025; Buonaiuto et al., 2025).

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