

Review

Amino Acid Metabolic Remodeling in Bivalves Under Environmental Stress: Roles, Mechanisms, and Implications for Bivalve Health—A Review

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Abstract

Climate change and increasing instability in coastal marine environments have intensified stressors such as elevated temperature, hypoxia, salinity variation, and pollutant exposure, posing major challenges to the survival, health, and culture performance of bivalves. As economically important aquaculture species and key components of coastal ecosystems, bivalves are highly sensitive to environmental fluctuations, making their metabolic responses highly relevant to both physiological adaptation and aquaculture sustainability. Increasing evidence indicates that metabolic remodeling is an important adaptive strategy supporting bivalve tolerance to environmental stress, with amino acid metabolic remodeling emerging as one of its most sensitive and functionally important components. This review summarizes the major response patterns, key pathways, and potential regulatory mechanisms of amino acid metabolism in bivalves under different stress conditions. Different environmental stressors induce distinct yet integrated shifts in amino acid metabolism, including enhanced catabolism, carbon–nitrogen redistribution, osmotic regulation, and antioxidant defense, thereby supporting energy homeostasis and physiological stress tolerance in bivalves. By highlighting amino acid metabolic remodeling as a central mechanism of bivalve adaptation to environmental stress, this review provides insights into adaptive responses, metabolite-based indicators for monitoring aquaculture environments and bivalve health, and management strategies for improving resilience in bivalve aquaculture.



Academic Editor: Jiejie Sun

Received: 30 June 2026

Revised: 26 July 2026

Accepted: 3 August 2026

Published: 6 August 2026

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Keywords: Bivalves; amino acid metabolism; metabolic remodeling; environmental stressors; physiological adaptation; health assessment

Key Contribution: This review synthesizes current evidence showing that amino acid metabolic remodeling coordinates energy reallocation, osmoregulation, redox balance, immune defense, and detoxification in stressed bivalves. Key amino acid-based signatures are proposed as potential tools for evaluating bivalve health, improving stress resilience, and supporting sustainable aquaculture management.

1. Introduction

Bivalves, particularly marine and estuarine species, are economically important aquaculture organisms worldwide, with their growth, health, and production performance being highly dependent on coastal environmental conditions. Owing to their filter-feeding habits and benthic lifestyle, they are directly exposed to a wide range of environmental stressors present in both the water column and sediments. Multiple stressors, including elevated temperature, hypoxia, salinity fluctuation, ocean acidification, and pollutants, can substantially affect bivalve survival, growth, health, and aquaculture performance [1]. These stressors disrupt key physiological processes such as energy metabolism, immune function, reproduction, and redox homeostasis, thereby imposing strong demands on metabolic adjustment in bivalves [2–4]. In this context, elucidating how bivalves cope with multiple environmental stressors through flexible metabolic adjustments has become a major focus in bivalve physiology and aquaculture research.

“Metabolic remodeling” refers to the systematic adjustment of metabolic networks in cells or tissues under environmental stress, as reflected by rapid changes in metabolite abundance, metabolic flux, key enzyme activity, and the distribution of metabolites among tissues [5,6]. In the broader literature, terms of “metabolic remodeling” and “metabolic reprogramming” often overlap, with the latter also encompassing regulatory changes beyond transcription, including enzyme activity, post-translational modifications, and metabolic flux [7,8]. In this review, the term “metabolic remodeling” is used operationally to describe rapid and reversible metabolic adjustments under stress, particularly those supported by metabolomic and enzymatic evidence, without implying a strict dichotomy between remodeling and reprogramming. In recent years, studies integrating metabolomics, transcriptomics, and proteomics have revealed pronounced metabolic remodeling in bivalves exposed to environmental stressors such as heavy metals, hypoxia, and temperature fluctuations, with amino acid metabolic networks occupying a central role in these responses [9–12]. These findings indicate that metabolic remodeling is a fundamental mechanism by which bivalves maintain physiological homeostasis and adapt to changing environments.

Amino acid metabolism is among the most consistently remodeled metabolic pathways in stress responses [13], because amino acids are not only the basic building blocks for protein synthesis but also key mediators of energy supply, osmoregulation, antioxidant defense, and immune signaling [14]. In marine invertebrates, free amino acids (FAAs) account for approximately 6–11% of tissue dry weight, and in bivalves, taurine, glycine, and alanine are often the dominant FAA components, as observed in representative species such as the blue mussel (*Mytilus edulis*), the Baltic clam (*Macoma balthica*), and the lagoon cockle (*Cerastoderma glaucum*) [15,16]. Under stress conditions, FAA pools in bivalves can change rapidly, supporting osmotic regulation, energy homeostasis, and antioxidant defense [17]. During abrupt salinity changes, FAAs—particularly glycine and alanine—act together with inorganic ions to maintain osmotic balance [18]. Under hypoxic or starvation conditions, bivalves may also rely on amino acid metabolism by directly absorbing environmental FAAs and mobilizing amino acid catabolism to sustain energy homeostasis [19,20]. Collectively, these findings highlight amino acid metabolism as a central and highly responsive component of the metabolic stress response in bivalves.

In this review, amino acid metabolic remodeling is defined as the coordinated adjustment of amino acid pools, catabolic and biosynthetic fluxes, enzyme activities, transporter-mediated exchange, and interactions with carbon, nitrogen, and redox metabolism in response to environmental challenges [21–23]. This process is reflected not only in dynamic changes in key amino acid concentrations, but also in the regulation of metabolic enzymes, such as aminotransferases and dehydrogenases, and amino acid transporters [13]. Based on this framework, this review summarizes metabolomic evidence, general response patterns,

and key pathway mechanisms of amino acid metabolic remodeling in bivalves exposed to major environmental stressors relevant to aquaculture systems. It then examines major amino acid metabolic pathways based on KEGG classification and discusses their potential applications in precision nutrition, selective breeding, stress-resilience improvement, and aquaculture health management. By integrating current evidence, this review aims to advance our understanding of stress adaptation in bivalves and provide a basis for developing metabolite-informed indicators and intervention strategies to support bivalve health and production resilience.

2. General Features of Amino Acid Metabolic Remodeling in Stressed Bivalves

2.1. Metabolomic Evidence for Amino Acid Metabolic Shifts in Stressed Bivalves

Metabolomic studies based on nuclear magnetic resonance and mass spectrometry have provided direct evidence that environmental stress induces broad metabolic shifts in bivalves [13,24–26]. Across diverse stressors, including elevated temperature [22,23,27], hypoxia [28], salinity change [29], ocean acidification [1,25,30], and pollutant exposure [31,32], these studies consistently reveal coordinated changes in pathways related to sulfur-containing amino acids, branched-chain amino acids, osmoregulatory free amino acids, and aromatic amino acids [13]. Within this broader metabolic response, amino acid metabolism repeatedly emerges as one of the most sensitive and frequently affected modules, alongside glycolysis, the tricarboxylic acid (TCA) cycle, fatty acid β -oxidation, and osmotic adjustment pathways [24–26].

Amino acid-related pathways, including arginine and proline metabolism, alanine–aspartate–glutamate metabolism, taurine metabolism, and β -alanine metabolism [33,34], are frequently altered under heat stress, hypoxia, and salinity fluctuation [26]. For example, proline and taurine often increase under thermal or osmotic stress and may contribute to membrane stabilization, osmotic balance, and protection against oxidative damage [26]. Glycine and alanine are commonly involved in intracellular osmotic adjustment, whereas glutamate and aspartate can support energy metabolism by entering the TCA cycle through transamination [33,35]. Together, these findings suggest that amino acid metabolism integrates stress perception with osmoregulatory, redox, and energetic responses in bivalves. Table 1 summarizes key stressor-specific patterns, while Supplementary Table S1 provides detailed supporting evidence.

Importantly, stress-induced amino acid metabolic responses are time-dependent. Acute stress often triggers transient accumulation of free amino acids to meet short-term demands for energy production and osmotic adjustment, whereas prolonged stress is generally associated with depletion of amino acid pools, indicating their continued utilization in energy maintenance and protein turnover [30]. However, these shifts should not be assumed to be adaptive. Amino acid accumulation may indicate metabolic bottlenecks, impaired catabolism, or cellular damage, whereas depletion may reflect energetic exhaustion or disrupted biosynthesis [36,37]. Distinguishing compensatory remodeling from pathological disturbance therefore requires integration with physiological performance indicators, such as survival, growth, and reproduction, as well as flux-based approaches.

A key caveat in interpreting the metabolomic findings summarized above is that most studies rely on steady-state metabolite abundance, which provides a snapshot of the metabolome rather than a direct measure of metabolic flux. Changes in amino acid levels may reflect altered synthesis, degradation, catabolism, tissue redistribution, or depletion of free amino acid pools, and therefore cannot alone define the direction or magnitude of pathway flux. Confirming flux changes, such as enhanced branched-chain amino acid catabolism or TCA cycle activity, requires complementary approaches including

stable-isotope tracing, metabolic flux analysis, rate-limiting enzyme assays, and isotope-assisted high-resolution mass spectrometry. Integrating these methods with conventional metabolomics will be essential for establishing causal links between environmental stress and amino acid metabolic adjustments in bivalves.

Table 1. Major amino acid metabolic responses and physiological implications in environmentally stressed bivalves.

Environmental Stressor	Representative Amino Acid Signatures	Main Physiological Implications	Major Metabolic Pathways Involved
Salinity fluctuation [16,18,38–43]	Altered FAA pools, especially Tau, Gly, Ala, Pro, Ser, Glu, GABA and betaine	Osmoregulation, cell volume control, compatible solute adjustment, oxidative/immune modulation, and ion-transport energy demand	Taurine transport/metabolism; glycine-betaine metabolism; Ala/Asp/Glu and Arg/Pro metabolism; GABA shunt; glutathione and energy metabolism
Thermal stress [23,27]	Increased BCAAs, aromatic amino acids, Glu, Gln, Arg, Pro, Ala and Tau; altered Orn and Gly	Energy reallocation, protein homeostasis, cytoprotection, antioxidant response, and thermotolerance	BCAA metabolism; Ala/Asp/Glu metabolism; TCA cycle; anaerobic metabolism; Arg/Pro metabolism
Hypoxia [28,44–46]	Increased Ala and Glu; altered Asp, Lys, Pro, Phe and Arg depending on exposure duration	Anaerobic compensation, ATP maintenance, nitrogen balance, oxidative/immune modulation, and energy conservation	Aspartate transamination; Ala/Asp/Glu metabolism; anaerobic and succinate-related metabolism; GABA transport; aminoacyl-tRNA biosynthesis
Ocean acidification [4,47]	Increased Ala and GABA; decreased Orn, Lys, Ser, Thr and Leu	Acid–base and energy adjustment, altered carbon metabolism, and potential effects on growth/calcification	Ala/Asp/Glu metabolism; Gly/Ser/Thr metabolism; TCA cycle-related metabolism
Food limitation and energy variation [2,29]	FAA depletion under food limitation; conserved essential amino acids; higher Ala, Pro, Gly, Asp, Glu, Gln, His, Met, Ile and Val in high-glycogen oysters	Metabolic depression, protein turnover, energy reserve mobilization, fuel switching, antioxidant adjustment, and reduced performance	Amino acid metabolism; Ala/Asp/Glu and Arg/Pro metabolism; glycolysis; TCA cycle; gluconeogenesis; lipid metabolism; protein turnover
Micro- and nanoplastics [48–53]	Altered Glu, Gln, Ala, Asp, Pro, Lys, His, BCAAs, aromatic amino acids, Cys, Met, Tau, Gly, Ser and Thr, depending on polymer and exposure conditions	Oxidative stress, inflammation, neurotoxicity, protein synthesis disturbance, energy/lipid disruption, impaired osmoregulation, reproductive risk, and microbiota adaptation	Ala/Asp/Glu, Arg/Pro, Gly/Ser/Thr and Cys/Met metabolism; phenylalanine metabolism; aminoacyl-tRNA biosynthesis; glutathione, lipid and energy metabolism
Metals and metalloids [12,54–57]	Altered Ala, Glu, Tau, Thr, Arg, Asp, His, BCAAs, Lys, Tyr, Cys and Orn in a metal- and tissue-dependent manner	Oxidative stress, detoxification, metal imbalance, osmotic disturbance, neurotoxicity, immune response, apoptosis/signaling modulation, and energy disruption	Glutathione metabolism; Ala/Asp/Glu, Arg/Pro and Tau/hypotaurine metabolism; aminoacyl-tRNA biosynthesis; purine metabolism; carbohydrate/anaerobic metabolism; metal homeostasis
Organic pollutants and emerging contaminants [58–63]	Altered BCAAs, Pro, Arg, Gln, Phe, Tyr, Met, Cys, His, Ala, Tau and Glu, with compound- and mixture-specific responses	Oxidative stress, detoxification, energy compensation, immune/reproductive impairment, ER/protein stress, osmoregulatory disturbance, microbiota dysbiosis, and reduced performance	Amino acid metabolism; Cys/Met and glutathione metabolism; energy metabolism; purine/pyrimidine metabolism; lipid metabolism; ABC transporters; detoxification and inflammatory signaling
Combined stressors [47,64,65]	Altered Pro, Tau, Phe, Orn, Asn, Lys, BCAAs, Gly, Ser and Thr, with mixture-dependent responses	Interactive effects on energy metabolism, oxidative defense, neurotoxicity, osmoregulation, immune response, protein turnover, cytoskeletal remodeling, and salinity tolerance	Glycolysis and TCA cycle; glutathione and taurine/hypotaurine metabolism; amino acid/lipid metabolism; purine/pyrimidine metabolism; calcium, HIF-1 and neurotransmission signaling

2.2. Physiological Roles of Amino Acid Metabolism in Bivalve Stress Tolerance

As filter-feeding benthic organisms, bivalves remain in direct and continuous contact with the surrounding water, which facilitates nutrient acquisition but also increases their exposure to dissolved pollutants and suspended particles. This ecological characteristic underlies their widespread use as sentinel organisms for environmental contamination and partly explains their pronounced metabolic and physiological sensitivity to external stressors [66,67]. Because bivalves have limited capacity to actively avoid unfavorable conditions, they are frequently subjected to multiple concurrent stressors, including fluctuations in temperature and salinity, hypoxia, and pollutant exposure. Under these conditions, survival depends heavily on intrinsic metabolic regulation. Previous reviews have shown that amino acid metabolism is closely coordinated with energy metabolism and antioxidant pathways in bivalves, allowing rapid metabolic remodeling to maintain internal homeostasis [13]. Within this regulatory framework, amino acid metabolism serves as a key component of bivalve stress tolerance.

Compared with fish and crustaceans such as shrimps and crabs, bivalves appear to rely particularly strongly on amino acid metabolism during environmental stress. Bivalves can absorb dissolved free amino acids directly from the surrounding water and incorporate them into metabolic pathways, where they may feed into the TCA cycle or anaerobic routes to support energy production under adverse conditions [19]. Although fish can also oxidize amino acids as energy substrates, amino acids in fish are more commonly associated with growth and protein accretion, while lipids and carbohydrates generally provide greater metabolic flexibility [11,68]. In bivalves, the prominent role of amino acid catabolism may be linked to their well-developed anaerobic capacity and to the dual function of free amino acids as both osmotic effectors and energy substrates [20]. Under hypoxia or starvation, amino acid deamination can generate intermediates such as pyruvate and succinate, thereby helping to sustain ATP production when aerobic metabolism is limited. However, this pattern should not be overgeneralized. Many bivalves also possess substantial glycogen reserves, and the relative contribution of amino acids, carbohydrates, and lipids to energy metabolism varies markedly among species, tissues, and physiological states. In crustaceans, energy metabolism often depends heavily on glycogen and lipid stores, but free amino acids also contribute importantly to intracellular osmotic regulation, particularly in muscle, and should not be regarded as merely supplementary [69,70]. Similarly, in bivalves, free amino acids such as glycine, proline, and taurine are central components of physiological regulation under environmental change [16]. Together, these features suggest that bivalves exhibit a distinctive integration of amino acid metabolism with stress-related energy production and osmotic regulation, while the balance among amino acid, carbohydrate, and lipid use remains highly context-dependent and should be interpreted with taxon-, tissue-, and stage-specific caution.

2.3. Stress-Specific Patterns of Amino Acid Metabolic Remodeling

2.3.1. Thermal Stress

Thermal stress causes extensive metabolic remodeling in bivalves, particularly in pathways related to amino acid turnover, energy metabolism, and redox regulation. Under heat stress, branched-chain amino acids (BCAAs) commonly accumulate rapidly, together with increased levels of proline, taurine, glycine, glutamate, and alanine [22]. These changes indicate substantial remodeling of amino acid metabolism and may be associated with stress-related energy production, osmotic regulation, and antioxidant responses. In contrast, low-temperature exposure generally suppresses metabolic activity and is often accompanied by the accumulation of compatible solutes such as glycine and alanine.

Amino acid remodeling under thermal stress is closely integrated with broader shifts in energy metabolism. Early temperature elevation enhances glycolysis for ATP production, whereas prolonged warming promotes a gradual transition toward anaerobic pathways, including lactate fermentation, the opine pathway, and succinate-producing mitochondrial anaerobic metabolism. Amino acids such as aspartate and alanine are closely involved in these transitions, highlighting their role in balancing aerobic and anaerobic energy production [46]. Thermal acclimation may further delay the onset of anaerobic metabolism and maintain higher aerobic metabolic capacity [22]. Overall, amino acid metabolism is an important component of the thermal stress response in bivalves.

2.3.2. Osmoregulatory Stress

Osmoregulatory stress is one of the most direct drivers of amino acid metabolic remodeling in bivalves, mainly through changes in free amino acid pools. Under salinity fluctuation or nutritional stress, amino acids such as alanine, proline, glycine, and taurine accumulate as major organic osmolytes to maintain intracellular osmotic balance [29]. Glycine and taurine are particularly responsive, with their accumulation closely associated with salinity level and exposure duration [16,42].

In addition to their osmotic function, free amino acids participate in metabolic adjustment during salinity stress. Some amino acids can enter intermediary metabolism through transamination or conversion into TCA cycle intermediates, thereby linking osmotic regulation with energy supply [38]. Proline and taurine are further associated with antioxidant defense and maintenance of cellular homeostasis under salinity fluctuation [15]. Thus, amino acid metabolism contributes to osmoregulatory stress responses through coordinated roles in osmotic adjustment, metabolic support, and cellular protection [13,71].

2.3.3. Hypoxic Stress

Hypoxic stress in bivalves is characterized by a distinct pattern of anaerobic metabolic adjustment in which amino acid metabolism plays a central role. Under hypoxia, pyruvate derived from glycolysis is preferentially converted to alanine via transamination rather than reduced to lactate, while partial operation of the TCA cycle is accompanied by marked succinate accumulation. Glutamate functions both as an amino donor for alanine formation and as a precursor for succinate production through the GABA shunt [4].

These metabolic features indicate that amino acid metabolism supports anaerobic energy balance under oxygen limitation and may also help reduce intracellular acidification. However, alanine and succinate accumulation may have a dual significance: while they may contribute to temporary anaerobic compensation and ATP maintenance, they may also indicate reduced aerobic capacity, metabolic stress, or impaired flux through downstream oxidative pathways. Therefore, these changes should not be viewed exclusively as an adaptive strategy. Compared with the lactate-centered anaerobic response commonly described in many fish and crustaceans, the alanine- and succinate-associated pathway observed in bivalves may represent a more characteristic metabolic adjustment under hypoxia, but its interpretation requires integration with physiological performance indicators to distinguish compensatory remodeling from pathological disturbance [3,26]. Hypoxic exposure is also frequently accompanied by oxidative stress, and increased ROS production has been linked to changes in glutathione metabolism and antioxidant enzyme activities [13]. Thus, amino acid metabolic remodeling under hypoxia is closely associated with both energy compensation and redox homeostasis.

2.3.4. Pollutant Stress

Pollutant-induced remodeling of amino acid metabolism in bivalves has been widely reported across diverse contaminant classes, including heavy metals, microplastics, and

organic pollutants. Although these stressors differ in their primary modes of action, they commonly affect pathways involved in energy metabolism, nitrogen handling, osmotic regulation, antioxidant defense, and detoxification.

Under heavy metal exposure, amino acid changes frequently involve glutamate, arginine, taurine, and sulfur-containing amino acids, while the accumulation of alanine and succinate suggests a shift toward anaerobic metabolism [12,72–74]. Increased histidine levels have also been reported, potentially reflecting its role in metal chelation [12,75]. Microplastic exposure often alters branched-chain amino acids, alanine, and glutamate, indicating disruption of amino acid utilization and energy-related metabolism [24,48,49,76]. Organic pollutants, including phthalates and pharmaceuticals, can affect glutathione, arginine, and aromatic amino acid metabolism, suggesting combined impacts on antioxidant defense, nitrogen metabolism, and protein turnover [58,77]. Overall, pollutant stress reshapes amino acid metabolism through both shared and contaminant-specific responses, with common features including metabolic compensation, osmotic imbalance, oxidative stress, and altered detoxification capacity.

2.3.5. Ocean Acidification

Ocean acidification (OA), driven by the continuous uptake of atmospheric CO₂, reduces seawater pH and carbonate saturation and consequently affects acid–base regulation, energy metabolism, calcification, and cellular homeostasis in bivalves [1,78,79]. Recent studies indicate that OA induces broad metabolic remodeling, with amino acid metabolism being one of the most responsive components. Affected pathways commonly include alanine, aspartate, and glutamate metabolism; arginine and proline metabolism; glycine, serine, and threonine metabolism; taurine and hypotaurine metabolism; and branched-chain amino acid metabolism, suggesting coordinated changes in nitrogen metabolism, protein turnover, and energy balance [33,34,80].

Metabolomic studies in species such as *Mytilus coruscus* and *Crassostrea gigas* have shown that OA alters amino acids including glutamate, alanine, glycine, taurine, and BCAAs, often accompanied by changes in energy reserves, cellular energy allocation, and antioxidant-related metabolites [25,78,80]. These responses suggest that amino acid remodeling under OA is closely linked to increased energetic demand, mitochondrial disturbance, and oxidative stress. When OA co-occurs with microplastics or other stressors, disruptions in glutamate, taurine, glutathione, and energy-related pathways may be further intensified [25]. Functionally, glutamate and aspartate can support ATP production by replenishing TCA cycle intermediates, taurine and glycine contribute to osmotic and acid–base homeostasis, and proline participates in ROS scavenging and antioxidant defense [33,78,79]. Overall, OA induces systematic remodeling of amino acid metabolism in bivalves, with response patterns depending on species, tissue type, developmental stage, exposure duration, and co-occurring environmental factors.

2.3.6. Food Limitation

Food limitation is a common ecological stressor in natural and aquaculture environments. Seasonal changes in phytoplankton abundance, nutrient availability, and stocking density can reduce food supply, leading to energy deficiency and impaired growth, reproduction, and stress tolerance in bivalves. Under food-limited conditions, bivalves generally rely more heavily on endogenous reserves to maintain basal metabolism, and amino acid metabolism becomes an important pathway for metabolic adjustment [2,81].

Food limitation can alter free amino acid pools and multiple amino acid metabolic pathways, including alanine, aspartate, and glutamate metabolism; glycine, serine, and threonine metabolism; arginine and proline metabolism; and branched-chain amino

acid metabolism [2,81,82]. These changes reflect enhanced protein turnover, amino acid catabolism, and substrate recycling to meet energy demands. In particular, BCAAs and their corresponding branched-chain α -keto acids may serve as alternative energy substrates, while glutamate, aspartate, and alanine can contribute to TCA cycle replenishment and gluconeogenesis [83–85]. Several free amino acids also contribute to cellular protection during nutritional stress; taurine, glycine, and proline function as osmolytes and participate in antioxidant defense and ROS scavenging [33,34]. Overall, food limitation reshapes amino acid metabolism by promoting protein turnover, amino acid catabolism, and central carbon metabolism. However, the dynamics of BCAA metabolism and metabolic flux under long-term food limitation remain poorly understood, and future studies integrating metabolomics, transcriptomics, and stable isotope tracing are needed to clarify these regulatory mechanisms.

However, in natural environments, organisms are rarely exposed to a single stressor; instead, multiple perturbations often occur simultaneously or sequentially. Their combined effects can be additive, synergistic, or antagonistic, depending on species, life stage, acclimation history, exposure intensity, and timing. For example, warming may intensify hypoxia by increasing metabolic oxygen demand while reducing oxygen availability. Because potential stressor combinations are extensive and context-dependent, a comprehensive treatment is beyond the scope of this review. Here, the selected examples summarized in Table 1 further highlight the need for more environmentally realistic multifactorial experiments and integrated modelling approaches to better predict organismal responses under global change.

3. Central Roles of Key Amino Acid Metabolic Pathways in Bivalve Stress Adaptation

The following sections are organized according to major KEGG amino acid metabolic modules and summarize their roles in bivalve stress adaptation. These pathways are discussed in relation to energy homeostasis, nitrogen balance, osmotic regulation, antioxidant defense, immune signaling, and detoxification. This framework helps link pathway-specific metabolic responses to the broader stress-adaptation networks of bivalves.

3.1. Branched-Chain Amino Acid Metabolism: Energy Homeostasis and Protein Turnover

Branched-chain amino acids (BCAAs), namely leucine, isoleucine, and valine, may provide an important alternative energy substrate in bivalves during stress, especially when carbohydrate- and lipid-derived energy supply is constrained. In vertebrate models, their catabolism is initiated by branched-chain amino acid transaminase (BCAT), generating branched-chain α -keto acids (BCKAs), which are further oxidized by the branched-chain α -keto acid dehydrogenase complex (BCKDH) and ultimately enter the TCA cycle [86]. Although this enzymatic pathway has not been fully characterized in bivalves, similar catabolic routes are presumed to operate based on conserved biochemistry and the presence of homologous enzymes. In sessile or weakly mobile bivalves, this pathway may provide alternative carbon substrates when carbohydrate- or lipid-derived energy is limited, while helping reduce excessive degradation of structural proteins, especially in the adductor muscle.

BCAA metabolism is frequently remodeled under environmental stressors such as heat, hypoxia, and pollutant exposure. In Mediterranean mussels *Mytilus galloprovincialis* exposed to wastewater effluents, changes in leucine and other amino acids were accompanied by altered TCA-cycle intermediates, suggesting enhanced amino acid-derived energy compensation [64]. Under high-temperature stress, leucine, isoleucine, and valine accumulated rapidly in mussel tissues, particularly in heat-hardened individuals, together with

increased TCA-cycle activity [22,23]. Similar energy-compensatory responses have been reported in scallops and Manila clams, including changes in ATP, COX (cytochrome c oxidase), glycogen, and ATPase-related enzymes [27].

Overall, BCAA metabolism appears to be dynamically regulated during bivalve stress responses. Acute stress may promote BCAA accumulation through enhanced mobilization or adaptive metabolic remodeling, whereas prolonged or severe stress may lead to BCAA depletion through intensified catabolism. Therefore, BCAA metabolism reflects a balance among emergency energy supply, protein turnover, antioxidant protection, and maintenance of tissue homeostasis.

3.2. Alanine, Aspartate and Glutamate Metabolism: Central Hub of Nitrogen and Energy Metabolism

Alanine, aspartate, and glutamate metabolism forms a central hub connecting nitrogen balance, anaerobic energy production, and redox regulation in bivalves. Glutamate can interconvert with alanine and aspartate through transamination reactions and can be reversibly converted to α -ketoglutarate by glutamate dehydrogenase (GDH), thereby replenishing TCA-cycle intermediates under stress. This pathway is especially important in bivalves inhabiting intertidal or benthic environments, where hypoxia, salinity fluctuation, and pollutant exposure are frequent. Alanine is a typical anaerobic product in these animals and often accumulates during oxygen limitation, while glutamate also supports glutathione (GSH) synthesis, enhancing ROS scavenging and limiting lipid peroxidation [13,87].

Stress-induced remodeling of this pathway has been reported under hypoxia, salinity fluctuation, and pollutant exposure. Under hypoxia, aspartate transamination can be coupled with glycolysis to support ATP production. Aspartate can be converted to glutamate and oxaloacetate; glutamate and pyruvate then generate alanine, whereas oxaloacetate is further converted to malate, fumarate, and succinate, accompanied by ATP generation [45]. Under low salinity, alanine, lactate, and succinate accumulated in hard clam *Merccenaria mercenaria*, whereas aspartate declined, indicating stress-related reallocation of carbon and nitrogen metabolism [39]. Copper exposure in deep-sea mussels *Gigantidas platifrons* also increased alanine, aspartate, and glutamate levels, together with changes in succinate and stress-related genes [12].

Overall, alanine, aspartate, and glutamate metabolism is commonly involved in environmental stress responses, although individual metabolites may change in different directions. Alanine and succinate often accumulate as anaerobic or compensatory products, whereas aspartate may decline when consumed for transamination. This pathway therefore supports energy redistribution, nitrogen balance, antioxidant defense, and cellular homeostasis in stressed bivalves.

3.3. Glycine, Serine and Threonine Metabolism: One-Carbon Metabolism and Osmotic Regulation

Glycine, serine, and threonine metabolism is closely associated with osmotic regulation and one-carbon metabolism in bivalves. As osmoconforming animals living in estuarine and intertidal habitats, bivalves rely heavily on free amino acids as compatible osmolytes to regulate cell volume through regulatory volume increase (RVI) and regulatory volume decrease (RVD). Glycine, serine, and threonine can be reversibly interconverted, contributing to intracellular osmotic balance while also supplying one-carbon units [88]. Through the folate and methionine cycles, this pathway generates S-adenosylmethionine (SAM), thereby supporting DNA and histone methylation, biosynthesis, and antioxidant capacity via NADPH and formate production [10,12].

This pathway is particularly responsive to salinity stress. In the Japanese hard clam *Meretrix lusoria*, increasing salinity significantly elevated total free amino acid levels in the gill and mantle, with redistribution of small amino acids such as glycine, indicating their

role in osmotic adjustment [16]. In the razor clam *Sinonovacula constricta*, low-salinity stress altered metabolites associated with glycine and serine metabolism, methionine metabolism, the SAM cycle, and compatible solute synthesis [40]. Similarly, physiological analyses of the Manila clam *Ruditapes philippinarum* showed significant changes in glycine, serine, and threonine metabolism under salinity variation, accompanied by accumulation of related amino acids [41].

Overall, glycine, serine, and threonine metabolism shows salinity-dependent regulation in bivalves. Under hyperosmotic stress, glycine and other free amino acids often accumulate to stabilize intracellular osmotic pressure, whereas under hypoosmotic stress they may be released, degraded, or redistributed to promote volume reduction. Thus, this pathway integrates compatible solute regulation, methyl-group transfer, and cellular homeostasis during bivalve adaptation to salinity stress.

3.4. Cysteine and Methionine Metabolism: Sulfur Metabolism and Redox Regulation

Cysteine and methionine metabolism is a key sulfur-containing amino acid network linking antioxidant defense, methyl-group transfer, and osmotic regulation in bivalves [12,64]. Cysteine is the rate-limiting precursor for glutathione (GSH) synthesis, and the GSH system cooperates with glutathione peroxidase (GPx) and glutathione reductase (GR) to maintain redox balance and limit oxidative damage [24,64,89]. In parallel, methionine enters the S-adenosylmethionine (SAM) cycle to support methylation-dependent regulation of gene expression and metabolism [26]. In bivalves, this pathway is also closely connected to taurine biosynthesis, which is particularly important because taurine is abundant in many species and functions as a compatible osmolyte and membrane stabilizer [90].

Environmental stress often induces pronounced remodeling of cysteine and methionine metabolism. Under salinity change, Japanese hard clams *Meretrix lusoria* showed increased total free amino acids and elevated taurine proportion in gill and mantle tissues, accompanied by altered taurine transporter expression, indicating active taurine-mediated osmoregulation [16]. In the Pacific oyster, low-salinity stress significantly upregulated cysteine sulfinic acid decarboxylase and promoted taurine accumulation, confirming the importance of the cysteine–taurine branch in salinity adaptation [42]. Under pollutant stress, such as microplastic exposure, oyster metabolomes showed broad disturbance of cysteine and methionine metabolism together with oxidative stress responses [48].

Overall, cysteine and methionine metabolism is commonly associated with salinity and pollutant stress responses, but the direction of metabolite change may depend on stress intensity and duration. Taurine and GSH often increase during early adaptation, whereas prolonged stress may exhaust sulfur-containing substrates. This pathway therefore contributes to redox homeostasis, osmotic adjustment, and metabolic resilience in bivalves.

3.5. Arginine and Proline Metabolism: Immune Regulation and Osmotic Balance

Arginine and proline metabolism represents an important interface connecting energy buffering, immune defense, osmotic regulation, and redox homeostasis in bivalves. Arginine can be converted to nitric oxide (NO) through the nitric oxide synthase (NOS) pathway, thereby participating in immune signaling and pathogen defense [91]. Arginine is also involved in the arginine kinase (AK) system, a characteristic phosphagen system in invertebrates that rapidly mobilizes arginine phosphate to regenerate ATP during acute energy demand, such as valve closure, burrowing, or muscle contraction [92]. Proline functions as a compatible osmolyte and can accumulate under salinity, temperature, or desiccation stress to stabilize intracellular osmotic pressure. It may also contribute to mitochondrial redox regulation through proline dehydrogenase (PRODH), supplying reducing equivalents and alleviating oxidative stress [29,93].

This pathway is strongly remodeled under osmotic and immune-related stress. In low-salinity-tolerant families of the razor clam *S. constricta*, arginine and proline metabolism was identified as a shared core pathway, suggesting its early involvement in salinity adaptation [40]. Under high-salinity stress, proline content in gill tissue increased with both salinity level and exposure time, accompanied by enhanced biosynthesis and inhibited degradation. Exogenous proline further accelerated hemolymph osmotic recovery, confirming its direct role in osmotic adjustment [43]. Proline supplementation also improved survival, reduced gill injury, increased antioxidant capacity, and decreased ROS and malondialdehyde levels [94]. Meanwhile, arginine-derived NO has been detected in bivalve hemocytes and shown to modulate phagocytosis-related immune responses [95].

Overall, arginine and proline metabolism is generally activated under osmotic and immune challenges. Proline accumulation supports osmotic balance and antioxidant protection, whereas arginine metabolism provides both rapid energy buffering and immune-related signaling molecules. Therefore, this pathway functions as a key node linking osmotic homeostasis, redox defense, energy supply, and immune regulation in stressed bivalves.

3.6. Aromatic Amino Acid Metabolism: Signaling and Stress Response

Aromatic amino acid metabolism provides essential precursors for neuroendocrine signaling and immunometabolism regulation in bivalves. In vertebrate models, phenylalanine and tyrosine are converted into catecholamines, including dopamine, norepinephrine, and epinephrine, through tyrosine hydroxylase-dependent reactions [96–98]. Tryptophan can be metabolized to serotonin (5-HT) through tryptophan hydroxylase or to kynurenine derivatives through indoleamine 2,3-dioxygenase [99]. These pathways have been well-characterized in vertebrates, but direct evidence for the full enzyme cascades in bivalves remains limited. However, these metabolites are particularly relevant to bivalves because neuroactive compounds are known to regulate heart activity, gill ciliary beating, valve movement, reproduction, and hemocyte-mediated immune responses in these organisms [100]. Thus, this pathway links external stress perception with physiological coordination, although the precise mechanisms await further investigation in bivalves.

Aromatic amino acid metabolism is sensitive to environmental stress, especially thermal and salinity stress. Direct evidence from bivalves shows that in heat-hardened Mediterranean mussels *M. galloprovincialis*, phenylalanine, tyrosine, and tryptophan generally increased in mantle tissues during exposure to 24–28 °C, with earlier and stronger accumulation in the heat-hardened group. This pattern suggests that prior thermal conditioning enhances the capacity to mobilize neurotransmitter precursors and stress-related signaling molecules [23]. Under salinity stress, metabolomic analyses of low-salinity-tolerant families of the razor clam *S. constricta* showed enrichment of phenylalanine and tyrosine metabolism, with tyrosine and L-epinephrine identified as differential metabolites [40]. These findings indicate that aromatic amino acid remodeling may extend beyond substrate metabolism to catecholamine-like signaling involved in osmotic adaptation and systemic homeostasis.

Overall, aromatic amino acids tend to accumulate or be redistributed during thermal and salinity stress. By supporting the production of catecholamines, serotonin, kynurenine derivatives, and other neuroactive or immune-related metabolites—pathways that are well-established in vertebrate systems—aromatic amino acid metabolism may contribute to neuroregulation, immune signaling, and coordinated stress adaptation in bivalves.

3.7. Lysine Metabolism and Histidine Metabolism: Stress Adaptation and Metal Binding

Lysine and histidine metabolism have distinct but complementary roles in bivalve stress adaptation. Histidine is functionally important because its imidazole side chain has

a pKa close to physiological pH, allowing for reversible protonation and deprotonation under intracellular conditions. This property enables histidine and histidine-rich proteins to participate in acid–base buffering, metal coordination, and redox regulation [101]. These functions are particularly relevant to bivalves, which are filter-feeding animals that often inhabit coastal environments with fluctuating pH, suspended particles, and metal pollutants. Lysine, in contrast, is important both as a metabolic substrate whose degradation products can enter the TCA cycle and as a major site for post-translational modifications, especially lysine acetylation, which regulates enzyme activity, cytoskeletal organization, and gene expression [91].

Under environmental stress, histidine-related metabolism is frequently associated with detoxification and antioxidant buffering, whereas lysine-related responses are often linked to stress-responsive protein regulation. In Mediterranean mussels *M. galloprovincialis* exposed to microplastics, histidine metabolism was among the most significantly disturbed pathways, with marked changes in histidine and related metabolites, suggesting its involvement in oxidative stress responses and metabolic compensation [49]. In blue mussels, histidine-rich glycoproteins in body fluids were shown to bind multiple metals, including Cu, Zn, Cd, Hg, and Ni, supporting their role in metal transport and detoxification in hemolymph [75]. Cadmium exposure experiments further demonstrated that histidine-rich glycoproteins alter cadmium speciation in mussel plasma, indicating their contribution to metal complexation and internal distribution [102]. For lysine, acetylome analysis in pearl oysters after nucleus implantation stress showed that differentially acetylated proteins were enriched in cytoskeletal regulation, stimulus response, and metabolic processes, implying rapid remodeling of protein networks under stress [103].

Overall, histidine metabolism is mainly characterized by buffering, metal-binding, and detoxification-related functions, whereas lysine metabolism contributes more strongly to stress-responsive protein regulation through reversible acetylation. Together, these pathways provide bivalves with chemical buffering capacity and regulatory flexibility, supporting cellular homeostasis under pollutant, implantation, and other environmental stresses.

3.8. Integration of Amino Acid Metabolic Pathways with Central Stress-Response Networks

Amino acid metabolism in bivalves can be regarded as an integrated stress-response network rather than a collection of isolated pathways [13]. As discussed above, environmental stressors such as heat stress, hypoxia, salinity fluctuations, pollutant exposure, and pathogen challenge elicit both stressor-specific and shared alterations in amino acid profiles [4,12,24–26]. To conceptualize these interactions, a putative metabolic network is proposed in Figure 1. Within this framework, branched-chain amino acid metabolism, together with alanine, aspartate, and glutamate metabolism, is closely linked to the TCA cycle, anaerobic energy compensation, and nitrogen balance, thereby supporting ATP production and energy redistribution under stress [4,12,26]. Glycine, serine, and threonine metabolism, together with cysteine and methionine metabolism, is associated with compatible osmolyte accumulation, one-carbon metabolism, sulfur metabolism, glutathione synthesis, and antioxidant defense [9,64,91]. Arginine and proline metabolism contributes to nitrogen disposal, nitric oxide signaling, ATP buffering, immune modulation, and osmotic regulation, whereas aromatic amino acid metabolism participates in neuroendocrine signaling and stress coordination through catecholamine-, serotonin-, and kynurenine-related pathways [26,100]. In addition, lysine- and histidine-associated metabolism may facilitate protein regulation, acid–base buffering, metal binding, and detoxification [12]. Although metabolite responses vary depending on stress type, intensity, exposure duration, tissue, developmental stage, and species, these pathways ultimately converge on several core physiological processes, including energy reallocation, redox homeostasis, cell

volume regulation, immune defense, and cellular homeostasis [1,25]. Collectively, amino acid metabolic remodeling provides a key biochemical basis for enhanced stress tolerance in bivalves.

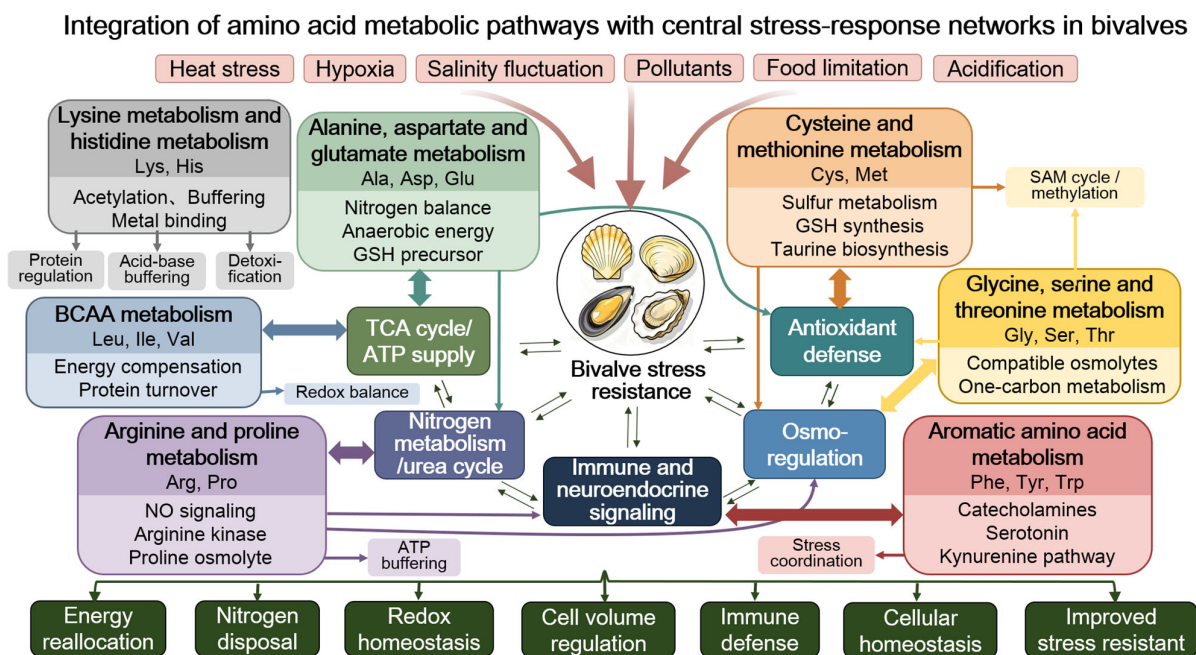


Figure 1. Schematic representation of the integrated amino acid metabolic network in bivalves under environmental stress. The diagram depicts major amino acids and their related metabolic pathways, organized according to KEGG classification and corresponding to the pathways discussed in Sections 3.1–3.8. Amino acids are grouped by pathway and displayed with color-coded frames to distinguish different KEGG pathways for visual clarity; these colors do not imply quantitative or functional differences. Arrows indicate metabolic flow or functional coupling between pathways and metabolites, and line styles do not imply quantitative flux magnitudes. Abbreviations: Met, methionine; Cys, cysteine; Tau, taurine; Hyp, hypotaurine; β -Ala, β -alanine; Ser, serine; Gly, glycine; Thr, threonine; Ala, alanine; Asp, aspartate; Asn, asparagine; Glu, glutamate; Gln, glutamine; Arg, arginine; Pro, proline; GSH, glutathione; GSSG, glutathione disulfide; BCAA, branched-chain amino acids (leucine, isoleucine, valine); Lys, lysine; Phe, phenylalanine; Tyr, tyrosine; Trp, tryptophan; His, histidine; TCA, tricarboxylic acid; GABA, γ -aminobutyric acid.

4. From Mechanistic Insights to Aquaculture Applications: Improving Bivalve Health and Resilience

4.1. Precision Nutrition Strategies

Nutritional intervention has been proposed as a potential route to improve bivalve stress tolerance, but its application must account for the feeding characteristics of bivalves. During grow-out in raft, bottom, or offshore culture systems, bivalves mainly rely on natural plankton and are rarely supplied with formulated diets [104,105]. Thus, precision nutrition is most feasible during hatchery and broodstock conditioning stages. In hatcheries, amino acid supply can be adjusted by optimizing microalgal diets or microencapsulated feeds, whereas in broodstock conditioning, diets with balanced amino acid profiles may enhance nutrient reserves, reproductive performance, and offspring robustness [53,106,107]. In addition, the ability of bivalves to absorb dissolved free amino acids through the gills provides a potential short-term intervention route during acute stress in grow-out systems [108,109]. However, these strategies remain largely speculative and await systematic validation under practical culture conditions.

Different amino acids may be targeted according to stress type and production stage. Under heat or hypoxic stress, branched-chain amino acids can be catabolized to provide reducing equivalents and TCA-cycle intermediates, thereby supporting mitochondrial energy metabolism [86,110]. Proline, glycine, and taurine are more closely associated with osmotic regulation, membrane stabilization, and antioxidant defense, making them particularly relevant for salinity-fluctuating habitats [16,93]. Although direct bivalve-specific evidence is scarce, fish studies are cited here to illustrate conserved metabolic and nutritional principles, based on the evolutionary conservation of gene function and enzyme structure. On this basis, it might be hypothesized that BCAAs and glutamate could be supplied through enriched microalgae, microencapsulated diets, waterborne addition, or slow-release formulations during summer heat and hypoxia, whereas proline, glycine, and taurine might be useful in estuarine areas with strong salinity variation. These proposals, however, remain speculative at present. Further studies are needed to determine effective doses, delivery methods, ecological safety, and field applicability before any of these approaches can be considered for practical application.

4.2. Molecular Markers for Selective Breeding

Genetic improvement provides a complementary strategy to nutritional intervention for enhancing stress resistance in bivalves. With the increasing availability of transcriptomic, genomic, and metabolomic data, genes involved in key stress-related metabolic pathways have become promising sources of molecular markers [111]. For example, enzymes involved in glutathione synthesis, such as glutamate–cysteine ligase (GCL) and glutathione synthetase (GSS), are often highly expressed in pollution-tolerant bivalves, suggesting that favorable alleles or expression patterns of these genes may be used as candidate markers for selecting pollution-resistant strains [3]. Similarly, the differential expression of proline transporter (PROT) and taurine transporter (TAUT) under salinity stress provides potential indicators for screening salinity-tolerant lines [16]. Markers associated with energy metabolism may also be useful for improving thermal and hypoxia tolerance. Branched-chain α -keto acid dehydrogenase complex-related genes, which regulate BCAA catabolism, and arginine kinase (AK), which buffers cellular energy supply, have been linked to high-temperature tolerance [86]. These genes may therefore serve as candidate markers for identifying individuals with stronger metabolic flexibility under environmental stress.

In future breeding programs, such pathway-based markers should be integrated with genome-wide association studies, quantitative trait loci mapping, and family-based selection to improve their reliability and applicability [112–115]. Validation across species, populations, and farming environments will be essential before these markers can be routinely used in selective breeding.

4.3. Metabolite-Based Indicators for Bivalve Health Assessment

Amino acid profiles provide sensitive metabolic readouts for assessing bivalve health, stress burden, and physiological resilience in aquaculture environments. Metabolomics studies show that disruptions in amino acid metabolism are common early responses to pollutant exposure [13,54,55]. Metabolites such as taurine, glutathione, proline, and alanine are frequently altered across contaminant types and participate in key processes, including osmoregulation, antioxidant defense, and energy metabolism, making them promising candidates for biomonitoring.

However, their use as biomarkers faces several challenges. First, these metabolites are not specific to a single stressor; their levels can be influenced by environmental factors such as temperature, salinity, and oxygen availability, as well as physiological variables

including nutritional status, reproductive stage, and tissue type. Their interpretation therefore requires contextualization rather than direct attribution to a specific pollutant. Second, biomarker sensitivity may vary across species, tissues, and developmental stages, while both the direction and magnitude of responses are often exposure-dependent, complicating the establishment of universal reference ranges. Third, steady-state metabolomics is descriptive and does not directly quantify pathway flux; complementary approaches, such as stable-isotope tracing or enzyme activity assays, are needed to support functional interpretation [5,6].

Thus, although amino acids and their derivatives are promising candidate biomarkers for early pollutant-induced physiological disturbance, their application in routine aquaculture health assessment requires systematic field validation across species, tissues, life stages, and exposure scenarios. Integration with physiological and environmental data will be essential to improve specificity and interpretability.

4.4. Future Research Directions

Future research on amino acid metabolism in bivalves should move toward higher resolution and greater integration. First, emerging approaches such as single-cell sequencing and spatial metabolomics can help identify cell-type-specific metabolic responses to aquaculture-relevant environmental challenges. For example, ion-transporting cells in the gills and immune-related cells in the mantle may regulate amino acid metabolism differently under the same stressor, consistent with tissue-specific metabolic patterns reported in previous studies [68]. These tools will provide a clearer understanding of how distinct cell populations contribute to stress adaptation and physiological resilience. Second, the role of host-associated microbiota warrants further investigation. Microorganisms inhabiting filter-feeding bivalves may participate in amino acid deamination, taurine metabolism, and other metabolic processes that indirectly influence host stress tolerance [22,29]. Combining metagenomics, metabolomics, and metabolic flux analysis would help quantify the contribution of host–microbe co-metabolism to amino acid homeostasis under aquaculture-relevant environmental fluctuations. Third, more attention should be given to the combined effects of multiple stressors. In natural and farming environments, bivalves are rarely exposed to a single factor, but instead face concurrent challenges such as warming, ocean acidification, hypoxia, and pollution. Although single-stressor studies provide useful mechanistic baselines, combined exposures may generate synergistic or antagonistic metabolic responses [49]. Factorial experimental designs and realistic multi-stress models are therefore needed to improve predictions of bivalve performance, health status, and production resilience. Finally, laboratory-based mechanistic studies should be more closely linked with aquaculture applications. Molecular markers associated with amino acid metabolism, including key enzyme genes and metabolite signatures, could be integrated with functional feed development to establish a “gene–metabolism–nutrition” regulatory framework. This strategy would help translate basic research into practical tools for improving stress resistance and supporting sustainable bivalve aquaculture.

4.5. Methodological Considerations and Knowledge Gaps

Before concluding, several limitations of the current literature should be acknowledged. First, the studies reviewed here differ substantially in experimental design, including exposure duration, stress intensity, tissue selection, analytical platform, and bivalve species. This methodological heterogeneity complicates cross-study comparisons and may partly explain inconsistent findings, such as opposite changes in the same amino acid under different conditions. These discrepancies suggest that amino acid responses are highly context-dependent, and their underlying mechanisms remain unclear, warranting

systematic investigation under standardized frameworks. Second, most available evidence is derived from acute laboratory exposures, whereas chronic, multigenerational, and field-based studies remain limited. As a result, it is still unclear whether the metabolic changes observed in short-term experiments represent adaptive responses with long-term fitness benefits or transient physiological disturbances. Third, most metabolomic studies are inherently correlative. Steady-state metabolite levels do not directly reflect pathway flux, and changes in amino acid abundance may result from multiple processes, including altered synthesis, degradation, transport, or tissue redistribution. Establishing causal links between specific metabolic adjustments and organismal performance, such as survival, growth, and reproduction, will require complementary approaches, including stable-isotope tracing, metabolic flux analysis, enzyme activity assays, and functional perturbation experiments. In addition, nearly all studies reviewed here focus on marine bivalves; whether freshwater species exhibit comparable patterns of amino acid metabolic remodeling under thermal or hypoxic stress remains an open question that warrants comparative investigation. Addressing these limitations will be essential for moving beyond descriptive metabolomic patterns toward a mechanistic understanding of bivalve stress physiology and for developing evidence-based applications in aquaculture.

5. Conclusions

In summary, bivalves respond to aquaculture-relevant environmental stressors, including elevated temperature, hypoxia, salinity fluctuation, and pollutants, through coordinated remodeling of amino acid metabolism. These responses mainly involve four interconnected functions. First, branched-chain amino acids, alanine, and glutamate are mobilized to support energy production through transamination, deamination, and replenishment of the TCA cycle. Second, free amino acids such as proline, glycine, and taurine act as compatible osmolytes to maintain cell volume and ion balance. Third, sulfur-containing amino acids, including cysteine and methionine, contribute to glutathione synthesis and antioxidant defense. Fourth, arginine-related pathways, aromatic amino acid metabolism, and one-carbon metabolism participate in immune regulation, signaling, and methylation processes. Together, these mechanisms form an integrated metabolic network that supports bivalve stress tolerance and physiological resilience under variable culture and marine conditions.

From an applied perspective, amino acid metabolism provides useful targets for sustainable bivalve aquaculture. Hypothetically, functional amino acid supplementation might enhance tolerance to heat, hypoxia, salinity fluctuation, and pollutant-related stress, but effective doses, delivery methods, and field applicability remain to be determined. Similarly, key metabolic genes and metabolite signatures could, in principle, inform the breeding of stress-resistant strains, although such markers have yet to be validated in actual selective breeding programs. Future integration of metabolomics, genomics, and functional validation will be essential to further clarify the role of amino acid metabolism in stress adaptation and to provide a scientific basis for improving bivalve health management and aquaculture practices.

Supplementary Materials: The following supporting information can be downloaded at <https://www.mdpi.com/article/10.3390/fishes11080460/s1>, Table S1: Summary of reported amino acid alterations, related metabolic pathways, and physiological responses in bivalves under environmental stress; Table S2: Abbreviations and full names.

Author Contributions: Conceptualization, Y.L. and Z.T.; methodology, Y.L.; validation, J.P.; formal analysis, W.C. and X.Z.; investigation, Y.L., W.C., J.P., X.Z., Y.D., M.G., Y.Z., H.W., G.Z. and Q.G.; resources, W.C.; data curation, Y.L., W.C., J.P., X.Z., Y.D., M.G., Y.Z., H.W., G.Z. and Q.G.; writing—original draft preparation, Y.L. and W.C.; writing—review and editing, Z.T.; visualization, Y.L., W.C., Y.D. and X.Z.; supervision, Z.T.; project administration, Z.T.; funding acquisition, Y.L. and Z.T. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the National Natural Science Foundation of China (42506128); the Natural Science Foundation of Shandong Province, ZR2024QD190; the Central Public-interest Scientific Institution Basal Research Fund, YSFRI, CAFS, 20603022024016; Central Public-interest Scientific Institution Basal Research Fund, CAFS, 2023TD76, 2026TX14; and the Earmarked Fund for CARS, CARS-49.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The original contributions presented in this study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Conflicts of Interest: The authors declare no conflicts of interest.

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