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Physiological Functions of Taurine and Its Applications in Swine Production (Postprint)

Authors: Hao Zhongyu, Yang Jiaming, Xiao Kequan, Yang Tai, Li Xue, Gao Fengxian

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Abstract

Taurine (Tau) is a free amino acid present in animal organisms, exhibiting antioxidant, immune-enhancing, and anti-apoptotic effects. As a feed additive, its application in livestock production has attracted increasing attention, demonstrating efficacy in improving production performance, reproductive performance, and alleviating stress-induced damage. This article expounds upon the physiological functions and mechanisms of action of taurine, and reviews the application effects of taurine in swine production in recent years, aiming to provide a reference for its improved utilization in pig production.

Full Text

Preamble

Taurine: Physiological Function and Application in Pig Production

HAO Zhongyu, YANG Jiaming, XIAO Kequan, YANG Tai, LI Xue, GAO Fengxian*

(College of Animal Science and Technology, Hunan Agricultural University; Hunan Co-Innovation Center of Animal Production Safety, Changsha 410128, China)

Abstract: Taurine is a free amino acid present in animal tissues that exhibits antioxidant, immunomodulatory, and anti-apoptotic properties. As a feed additive, taurine has garnered increasing attention in livestock production for its ability to enhance production performance, reproductive performance, and mitigate stress-induced damage. This review elaborates on the physiological functions of taurine and their underlying mechanisms, and summarizes recent research on the efficacy of taurine supplementation in pig production, aiming to provide a theoretical basis for its optimal application.

Keywords: taurine; physiological function; mechanism; application; pigs

Taurine is a semi-essential amino acid that exists in free form within animal bodies and is widely distributed across various tissues and vital organs, representing the most abundant free amino acid [1]. Due to the low activity of cysteinesulfinate decarboxylase (CSD), the key enzyme for taurine synthesis in animals, taurine must be obtained through both endogenous synthesis and dietary intake [2]. First isolated from bovine bile in 1827 [3], the first report on taurine's physiological functions did not appear until 1975 [4]. Taurine is derived from abundant sources and possesses extensive physiological functions, including antioxidant activity, immune regulation, and anti-apoptotic effects [5]. While recent research in the medical field has focused primarily on its pharmacological actions against cancer [6], tumors [7], and cardiovascular protection [8], studies in animals have predominantly examined its effects on improving production performance in poultry [9] and fish [10]. Research on taurine supplementation in pig production remains in its infancy. This article aims to synthesize recent domestic and international findings on taurine, summarizing its mechanisms of action and application effects in pig production to provide a theoretical reference for future research and development in animal agriculture.

1 Physical and Chemical Properties of Taurine

Taurine (molecular formula: $\text{H}_2\text{N}-\text{CH}(\text{CH}_3)-\text{SO}_3\text{H}$) is a light-yellow, small-molecule compound with a tetrahedral needle-like crystal structure, a relative molecular mass of 125.15, and a melting point of 328°C . It exists as a zwitterion in aqueous solution, exhibits acidic properties, and is insoluble in ethanol [11]. Its chemical properties are relatively stable, with a molecular structure comprising both carboxylic acid and sulfonic acid functional groups [12].

2 Physiological Functions and Mechanisms of Action

Taurine can be synthesized *in vivo* via the cysteine dioxygenase-cysteinesulfinate decarboxylase pathway or absorbed from the intestine into the bloodstream through the recombinant taurine transporter (TauT) and subsequently transported to tissue cells [13]. Studies have shown that TauT-deficient mice exhibit approximately 98% reductions in taurine levels in skeletal and cardiac muscle, and 70-90% reductions in brain, kidney, and liver tissues [14], demonstrating that taurine synthesis in tissue cells is insufficient and must rely on exogenous transport via the bloodstream. Moreover, normal blood taurine concentrations are only 1/100 of those in tissue cells, necessitating continuous accumulation to drive cellular uptake [15]. Thus, dietary taurine intake is crucial for meeting intracellular requirements.

2.1 Antioxidant Effects

After food is ingested and converted into "fuel" for mitochondrial energy production, free radicals are generated as byproducts. These radicals combine with free

unsaturated fatty acids in the cytoplasm to produce lipid peroxidation products such as malondialdehyde (MDA). Under normal conditions, endogenous antioxidants including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px) react with oxidative intermediates like superoxide anion (O_2^-), hydroxyl radicals (OH^\cdot), and hydrogen peroxide (H_2O_2) to maintain cellular homeostasis [16]. When this balance is disrupted, oxidative stress can trigger inflammation, apoptosis, tissue damage, and disease.

2.1.1 Free Radical Scavenging and Reactive Oxygen Species Inhibition

The primary sites of intracellular free radical generation are the mitochondrial respiratory chain complexes I and III (NADH-flavoprotein (FPN)-coenzyme Q (CoQ)-cytochrome C (CytC)) and complexes II and III (succinate-FPN-CoQ-CytC). Research has identified a sodium (Na^+)-dependent taurine bidirectional transporter on mitochondria similar to that on the nuclear membrane. Taurine can increase reduced CytC content on complexes II and III and antagonize homocysteine (Hcy)-induced decreases in reduced CytC that lead to oxygen free radical generation and increased electron leakage from the respiratory chain [17]. In studies of adriamycin (ADR)-induced non-infectious myocarditis, ADR damaged mitochondria, reducing activities of NADH dehydrogenase, cytochrome oxidase, cytochrome reductase, and succinate dehydrogenase in the respiratory chain, destabilizing mitochondrial oxidative phosphorylation and generating massive oxygen free radicals that caused lipid peroxidation. However, oral administration of 400 mg/(kg · d) taurine showed no significant difference from the control group, indicating that taurine can stabilize mitochondrial function and reduce free radical production [18]. Additionally, studies on H_2O_2 -injured myocardial cells (MC) demonstrated that taurine reduces intracellular reactive oxygen species levels [19].

2.1.2 Enhancement of Antioxidant Enzyme Activity and Reduction of Peroxide Levels

Antioxidant enzymes are crucial for clearing peroxide toxicity. Research shows that taurine supplementation can alleviate carbon tetrachloride-induced hepatic fibrosis by reducing cytochrome enzyme activation in mitochondria and decreasing reactive oxygen species (ROS) production. Taurine treatment lowered intracellular MDA content while increasing SOD activity [20], demonstrating its ability to enhance antioxidant enzyme activity and inhibit oxidative product formation. The Nrf2-ARE (nuclear factor E2-related factor 2-antioxidant response element) pathway is a critical component of cellular antioxidant signaling. Under stimulation by protein kinase C (PKC), mitogen-activated protein kinase (MAPK), and phosphatidylinositol 3-kinase (PI3K), Nrf2 dissociates from Kelch-like ECH-associated protein 1 (Keap1), becomes phosphorylated, translocates to the nucleus, and binds to ARE to express phase II detoxifying enzymes and antioxidant proteins including thioredoxin (TRX), glutathione peroxidase 1 (GPX1), and heme oxygenase 1 (HO-1) [21]. Studies on arsenic trioxide (As_2O_3)-induced autophagic injury in pancreatic cells of offspring rats revealed that taurine elevated Nrf2-TRX levels [22]. Taurine

also alleviated oxidative stress induced by methylmercury-activated Nrf2-HO-1 pathways while upregulating GPX1 expression [23], indicating that this pathway is activated by taurine during cellular oxidative stress responses. The PI3K/Akt pathway represents an anti-apoptotic signal triggered by oxidative stress, with research showing that taurine increased p-Akt protein expression in high glucose-induced oxidative stress, an effect abolished by PI3K inhibitors [24]. In studies of aluminum-induced oxidative stress in rat brain tissue, taurine supplementation significantly increased GSH-Px and SOD activities while decreasing MDA content, demonstrating its peroxide-reducing efficacy [25]. Taurine supplementation also elevated glutathione (GSH) levels, likely because both taurine and GSH share cysteine as a common precursor [26].

2.2 Anti-Apoptotic Effects

2.2.1 Mitochondrial Stress The anti-apoptotic effect of taurine is generally believed to protect mitochondria by stabilizing the electron transport chain and inhibiting reactive oxygen species production, thereby protecting cells and reducing apoptosis [27]. Vesce et al. [28] found that glutamate-induced apoptosis in cerebellar granule cells resulted from the combination of calcium ion (Ca^{2+}) overload and oxidative stress, as glutamate stimulated Ca^{2+} uptake, and excessive Ca^{2+} caused mitochondrial damage and massive ROS generation. Mitochondria play vital roles in energy metabolism and Ca^{2+} concentration regulation in myocardial cells, and mitochondrial damage further exacerbates Ca^{2+} overload [18]. Taurine protects rat myocardial cells from oxidative stress caused by mitochondrial damage by regulating the Ca^{2+} /Na⁺ exchange mechanism on the cell membrane to prevent excessive Ca^{2+} accumulation [29]. Gong et al. [30] found that during hypoxia/reoxygenation-induced apoptosis, taurine treatment significantly reduced intracellular calcium fluorescence intensity in a dose-dependent manner. Taurine stabilizes mitochondria by inhibiting the intrinsic apoptosis pathway: during mitochondrial stress, apoptotic protease activating factor-1 (Apaf-1) and CytC are released into the cytoplasm, activating caspase-9 and downstream caspase-3 [31]. Supplementing taurine in the diet of pregnant rats increased expression of glial cell line-derived neurotrophic factor and decreased caspase-3 expression in the cerebral cortex of fetuses with intrauterine growth restriction [32].

2.2.2 Endoplasmic Reticulum Stress (ERS) Studies on mouse embryonic cells revealed that non-receptor tyrosine kinase (c-Abl) participates in transmitting ERS signals to mitochondria, demonstrating that c-Abl resides in the endoplasmic reticulum and targets mitochondria through ERS to induce CytC release and apoptosis [33]. This suggests that ERS mechanisms may be upstream of mitochondrial stress during cellular stress responses. However, research on taurine's protection against purinergic ligand-gated ion channel 7 receptor (P2X7R)-mediated neurotoxicity found that Ca^{2+} overload in the endoplasmic reticulum was not transmitted to mitochondria [34], indicating that taurine protects against apoptosis induced by ERS alone.

Taurine protects cells from ERS through three signaling pathways mediated by endoplasmic reticulum transmembrane stress sensors: protein kinase R-like ER kinase (PERK), activating transcription factor 6 (ATF6), and inositol-requiring enzyme 1 (IRE1). Studies on 3'-O-(4-benzoyl)benzoyl adenosine 5'-triphosphate (Bz-ATP)-induced neurotoxicity in NG108-15 cells showed that taurine inhibited IRE1 upregulation in cortical neurons to rescue hypoxia-induced ERS [34]. PERK-eukaryotic initiation factor 2 (eIF2) signaling activation leads to expression of transcription factors ATF4 and ATF3, with ATF4 binding to amino acid regulatory elements [35]. ERS activation also induces expression of ATF6 and X-box binding protein 1 (XBP1), whose cytoplasmic portions translocate to the nucleus to express C/EBP homologous protein (CHOP), a growth arrest and DNA damage-inducible gene that triggers ERS responses and ultimately causes apoptosis [36]. CHOP may promote apoptosis by downregulating B cell lymphoma/leukemia-2 (Bcl-2) expression and upregulating Bcl-2-associated X protein (Bax) expression [37]. In a rat model of limb ischemia-reperfusion injury, taurine inhibited Bax gene expression upregulation [35]. Meanwhile, ERS activates caspase-12 apoptotic signaling, and Apaf-1 binding to CytC induces caspase-9 expression, with downstream caspase-3 driving apoptosis progression [33]. Studies showed that taurine treatment decreased caspase-12 and caspase-3 expression and reduced apoptosis rates in rat kidney NRK-52E cells [30]. Taurine also reduced caspase-8 and caspase-9 expression and inhibited ischemia/hypoxia-induced apoptosis in brain cells [32]. Glucose-regulated protein 94 (GRP94) and glucose-regulated protein 78 (GRP78) are immunoglobulin-binding proteins whose elevated levels indicate misfolded or unfolded proteins in the endoplasmic reticulum, serving as markers of ERS. Research demonstrated that taurine pretreatment downregulated GRP94 gene expression in ischemia-reperfused skeletal muscle tissue [38] and reduced GRP78 gene expression in ischemia-reperfused kidneys and hypoxia/reoxygenation-stimulated NRK-52E cells [30].

2.2.3 MAPK Signaling The MAPK signaling pathway is a critical component of apoptosis, with c-Jun N-terminal kinase (JNK), extracellular regulated protein kinases (ERK), and p38 proteins activated by different stimuli and forming interactive networks to regulate apoptosis. Studies on paraquat poisoning-induced oxidative stress in rat kidneys showed that taurine inhibited JNK and ERK1/2 activation, protecting against kidney damage [39]. In a myocardial ischemia-reperfusion rat model, taurine suppressed caspase-12 activation by reducing JNK levels [40], while increased taurine dosage decreased p38 expression [41]. Taurine also protected against acute lung injury in rats by reducing p38 pathway activation [42].

In summary, taurine protects cells by inhibiting calcium overload and oxidative stress to stabilize mitochondrial function, suppress intrinsic apoptosis pathways, reduce ERS-induced apoptosis, and modulate MAPK apoptotic signaling.

2.3 Immunomodulatory Effects

The thymus and spleen are primary immune organs involved in humoral and cellular immunity, while the bursa of Fabricius is a unique central immune organ for humoral immunity in poultry [43]. Dietary taurine supplementation can increase the relative indices of immune organs—including the thymus, spleen, and bursa of Fabricius—in 3-week-old broiler chickens [44-45]. Taurine accounts for over 50% of free amino acids in immune cells [46]. Taurine enhances T cell proliferation, with CD4⁺ T cells differentiating into helper T cells (Th1) that secrete interleukin-2 (IL-2) and tumor necrosis factor- α (TNF- α). IL-2 plays a crucial role in immune responses as an immunoregulatory and anti-inflammatory factor [47]. Under normal physiological conditions, TNF- α participates in immune reactions, but during disease, it triggers inflammation by inducing production of the inflammatory cytokine interleukin-1 (IL-1), which synergizes with TNF- α to promote inflammation and is also activated by caspases during ERS [48]. CD8⁺ T cells differentiate into cytotoxic T lymphocytes (CTL) that exert anti-tumor effects [49].

Supplementing the diet of 28-day-old weaned piglets with 1% taurine significantly increased the number of immunoglobulin A (IgA)-positive cells in the duodenal mucosal lamina propria, the α -naphthyl acetate esterase (ANAE) positive rate of T lymphocytes, the RNA-positive rate of B lymphocytes in jejunal mucosal lamina propria, and the number of IgA-positive cells in ileal lymphoid nodules [50]. In studies on cisplatin-induced damage to immune organs and cells in H22 tumor-bearing mice, cisplatin chemotherapy inhibited proliferation of B and T cells, whereas cisplatin combined with high-dose taurine significantly enhanced T cell proliferation, and cisplatin combined with low-dose taurine significantly improved B cell proliferation. All cisplatin-plus-taurine groups showed significantly increased blood levels of IL-2, TNF- α , and interferon- γ (IFN- γ) compared to cisplatin alone [49]. During carbon tetrachloride-induced hepatic fibrosis in mice, taurine increased IL-2 production by activated T cells, which bound to IL-2 receptors (IL-2R) on CTL surfaces to reduce extracellular matrix (ECM) accumulation [47]. In ADR-induced myocarditis with secondary myocardial fibrosis, taurine inhibited expression of transforming growth factor- β 1 (TGF- β 1) and TNF- α [51]. Dietary taurine supplementation significantly reduced blood TNF- α and IL-1 levels in heat-stressed broilers, demonstrating anti-inflammatory effects [52].

3 Application of Taurine in Pig Production

Taurine promotes intestinal absorption and improves feed utilization efficiency. Zhang et al. [53] supplemented the diet of 28-day-old weaned piglets with 0.1% taurine and found that it significantly improved digestibility of D-xylose, calcium, phosphorus, and crude protein (CP) at 11 days post-weaning, while also significantly increasing digestibility of dry matter (DM) and organic matter (OM). In concurrent research, Zhang et al. [54] reported that taurine significantly increased duodenal villus height and reduced crypt depth, while also sig-

nificantly enhancing villus height in the middle segments of the duodenum and jejunum. Taurine conjugates with bile acids in the liver to form taurocholic acid, which promotes fat emulsification, enhances lipase activity, and facilitates digestion and absorption of neutral fats, cholesterol, and fat-soluble substances [55]. Huang et al. [55] investigated the effects of all-plant-protein diets on weaned piglet performance and found that 3% taurine supplementation significantly increased average daily feed intake (ADFI) and reduced feed-to-gain ratio (F/G) by 7.26%. However, in a parallel experiment using high-animal-protein diets containing 14% fish meal, 3% taurine supplementation only significantly increased average daily gain (ADG) during the first week, with no significant differences in ADG or F/G in subsequent weeks [56], likely because fish meal provided sufficient taurine to meet piglet requirements. This suggests that taurine supplementation is more suitable for all-plant-protein diets. Chen et al. [57] reported that 0.1% taurine supplementation in corn-soybean meal-based diets significantly improved OM, DM, calcium, and phosphorus digestibility in weaned piglets but did not significantly affect ADFI, ADG, or F/G, differing from Huang et al.'s findings [55-56]. This discrepancy may be attributed to insufficient dietary nutrients to meet taurine requirements, though the study found that taurine significantly reduced diarrhea index in weeks 1 and 2, delayed diarrhea onset, and shortened diarrhea duration [58].

Liu et al. [59] investigated diets containing 4% fish meal supplemented with 0% (control), 0.3%, 1.5%, or 3.0% taurine for 21-day-old weaned piglets. Compared to the control, the 0.3% taurine group significantly reduced F/G and diarrhea index, increased villus height in the jejunum and ileum, decreased duodenal mucosal TNF- and glucagon-like peptide-2 (GLP-2) content, and reduced jejunal mucosal caspase-3 gene expression. Conversely, the 3.0% taurine group significantly increased F/G and diarrhea index, reduced duodenal villus height, increased crypt depth in the jejunum and ileum, elevated IL-6 and TNF- levels in jejunal and ileal mucosa and GLP-2 in duodenal mucosa, and increased caspase-3 content and gene expression in the duodenum, jejunum, and ileum. These results demonstrate that taurine has an optimal supplementation level, with only moderate amounts producing positive effects while excessive supplementation adversely affects production performance and intestinal health.

Taurine also improves reproductive performance. Chen et al. [60] found that 0.1% taurine supplementation in lactating sow diets increased sow ADFI and significantly improved piglet weaning weight and F/G, with a decreasing mortality trend. Results also showed a tendency for increased piglet survival during lactation and significantly improved F/G and weaning weight. Li et al. [61] reported that dietary taurine supplementation at 0, 2, 4, or 6 g/kg increased libido, semen quality, ejaculate volume, and sperm motility in boars during the 46-90 day period, with the 6 g/kg dose significantly increasing luteinizing hormone and follicle-stimulating hormone levels and significantly elevating testosterone while reducing MDA content and increasing SOD activity. The 4 g/kg dose significantly improved sperm density and morphology. Based on taurine's antioxidant and immunomodulatory actions, free radical scavenging and inhibition

of inflammatory cytokines TNF- and IL-1 appear to be important mechanisms for improving semen quality and sperm activity. Adding 5 mmol/L taurine to pig semen extender at room temperature significantly improved acrosome and plasma membrane integrity [62], possibly by increasing the ratio of cephalin to lecithin in cell membranes and enhancing membrane stability [63].

Taurine also modulates stress responses [64], regulating heat stress induced by high temperature and humidity [65] and activating stress-induced apoptotic signaling pathways [66]. Heat stress causes intestinal villus shedding [66], damages small intestinal mucosa [67], and upregulates apoptotic factors caspase-3, caspase-8, caspase-9, and Bax in small intestinal cells [66]. Taurine's protective mechanisms against heat stress likely involve its antioxidant properties, anti-apoptotic effects, and immune-enhancing capabilities.

4 Conclusion

In summary, taurine possesses specific physiological functions, and recent research on taurine supplementation in piglets and boars has achieved preliminary success. However, further investigation is needed regarding optimal supplementation levels, timing, and mechanisms in sow nutrition.

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