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Review

The Impact of Fermented Gamma-Aminobutyric Acid on Poultry Growth Performance Through Insulin-like Growth Factor-1 Activation

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Abstract: Gamma-aminobutyric acid (GABA) is becoming more well-acknowledged for its ability to improve the development performance of poultry, particularly by interacting with the Insulin-like growth Factor 1 (IGF-1) pathway. This review emphasizes the importance of GABA in optimizing poultry production by thoroughly examining its biochemical characteristics, physiological roles, and molecular mechanisms of action. GABA is a crucial inhibitory neurotransmitter that not only regulates neuronal excitability but also optimizes metabolic processes critical for growth. Supplementing poultry feeds with GABA has been shown to enhance feed conversion efficiency, increase body weight, and bolster immune function. The interplay between GABA and IGF-1 is crucial, as GABA modulates IGF-1 levels and receptor sensitivity, promoting muscle development and overall metabolic health. This review emphasizes the importance of fermentation processes in producing bioavailable GABA, presenting promising implications for sustainable poultry farming practices. Further investigation into GABA supplementation strategies in poultry could lead to improved growth performance and healthier production systems.

Keywords: gamma-aminobutyric acid; insulin-like growth factor-1; metabolism; growth performance; poultry

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1. Introduction

Gamma-aminobutyric acid (GABA) is a four-carbon non-protein amino acid with the chemical formula $C_4H_9NO_2$ and a 103.12 g/mol molecular weight. GABA exists naturally in plants, animals, and microbes [1,2]. The bioavailability of GABA through solid-state fermentation processes presents a promising implication for sustainable poultry farming practices. It is a crucial neurotransmitter in the central nervous system, maintaining the balance between excitation and inhibition by regulating neuronal excitability [3]. When GABA binds to its $GABA_A$ and $GABA_B$ receptors, it causes the hyperpolarization of neurons, reducing their excitability and lowering the likelihood of action potential firing. This mechanism is vital for motor control, preventing excessive muscle activity essential for

balance and coordination [4]. GABA's inhibitory effects promote calmness and tranquility by enhancing relaxation and alleviating anxiety, thus preserving the delicate equilibrium of brain neuronal activity while controlling various physiological processes [5]. GABA-related studies have gained popularity among researchers due to their numerous therapeutic applications, including their potential role in enhancing growth performance in poultry [6,7]. Understanding the mechanisms behind GABA can enable the development of targeted medicines and interventions for addressing growth performance and productive potential in poultry.

GABA can be produced through several processes, including chemical synthesis, plant enrichment, enzymatic processing, and microbial generation, each with implications for its use in animal feed. GABA is produced from L-glutamic acid via microwave-assisted decarboxylation with isophorone as an inducer, a method that may influence its efficacy in promoting growth [8]. While GABA chemical synthesis offers faster reaction rates and higher yields, health concerns associated with caustic reactants and toxic by-products limit its applicability in food products [9,10]. Due to these health concerns, chemically produced GABA has been prohibited as a food additive, necessitating alternative production methods for safe application in animal nutrition [6,7]. GABA can be efficiently produced using an enzymatic method involving L-glutamate as a raw material and glutamate decarboxylase (GAD) as a catalyst, which may enhance its suitability for poultry diets [11,12]. Microbial production represents a promising alternative for producing GAD from complex fermentation broth, utilizing renewable resources while minimizing environmental pollutants, an important consideration for sustainable practices in the food and pharmaceutical industries.

As we explore the therapeutic potential of GABA in enhancing growth performance, it is essential to consider its relevance to poultry farming. Poultry, including a wide variety of small- to medium-sized birds, has become a cornerstone of agricultural and culinary industries, valued for their meat and eggs, and representing a highly profitable segment of the livestock sector [13]. Understanding poultry growth performance is essential for optimizing yield and ensuring sustainable practices. The rapid growth rates of poultry contribute to shorter production cycles, allowing farmers to maximize profitability; some poultry breeds can reach market weight in as little as five to eight weeks [14,15]. Poultry are known for their high feed conversion efficiency, often requiring just 2 kg of feed to produce 1 kg of live weight [16,17]. This efficiency not only reduces feed costs but also enhances resource utilization, thereby improving farmers' cash flow compared to conventional livestock species [18]. Furthermore, poultry welfare is closely linked to overall health and growth performance, enabling breeders to monitor growth rates for the early detection of health issues [19,20]. Improved genetic selection has led to better-growing strains that satisfy consumer demand for ethically raised poultry, focusing on disease resistance and feed efficiency [21,22].

As we delve deeper into the factors influencing poultry growth performance, it is essential to highlight the role of Insulin-like Growth Factor 1 (IGF-1). IGF-1 is a crucial signaling molecule that influences cellular activities necessary for growth, development, and metabolism [23]. These 70-amino-acid peptide hormones, similar to insulin, play a vital role in health and disease [24]. Growth hormone stimulates IGF-1 production and interacts with the IGF-1 receptor (IGF-1R), a transmembrane tyrosine kinase [25]. The binding of IGF-1 to IGF-1R activates intrinsic kinase activity and downstream signaling pathways, which promote cell division, survival, differentiation, and proliferation [26,27]. IGF-1 levels are regulated by growth hormones, dietary conditions, and IGF-binding proteins (IGFBPs) [28]. This paper aims to demonstrate that GABA positively influences quail growth performance by modulating the IGF-1 pathway, thereby enhancing muscle development and improving

feed utilization. This underscores GABA's potential as a nutritional supplement in poultry farming to optimize growth performance and increase production efficiency.

2. GABA Production Through Fermentation

GABA is produced by effective and sustainable fermentation techniques that involve a variety of microorganisms, most notably lactic acid bacteria (LAB) and fungi [29]. The ability of LAB, including *Lactobacillus brevis*, *Lactobacillus plantarum*, *Lactococcus lactis*, and others, to use GAD to enzymatically convert L-glutamate, an abundant amino acid present in many protein sources, into GABA has made them important GABA producers. GABA is produced by this bioconversion, which also improves the safety and preservation of fermented foods, allowing them to be used in human and animal diets [30,31]. Research demonstrates that the ability of LAB to produce GABA can differ greatly among various strains. For example, *L. brevis* has been recognized for its notably high GABA output, reaching up to 205 g/L under ideal fermentation conditions [32]. Elements such as pH, temperature, and nutrient levels have been identified as factors that enhance GABA production during fermentation. LAB including *Lactobacillus buchneri*, *Lactobacillus delbrueckii subsp. bulgaricus*, and certain strains of *Streptococcus thermophilus* also exhibit GABA-producing potential, making them promising options for creating GABA-enriched fermented foods shown in Table 1 [33,34].

In contrast to LAB, several fungi, especially those from the *Rhizopus* genus, play a role in GABA generation during fermentation [35]. Varieties such as *R. oligosporus* and *R. oryzae* are known to raise GABA levels when fermenting soy products like tempeh, while marine yeasts, including *Pichia guilliermondii* and *Pichia anomala*, show notable abilities for GABA production [36]. Additionally, other fungi, like *Aspergillus oryzae*, serve as starter cultures in the fermentation of sake and soy sauce, consequently boosting the GABA content in these items [37].

The application of microbial fermentation not only promotes the production of GABA but also enhances the nutritional quality of the end products, increasing their digestibility and bioavailability. By incorporating GABA-rich fermented feeds into poultry diets, farmers may enhance growth performance, nutrient uptake, and overall health in livestock, thereby fostering more sustainable agricultural practices [38]. Ongoing research into GABA biosynthesis via fermentation methods offers opportunities to optimize nutritional strategies in the poultry sector, resulting in better productivity and health benefits for both animals and humans [39]. The potential application of GABA-rich fermented products in poultry nutrition highlights the need for further research into the stability and efficacy of these fermentation processes. By harnessing the capabilities of LAB and fungi in GABA production, the poultry industry can embrace innovative methods for enhancing animal welfare and optimizing production systems, contributing to a more sustainable approach to food production [40].

Table 1. GABA production using solid-state fermentation with different microorganism species.

Microorganism	Fermentation Condition	GABA Production (mg/L)	References
L. brevis RK03	30 °C, pH: 4.5, Inoculum: 1×10^{-9} CFU/mL, 88 h	62.523	[41]
S. thermophilus	37 °C, pH: 6.0, 48 h	8300	[41]
L. brevis	37 °C, 48 h	4	[42]
L. brevis	37 °C, pH: 5.0	205	[43]
L. brevis	37 °C, pH: 5.0	210	[43]
L. plantarum FNCC 260	37 °C, pH: 5.0	352	[30]
L. brevis HY1	30 °C, 48 hr, pH: 5.0	18.76	[44]

Table 1. *Cont.*

Microorganism	Fermentation Condition	GABA Production (mg/L)	References
L. plantarum K16 strain	34 °C, pH 5.5, 96 h	1284	[45]
Debaryomyces hansenii	29 °C for 24–48 h	6790	[46]
L. plantarum K154	7 days at 25 °C	15.53	[47]
L. plantarum FRT7	40 °C, pH 7.0, 48 h	1158.6 ± 21.22	[48]
K. marxianus JMY140K	40 °C for 48 h	125.6	[49]
Debaryomyces hansenii	30 hr at 30 °C	179.2	[50]
S. cerevisiae DL6–20	28 °C, pH 7	1890	[51]
Aspergillus oryzae NSK	7 days, 30 °C	354.08	[52]
Aspergillus oryzae	30 °C, pH 6.0	51.53	[53]
Rhizopus oryzae	30 °C, pH 6.0	50	[43]
L. futsaii CS3	pH 5, 37 °C	6.840	[54]

3. Mechanism of Action of GABA

3.1. Biochemistry of GABA

GABA, a four-carbon non-proteinogenic amino acid initially synthesized in 1883 and thought to be exclusive to plants and microbes, was later discovered in the mammalian brain and subsequently identified across diverse organisms, including animals, bacteria, and fungi [55]. In biological systems, GABA is synthesized from glutamate through the GABA shunt. This synthesis is catalyzed by the enzyme L-glutamic acid decarboxylase, with pyridoxal phosphate serving as a co-factor. Gamma-aminobutyrate transaminase then metabolizes GABA into an intermediate metabolite, succinate semialdehyde. This intermediate can either be reduced to gamma-hydroxybutyrate or oxidized to succinate, which is eventually converted to CO_2 and water via the citric acid cycle as documented in Figure 1 [56]. GABA is critical to the central nervous system functioning, where 60–75% of all synapses are GABAergic. In animals, GABA serves as the major inhibitory neurotransmitter in the CNS. It is estimated that at least one-third of all CNS neurons in poultry utilize GABA as their primary neurotransmitter. Additionally, approximately 30% of human cerebral neurons contain GABA, which influences nearly all neuronal activities [57]. The biological production of GABA is achieved by various strains of bacteria, fungi, and yeast using cell immobilization or co-culturing techniques. Biologically produced GABA is considered safe for food applications. Among different groups of microorganisms, LAB are significant GABA producers. LAB are considered safe and commercially used as starter cultures in many food fermentations. Notable LAB strains evaluated for GABA production include *Lactococcus lactis*, *Lactobacillus brevis*, *Lactobacillus helveticus*, *Lactobacillus paracasei*, *Lactobacillus plantarum*, and *Streptococcus thermophilus* [58]. Some food products are enriched with GABA through various LAB such as raspberry juice, soy yogurt, cheese, kimchi, and sourdough [59]. Moreover, it is expected that GABA is produced through the decarboxylation of glutamic acid by *Rhizopus*. Soy protein is rich in glutamic acid, and it has been reported that tempeh, a traditional non-salted soybean fermented by *Rhizopus* spp. in Indonesia, contains higher amounts of peptides and free amino acids than unfermented soybeans. This difference is attributed to the hydrolytic breakdown of soybean proteins that occur during fermentation. Consequently, the content of free glutamic acid in tempeh is suggested to be greater than that in unfermented soybeans [60].

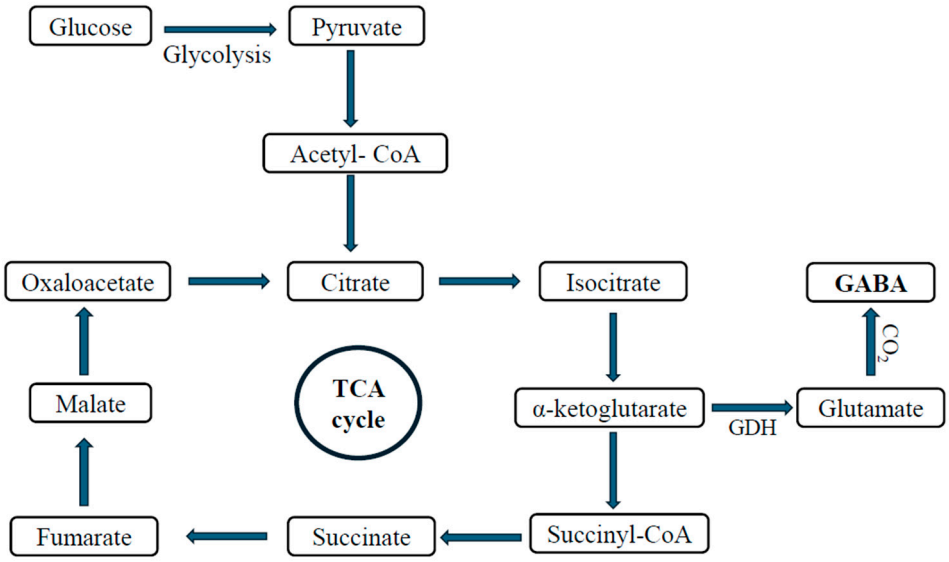


Figure 1. GABA synthesis through metabolic pathway associated with the tricarboxylic acid cycle.

3.2. Physiological Functions of GABA

The multifaceted role of GABA in poultry nutrition encompasses enhancing growth performance, improving resilience to stress, and supporting overall physiological health. By modulating the IGF-1 pathway, GABA contributes to optimizing metabolic functions, strengthening immune responses, and improving feed conversion efficiency [61]. In poultry, GABA's regulatory effects help maintain homeostasis, promote skeletal muscle development, and enhance nutrient absorption. Moreover, GABA plays a pivotal role in enabling poultry to adapt effectively to environmental stressors, such as heat and overcrowding, ultimately ensuring better growth and productivity under challenging rearing conditions [62]. Thus, understanding GABA's dual role in promoting growth performance while safeguarding neuronal integrity is essential for optimizing poultry farming practices. The physiological functions of GABA are significant, particularly in response to nerve tissue damage, which triggers an inflammatory response that releases various mediators, including cytokines, reactive oxygen species (ROS), and nitric oxide (NO). It has been demonstrated that GABA enhances neuroprotection by halting the deterioration caused by toxins or trauma [63]. For example, GABA produced by *Lactobacillus buchneri* from kimchi has been shown to protect against neurotoxicity-induced cell death [64]. By activating $GABA_A$ and $GABA_B$ receptors, GABA significantly impacts cholinergic and non-adrenergic noncholinergic (NANC) neurotransmission in the enteric nervous system (ENS), playing a crucial role in regulating gastrointestinal functions such as secretion, peristalsis, and sensory perception [65]. Apart from its role in the central nervous system, the ENS is a complex network of neurons located within the gut wall that controls gastrointestinal function. The myenteric plexus, which contains GAD, neurons, and mucosal endocrine-like cells, serves as a source of GABA in the gut. $GABA_B$ receptors are implicated in reducing the amplitude of electrically induced ileal cholinergic contractions, while $GABA_A$ receptors regulate excitation and inhibition in the small intestine by modulating NO production and acetylcholine release in longitudinal muscle preparations [66].

3.3. Molecular Mechanisms of GABA Action

The observed benefits of GABA in enhancing growth efficiency underscore the need to explore its underlying molecular mechanisms. Understanding how GABA interacts with its receptors and crosses the blood-brain barrier is crucial for elucidating its health benefits and therapeutic applications in promoting optimal growth. GABA, a neurotransmitter, has

historically been thought to be unable to cross the blood-brain barrier (BBB), prompting questions about the mechanisms behind its health benefits. Differing perspectives exist regarding BBB permeability, with some suggesting only limited GABA crossing and others proposing significant amounts. The discovery of GABA-transporter systems in the brain facilitating the passage of solutes via transcytosis, carrier-mediated transport, or simple diffusion of hydrophobic substances adds complexity to this debate as shown in Figure 2 [67]. Moreover, GABA's presence in the enteric nervous system suggests that it may influence the peripheral nervous system through the gut-brain axis [68]. Neurotransmitters are chemical substances that are crucial for transmitting nerve activity. Released in the synaptic cleft during nerve activity, they operate in a calcium-dependent manner. Specialized structures in synapses connect nerve cells and non-neuronal cells, mediating nerve activity through neurotransmitters [69]. These substances interact with specific receptors on the postsynaptic membrane, facilitating the transmission of nerve signals. Glutamate serves as the primary neurotransmitter for rapid excitatory synaptic transmission, while GABA is essential for rapid inhibitory synaptic transmission in the mammalian central nervous system [70].

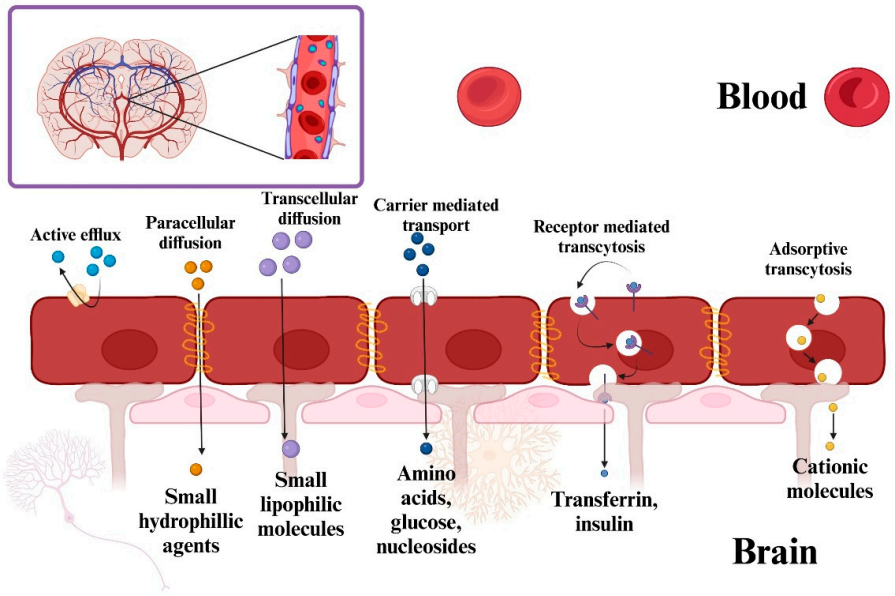


Figure 2. The transport of multiple specialized pathways across the blood-brain barrier into the brain involves paracellular diffusion, the solute-carrier transporter, receptor-mediated transcytosis, adsorptive transcytosis, and the efflux transporter.

About 20–50% of synapses in the CNS utilize GABA for fast and slow inhibitory synaptic transmission. GABA binds specific transmembrane receptors on the plasma membrane of pre-and postsynaptic neurons, particularly at inhibitory synapses in the brain. This binding opens ion channels, allowing Cl^- ions to enter the cell or K^+ ions to exit, resulting in a negative change in transmembrane potential and causing hyperpolarization as mentioned in Figure 3. GABAergic neurotransmission involves three receptor types: $GABA_A$, $GABA_B$, and $GABA_C$. $GABA_A$ and $GABA_C$ are ionotropic receptors, while $GABA_B$ is a metabotropic G-protein-coupled receptor [71]. Around 20–50% of synapses in the central nervous system contain inhibitory $GABA_A$ receptors, which are the primary receptors in the brain. $GABA_A$ receptors belong to the cystine loop ligand-gated ion channel superfamily and feature a loop with 13 conserved amino acids between two cysteine residues [72]. Composed of five protein subunits arranged in a ring, these receptors form pores that are selective for Cl^- ions. There are diverse types of $GABA_A$ receptors formed from at least 19 different subunits, exhibiting distinct spatial and temporal expressions

that influence the functional properties of $GABA_A$ inhibition. $GABA_A$ receptors can be activated by various compounds, leading to increased chloride conductance, and they are selectively blocked by bicuculline while being modulated by benzodiazepines, steroids, and barbiturates [73]. $GABA_B$ receptors, which belong to the metabotropic G-protein-coupled receptor family, function through G-protein-mediated calcium and potassium signaling mechanisms. They inhibit neurotransmission by suppressing presynaptic calcium channels and exert inhibitory effects in the postsynaptic phase via G-protein-coupled potassium signaling. Molecular studies, including cloning and mutagenesis, highlight the essential role of $GABA_B$ receptors in the central nervous system. Two genes, $GABA_{BR1}$ and $GABA_{BR2}$, code for subunits with multiple isoforms. $GABA_B$ receptors exist as heterodimers and activate second messenger systems such as phospholipase C and adenylate cyclase while also influencing K^+ and Ca^{2+} ion channels through G-protein-coupled signaling [74].

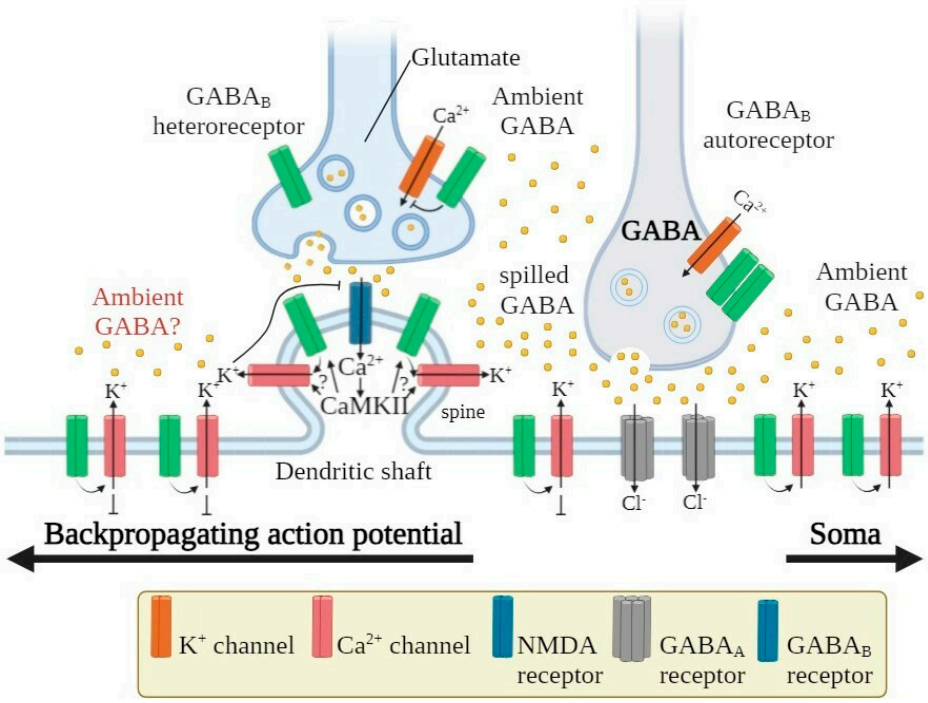


Figure 3. Chloride and potassium ion exchange channel pathway.

4. IGF-1 Pathway

4.1. Overview of IGF-1 and Its Role in Growth Regulation

Understanding the intricate interactions between ligands such as IGF-1 and their receptors is essential for elucidating the molecular mechanisms that influence poultry growth performance. The activation of the IGF-1 pathway not only regulates cellular functions but also plays a critical role in optimizing growth and development in poultry. Three ligands IGF-1, IGF-2, and insulin along with three cell membrane receptors IGF-1R, the insulin receptor (IR), and the IGF-2 receptor, as well as six high-affinity IGF binding proteins (IGFBPs), form the foundation of the IGF-1 pathway. IGFBPs regulate the bioavailability of these ligands in tissues by binding to IGF-I and IGF-II in the blood [28]. The IGF-1R is a receptor tyrosine kinase composed of a heterotetramer of two extracellular ligand-binding α subunits and two β subunits that form the transmembrane and tyrosine kinase domains. At the amino acid sequence level, it shares a 60% similarity with the IR [75]. Both IGF-1 and IGF-2 have a high affinity for the IGF-1R. Tyrosine residues become auto-phosphorylated as a result of the de-inhibition of intrinsic tyrosine kinase activity caused by ligand binding to the IGF-1R. Consequently, substrates bind to the protein, initiating phosphorylation

cascades that help convey the IGF-1R signal, which primarily promotes cell proliferation; as a consequence, cell survival is enhanced [76].

4.2. Signaling Pathways Activated by IGF-1

IGF-1 is an essential hormone involved in development, growth regulation, and metabolism, mediating the anabolic effects of GH. Its actions are crucial for cellular processes such as protein synthesis and cell proliferation, particularly in muscle and bone tissues. It has a variety of local and systemic effects and is primarily produced in the liver. The growth hormone from the pituitary gland stimulates the production of IGF-1. Additionally, factors such as age, hormonal balance, and nutrition can influence IGF-1 levels [77]. IGF-1 binds to the tyrosine kinase receptor known as the IGF-1R to initiate its effects. This interaction activates the main downstream signaling pathways, which increase protein production and inhibit apoptosis, promoting cell growth, survival, and metabolism. These processes are particularly important for the division and proliferation of cells in tissues such as bone and muscle [76]. IGF-1 promotes the growth of various tissues, including cartilage, muscle, and bone. It is vital for muscle growth and repair, as it promotes the proliferation of satellite cells and their differentiation into muscle fibers. Additionally, IGF-1 plays a crucial role in bone development by encouraging osteoblasts [23]. IGF-1 affects energy homeostasis, improves insulin sensitivity, and influences the metabolism of fats and carbohydrates. It plays a crucial role in the growth and maturation of organs during prenatal and postnatal development. Exercise raises IGF-1 levels, which can promote muscle adaptation and recovery. However, IGF-1 levels decrease with age, impacting bone density, muscle mass, and overall metabolic health [78]. IGF-1 is a critical growth factor that regulates various physiological processes, including metabolism and muscle growth. It significantly impacts both health and disease through specific receptors and downstream signaling cascades. Understanding how IGF-1 functions in both healthy and diseased states can help identify potential therapeutic targets for conditions related to growth and metabolism [79].

4.3. Interaction Between GABA and the IGF-1 Pathway

GABA, the main inhibitory neurotransmitter in the CNS, is essential for synaptic plasticity, neuronal excitability, and overall brain function [80]. Recent research has begun to clarify the complex relationships between GABA and the IGF-1 pathway, highlighting their importance in maintaining homeostasis and regulating biological functions. Beyond its primary role as an inhibitory neurotransmitter, GABA also influences the IGF-1 pathway, contributing to the body's overall homeostatic balance [81]. GABA acts on both neuronal and non-neuronal cells to regulate the release of several hormones, including IGF-1. The regulation of growth and metabolic processes depends on the control of IGF-1 signaling, as it fundamentally influences cell proliferation, differentiation, and survival. In a physiologically healthy environment, GABA can enhance IGF-1 signaling, promoting cellular responses that support development and growth. Conversely, the disruption of GABA signaling can lead to decreased IGF-1 activity, contributing to various pathological conditions, including metabolic dysfunction and growth disorders [82].

$GABA_A$ receptors are ligand-gated ion channels that allow the entry of chloride ions (Cl^-) when activated by GABA. The resulting hyperpolarization of postsynaptic neurons increases neuronal excitability, which may indirectly influence IGF-1 secretion in the liver and other tissues [83]. This influx of chloride ions leads to the hyperpolarization of postsynaptic neurons, making them less exciting [84]. As a result, the overall neuronal excitability decreases, which can have significant implications for various physiological processes. Interestingly, this change in excitability may indirectly influence the secretion of IGF-1 in the

liver and other tissues [85]. Elevated IGF-1 levels are crucial for growth and metabolic regulation, highlighting the interconnectedness of neurotransmitter signaling and hormonal pathways. Furthermore, GABA's role extends beyond mere inhibition; it can modulate the activity of other signaling pathways involved in growth and metabolism [48,55]. Understanding these interactions provides insights into how GABA can affect not only neuronal function but also broader metabolic processes. Thus, the relationship between GABA and IGF-1 signaling underscores the importance of neurotransmitter balance in maintaining overall physiological homeostasis [86].

$GABA_B$ receptors are G-protein coupled receptors that utilize second messenger systems to regulate neuronal excitability. The activation of $GABA_B$ receptors can inhibit adenylyl cyclase, leading to reduced cyclic AMP (cAMP) levels, which may affect downstream signaling pathways, including those involving IGF-1. $GABA_B$ receptors are G-protein-coupled receptors that utilize second messenger systems to regulate neuronal excitability. Upon activation, these receptors inhibit adenylyl cyclase, leading to a decrease in cyclic AMP levels [85]. This reduction in cAMP can significantly affect various downstream signaling pathways, including those involving IGF-1. By modulating the levels of cAMP, GABAB receptors influence the activity of protein kinases and other signaling molecules that are crucial for cellular responses. This interaction highlights the intricate relationship between neurotransmitter signaling and hormonal pathways [87]. Additionally, GABAB receptor activation can also impact ion channel activity, further contributing to changes in neuronal excitability. The overall effect of $GABA_B$ receptor signaling is a fine-tuning of neuronal communication and metabolic processes.

Through protein-protein interactions, GABA can directly or indirectly influence the activity of IGF-1R. For instance, the GABA-induced activation of GABA receptors may lead to alterations in the phosphorylation of proteins associated with IGF-1 signaling, such as Akt and Insulin Receptor Substrate-1 (IRS-1). Depending on the specific context and type of GABA receptor activated, this modulation can either enhance or inhibit the signaling cascades downstream of IGF-1R [88].

Changes in the interaction between GABA and the IGF-1 pathway can significantly impact the growth and development of poultry as demonstrated in Table 2. For example, reduced IGF-1 levels have been associated with decreased GABA signaling, which may hinder cell proliferation and differentiation in tissues such as muscle and bone. This impairment can lead to stunted growth in poultry, underscoring the importance of GABA in their developmental processes [81]. On the other hand, excessive GABA signaling may inhibit IGF-1 activity, potentially leading to growth deficiencies in poultry. Healthy developmental trajectories in poultry depend on the delicate balance between GABAergic repression and IGF-1-mediated growth promotion. The impact of GABA on the IGF-1 pathway also extends to metabolic control. By interacting with IGF-1 signaling, GABA can enhance glucose metabolism and improve insulin sensitivity in poultry. GABA is essential for modulating IGF-1 signaling through various biochemical pathways that influence cellular functions. Changes in this interaction can lead to pathological conditions, making therapeutic approaches targeting the GABA-IGF-1 pathway appealing for treating issues related to growth and metabolism. With further investigation, a deeper understanding of this interaction could result in innovative therapeutic strategies that leverage GABA's regulatory effects on the IGF-1 pathway.

Table 2. Impact of dietary GABA supplementation on growth performance and productivity effectiveness of poultry.

Species	Conditions	Outcome	Reference
Broiler Ross 308	100 mg/kg of GABA in feed, exposed to dexamethasone-induced stress	Improved growth performance, enhanced antioxidant status, and reduced inflammation response.	[89]
Broiler Ross 308 and Cobb 500	100 mg/kg of GABA in diet, exposed to heat stress (33 ± 2 °C for 5 h/day for 2 weeks)	Increased body weight, weight gain, and feed intake; reduced body temperature under heat stress.	[90]
Broilers	Dietary GABA supplementation, and growth and immune response assessment	Improved growth metrics and enhanced immune function.	[91]
Broiler strain Ross 308	100 mg/kg of GABA in feed, chronic heat stress (33 ± 2 °C for 5 h/day over 3 weeks)	Improved jejunal histology, reduced villus atrophy and crypt hyperplasia, enhanced intestinal integrity and nutrient absorption, and lower oxidative stress markers (e.g., malondialdehyde levels).	[92]
Quail	20–100 mg/kg of GABA in feed,	Increased body weight gain and feed efficiency (e.g., +10–15% compared to control), improved feed conversion ratio, enhanced antibody production (increased IgG and IgM levels), and improved gut integrity.	[91]
Broiler chicks Ross 308 one-day-old	50–100 mg/kg of GABA dietary supplementation	Reduced corticosterone levels and heterophil-to-lymphocyte ratio and lower oxidative stress markers (e.g., malondialdehyde).	[93]
Broiler	In ovo injection of 0.1 g/mL of GABA	Enhanced body weight gain and feed conversion ratio in GABA-treated birds, and increased early post-hatch growth rates.	[94]
Broiler Ross 308 one-day-old chicks	50–100 mg/kg of dietary GABA supplementation under high stocking density	Improved body weight gain, enhanced feed conversion ratio, and reduced mortality rates under high-stocking-density stress.	[95]
Hy-Line Brown laying hens	25 mg/kg, 50 mg/kg, and 100 mg/kg	Improved egg production rate, reduced feed-to-egg conversion ratio, enhanced shell thickness and strength, and improved yolk color and Haugh unit.	[96]
Hy-line Brown layers (32 weeks old)	0, 25, 50, and 100 ppm of GABA supplementation	Increased egg production rate, improved feed-to-egg conversion ratio, enhanced yolk color and Haugh unit, and increased antioxidant enzyme activity (e.g., superoxide dismutase, glutathione peroxidase).	[97]
Cherry Valley ducks	50–100 mg/kg of GABA supplementation in feed	Improved body weight gain and better feed conversion ratio.	[98]

5. Molecular Insights into GABA's Influence on the IGF-1 Pathway

5.1. GABAergic Regulation of IGF-1 Expression

GABA serves as the primary neurotransmitter used by GABAergic neurons, playing a critical role in the central nervous system by modulating neuronal activity and ensuring homeostatic balance. Recent studies have highlighted their influence on peripheral metabolic processes, particularly in the regulation of IGF-1 expression. IGF-1, a peptide hormone, plays critical roles in the metabolism, growth, and development of tissues, organs, and overall physiological systems in poultry. Understanding how GABAergic neurons control the production of IGF-1 is vital for elucidating metabolic diseases and exploring

potential treatment options [80,86]. $GABA_A$ and $GABA_B$ receptors are the primary GABA receptors through which GABA exerts potential effects. Upon activation of $GABA_A$ receptors, chloride ions (Cl^-) flood into the postsynaptic neuron, leading to hyperpolarization of the cell. In contrast, the activation of $GABA_B$ receptors initiates G-protein-coupled signaling pathways that influence intracellular calcium levels and cAMP signaling [99,100]. The hyperpolarization induced by $GABA_A$ receptor activation can suppress excitatory neurotransmission, thereby altering overall neuronal activity, which plays a crucial role in the regulation of IGF-1 production [4]. GABAergic neurons in the hypothalamus play a crucial role in regulating metabolism. They can modulate the activity of neuropeptides associated with growth and metabolism, such as somatostatin and growth-hormone-releasing hormone (GHRH), which directly influence the liver's synthesis of IGF-1 [101]. For instance, when GABAergic transmission inhibits the release of GHRH, it leads to a decrease in GH secretion from the pituitary gland, subsequently reducing hepatic IGF-1 production [102].

GABAergic neuron activity significantly influences IGF-1-transcription-regulating signaling pathways, with the phosphoinositide 3-kinase (PI3K)/Akt pathway being particularly important. The activation of $GABA_B$ receptors can enhance PI3K signaling, leading to the phosphorylation and activation of transcription factors such as Forkhead box O (FoxO), which in turn boosts IGF-1 transcription [103]. Another key mechanism involves the mitogen-activated protein kinase (MAPK) pathway, where GABA signaling can modulate extracellular-signal-regulated kinases (ERKs), thereby affecting the expression of the IGF-1 gene [104]. Peroxisome proliferator-activated receptors (PPARs) are nuclear receptors whose expression can be modulated by GABAergic neurons and are linked to the regulation of IGF-1. The activation of PPARs can alter the transcription of the IGF-1 gene through interactions with specific response elements in its promoter region [105]. Furthermore, GABAergic signaling has been shown to influence the expression of neurotrophic factors such as brain-derived neurotrophic factors (BDNF), which indirectly affects IGF-1 regulation by modulating metabolic and neural processes [106]. GABAergic neurons utilize intricate signaling networks and chemical interactions to regulate the expression of IGF-1. By modulating hypothalamic activity, these neurons orchestrate a coordinated response that impacts growth and metabolism through the regulation of key intracellular signaling cascades and the expression of essential transcription factors and neurotrophic factors. Understanding these pathways could pave the way for new treatment options for metabolic diseases associated with dysregulated IGF-1 levels [107].

5.2. Crosstalk Between GABAergic Signaling and IGF-1 Pathway Components

The interplay between GABAergic signaling and the IGF-1 pathway is crucial for regulating poultry growth performance, as GABA influences IGF-1 expression and activity through various signaling mechanisms. Understanding this crosstalk can provide insights into optimizing growth and metabolic health in poultry. In the CNS, GABAergic signaling is primarily mediated by GABA, which is crucial for regulating neuronal activity and maintaining homeostasis. Recent data indicate that the IGF-1 pathway, essential for growth, body development, and metabolic regulation, interacts significantly with GABAergic signaling [108]. Complex pathways involving GABA receptors and associated proteins influence IGF-1 signaling components, contributing to this crosstalk that affects various physiological processes [88].

The primary receptors regulating GABAergic signaling are $GABA_A$ and $GABA_B$ receptors. The activation of $GABA_B$ receptors can modulate intracellular signaling pathways, which is essential for IGF-1 signaling [109]. In contrast, the activation of $GABA_A$ receptors inhibits excitatory neuronal activity, potentially affecting the release of neuropeptides to regulate the hepatic synthesis of IGF-1, including somatostatin and growth hormone-

releasing hormone [110]. When IGF-1 binds to IGF-1R, it activates several downstream signaling pathways. GABAergic signaling can enhance these pathways by altering intracellular calcium levels and cAMP, thereby influencing IGF-1R function [48]. Furthermore, GABAergic-signaling-related proteins, such as GAD and GABA transporters, can impact IGF-1 signaling and modify the bioavailability of GABA [111]. Changes in GAD expression can affect GABA levels, which in turn influence the mechanisms regulating IGF-1. Additionally, brain-derived neurotrophic factor (BDNF) has been shown to stimulate IGF-1 receptor signaling in neuronal contexts, which may indirectly impact IGF-1 signaling [81].

GABAergic signaling and IGF-1 work together to maintain glucose homeostasis. By modulating IGF-1 signaling, GABAergic neurons can influence insulin sensitivity and glucose uptake in peripheral tissues, suggesting that abnormalities in this crosstalk may lead to insulin resistance. IGF-1 is crucial for the development and differentiation of neurons [112]. Additionally, GABAergic signaling impacts IGF-1 expression during brain development, which has implications for synaptic plasticity and neurogenesis [61]. Understanding the interplay between GABAergic signaling and IGF-1 could aid in identifying new biomarkers and treatment targets for various metabolic conditions [113,114].

5.3. Implications for Poultry Growth Performance

The interplay between GABA and IGF-1 is crucial for optimizing poultry growth performance, as GABA influences neurotransmitter systems that regulate feeding behavior, leading to increased feed intake. This enhanced appetite, combined with IGF-1's role in promoting metabolic processes, underscores the importance of both factors in achieving better growth rates and feed conversion efficiency in poultry [81]. GABA affects the neurotransmitter systems that control feeding behavior, thereby modulating hunger. Higher GABA levels in poultry can lead to increased feed intake, enhancing the availability of energy for growth [115]. Both IGF-1 and GABA improve feed conversion efficiency; IGF-1 enhances metabolic processes that facilitate the utilization of nutrients for body mass accumulation, while GABA supports intestinal health and reduces stress to optimize nutrient absorption. Better growth rates are directly correlated with improved feed utilization [81]. In poultry, the interaction between GABA and IGF-1 contributes to increased body weight gain. Research indicates that IGF-1 encourages muscular hypertrophy and overall growth, while GABA's role in appetite promotion ensures that poultry consumes sufficient diets to support growth [116]. Supplementing a poultry diet with GABA has been shown to increase body weight and improve feed conversion rates. For example, poultry on a GABA-enriched diet exhibited significantly faster growth rates compared to control groups [117]. An adequate diet raises IGF-1 levels, promoting growth and improving carcass quality [118].

The effects of IGF-1 and GABA on poultry development hold considerable potential for advancing poultry production practices, improving growth performance, and enhancing overall efficiency. Farmers can enhance poultry growth rates, feed efficiency, and overall health by optimizing diets supplemented with GABA and creating environments that promote elevated IGF-1 levels [119]. Potential applications include (1) adding GABA to feed formulations to boost growth and increase appetite, particularly during brooding and rearing stages of development [120]; and (2) maximizing IGF-1 levels by providing optimal conditions for growth hormone release, such as sufficient space, low stress, and a proper diet [121]. Both IGF-1 and GABA are essential for poultry growth. Their influence on appetite, feed utilization, and body weight gain suggests that incorporating these factors into poultry farming practices could improve animal welfare and productivity [122]. Continued advanced research into their mechanisms and applications will advance the field of poultry nutrition and management.

6. Future Perspective

GABA is increasingly recognized as a potential growth enhancer for poultry. It may interact with the IGF-1 signaling pathway to influence growth performance. Understanding these mechanisms can improve the overall health and productivity of poultry production. GABA primarily serves as an inhibitory neurotransmitter in the central nervous system, its effects extend beyond neuronal regulation to include endocrine activities, such as hormone production, including IGF-1. GABA may stimulate the pituitary gland to secrete GH, which subsequently prompts the liver to produce IGF-1. By indirectly influencing IGF-1 levels, GABA could enhance nutritional metabolism, increasing the availability of amino acids and glucose, key substrates for IGF-1 production, by improving feed intake and digestion as mentioned in Figure 4. This increased nutrient supply may further stimulate IGF-1 synthesis, promoting muscle growth. Additionally, GABA's anxiolytic properties may reduce stress in poultry, which is crucial since stress can inhibit growth by affecting feeding and nutrient absorption. By enhancing feed conversion and elevating IGF-1 levels, GABA fosters a calm physiological state that supports growth performance. IGF-1 is vital for muscle growth and repair; thus, enhancing muscle protein synthesis through GABA's role in stimulating IGF-1 release can improve growth rates and carcass quality in poultry, especially during critical growth stages.

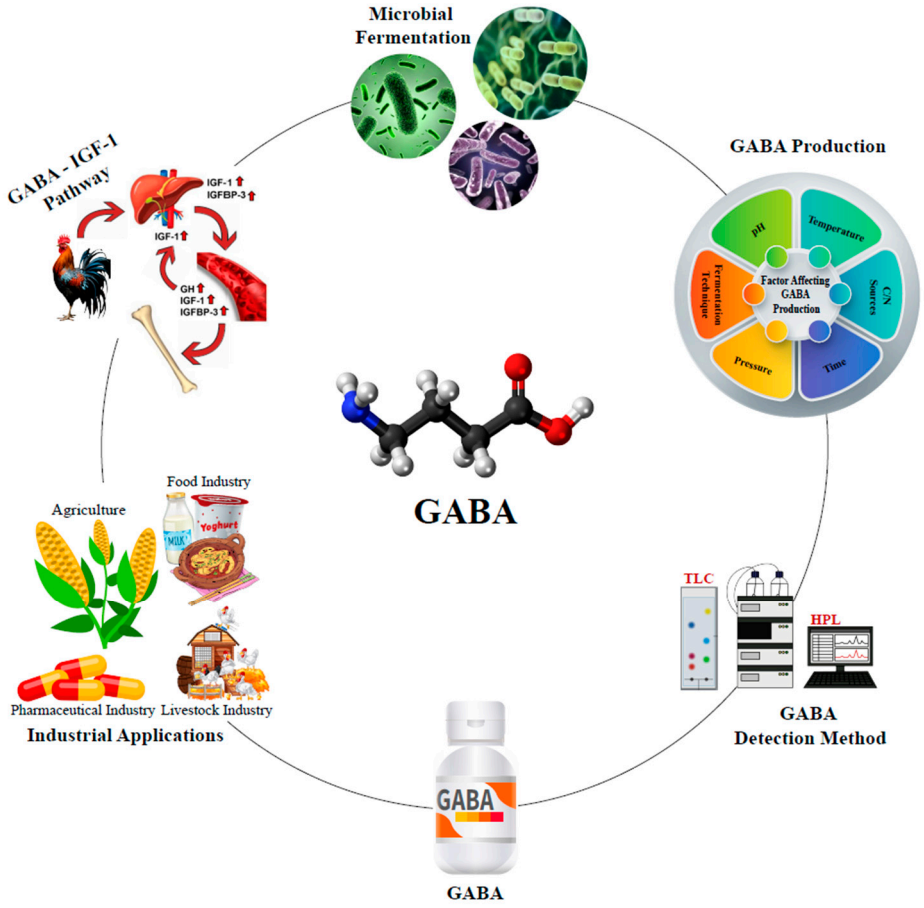


Figure 4. Schematic illustration of GABA-IGF-1 pathway in poultry.

Given its potential to boost growth rates via its interaction with the IGF-1 signaling pathway, GABA represents a promising feed additive in the poultry production industry. By stimulating appetite and enhancing the IGF-1 pathway, GABA could improve feed conversion rates, leading to reduced production costs and increased profitability for poultry producers. Higher IGF-1 levels are associated with enhanced muscle growth and meat

quality, which is essential for meeting global market demands for safe poultry products. Furthermore, by alleviating stress-related growth inhibition, GABA's anxiolytic effects may contribute to the overall health and well-being of poultry.

Establishing the optimal GABA dosage and delivery mechanism is crucial; excessive GABA could have adverse physiological effects or diminish growth potential. Different poultry species may exhibit varying sensitivities to GABA, influenced by factors such as age, genetics, and environment. Regulatory scrutiny may also apply to the application of GABA as a feed supplement for poultry. Widespread acceptance will require compliance with safety and efficacy standards. Although short-term benefits are promising, further studies are necessary to understand the long-term effects of GABA supplementation on poultry growth, health, and overall well-being. Continued research into the intriguing possibility that GABA can enhance poultry growth performance by modulating the IGF-1 signaling pathway is warranted. By exploring the mechanisms of action of GABA, its advantages, and its limitations, researchers and poultry farmers can develop strategies to maximize poultry yield. As demand for efficient and sustainable poultry farming practices rises, GABA may become an effective tool for enhancing flock health and growth performance. Further exploration of the interactions among GABA, IGF-1, and poultry physiology is crucial for fully understanding and harnessing their potential benefits.

7. Conclusions

In summary, this review highlights the pivotal role of GABA in enhancing poultry growth performance through its interaction with the IGF-1 signaling pathway. The evidence presented indicates that GABA not only functions as a critical neurotransmitter but also significantly promotes growth and metabolic efficiency in poultry. The modulation of IGF-1 levels and receptor sensitivity by GABA suggests a promising avenue for improving growth rates and overall health in avian species. By optimizing dietary GABA supplementation, poultry producers can potentially enhance the productivity and welfare of poultry populations. Further research should focus on elucidating the precise mechanisms by which GABA influences IGF-1 signaling and exploring its applications in various poultry management practices. Understanding these interactions will be crucial for developing targeted nutritional strategies that leverage GABA's benefits, ultimately contributing to more sustainable and efficient poultry production systems. In conclusion, integrating GABA into poultry nutrition represents a novel and impactful approach to enhancing growth performance, with implications that extend beyond various poultry species, including broilers, layers, and quails. Further exploration of this pathway may unlock new opportunities for advancing poultry science and improving agricultural outcomes.

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List of Abbreviations

GABA	Gamma-aminobutyric acid
IGF-1	Insulin-like Growth Factor-1
GAD	Glutamate 54 decarboxylase
IGF-1R	Insulin-like Growth Factor-1 receptor

LAB	Lactic acid bacteria
ROS	Reactive oxygen species
NO	Nitric oxide
ENS	Enteric nervous system
BBB	Blood–brain barrier
CNS	Central nervous system
IGFBPs	IGF binding proteins
Camp	Cyclic adenosine monophosphate
GHRH	Growth-hormone-releasing hormone
PI3K	Phosphoinositide 3-kinase
MAPK	Mitogen-activated protein kinase

References

1. Rashmi, D.; Zanan, R.; John, S.; Khandagale, K.; Nadaf, A. γ-aminobutyric acid (GABA): Biosynthesis, role, commercial production, and applications. *Stud. Nat. Prod. Chem.* **2018**, *57*, 413–452.
2. Li, H.; Cao, Y. Lactic acid bacterial cell factories for gamma-aminobutyric acid. *Amino Acids* **2010**, *39*, 1107–1116. [CrossRef]
3. Xu, N.; Wei, L.; Liu, J. Biotechnological advances and perspectives of gamma-aminobutyric acid production. *World J. Microbiol. Biotechnol.* **2017**, *33*, 64. [CrossRef] [PubMed]
4. Kilb, W. When are depolarizing GABAergic responses excitatory? *Front. Mol. Neurosci.* **2021**, *14*, 747835. [CrossRef] [PubMed]
5. Liwinski, T.; Lang, U.E.; Brühl, A.B.; Schneider, E. Exploring the Therapeutic Potential of Gamma-Aminobutyric Acid in Stress and Depressive Disorders through the Gut–Brain Axis. *Biomedicines* **2023**, *11*, 3128. [CrossRef]
6. Diana, M.; Quílez, J.; Rafecas, M. Gamma-aminobutyric acid as a bioactive compound in foods: A review. *J. Funct. Foods* **2014**, *10*, 407–420. [CrossRef]
7. Wu, Q.; Shah, N.P. High γ-aminobutyric acid production from lactic acid bacteria: Emphasis on Lactobacillus brevis as a functional dairy starter. *Crit. Rev. Food Sci. Nutr.* **2017**, *57*, 3661–3672. [CrossRef]
8. Lie, Y.; Farmer, T.J.; Macquarrie, D.J. Facile and rapid decarboxylation of glutamic acid to γ-aminobutyric acid via microwave-assisted reaction: Towards valorisation of waste gluten. *J. Clean. Prod.* **2018**, *205*, 1102–1113. [CrossRef]
9. Koubaa, M.; Delbecq, F.; Roohinejad, S.; Mallikarjunan, K. Gamma-aminobutyric acid. In *Encyclopedia of Food Chemistry*; Montoya; Elsevier: Oxford, UK, 2019; pp. 528–534.
10. Boonstra, E.; De Kleijn, R.; Colzato, L.S.; Alkemade, A.; Forstmann, B.U.; Nieuwenhuis, S. Neurotransmitters as food supplements: The effects of GABA on brain and behavior. *Front. Psychol.* **2015**, *6*, 167121. [CrossRef] [PubMed]
11. Wang, Q.; Xin, Y.; Zhang, F.; Feng, Z.; Fu, J.; Luo, L.; Yin, Z. Enhanced γ-aminobutyric acid-forming activity of recombinant glutamate decarboxylase (gadA) from Escherichia coli. *World J. Microbiol. Biotechnol.* **2011**, *27*, 693–700. [CrossRef]
12. Huang, Y.; Su, L.; Wu, J. Pyridoxine supplementation improves the activity of recombinant glutamate decarboxylase and the enzymatic production of gama-aminobutyric acid. *PLoS ONE* **2016**, *11*, e0157466. [CrossRef]
13. Mnisi, C.; Mararenі, M.; Manyeula, F.; Madibana, M. A way forward for the South African quail sector as a potential contributor to food and nutrition security following the aftermath of COVID-19: A review. *Agric. Food Secur.* **2021**, *10*, 48. [CrossRef] [PubMed]
14. Mahmud, M.A.; Shaba, P.; James, G. Growth performance of growing quails (*Coturnix japonica*) fed graded levels of Neem leave meal. *Int. J. Appl. Res.* **2015**, *1*, 4–7.
15. Adom, E.; Bir, C.; Lambert, L.H. A financial comparison of small-scale quail and laying hen farm enterprises. *Poult. Sci.* **2023**, *102*, 102507. [CrossRef] [PubMed]
16. Zhou, S.; Watcharaanantapong, P.; Yang, X.; Thornton, T.; Gan, H.; Tabler, T.; Prado, M.; Zhao, Y. Evaluating broiler welfare and behavior as affected by growth rate and stocking density. *Poult. Sci.* **2024**, *103*, 103459. [CrossRef]
17. Kaya Başar, E.; Narinç, D. Genetic Parameter Estimates of Growth Curve and Feed Efficiency Traits in Japanese Quail. *Animals* **2023**, *13*, 1765. [CrossRef] [PubMed]
18. El-Kholy, M.S.; El-Hindawy, M.M.; Alagawany, M.; Abd El-Hack, M.E.; El-Sayed, S.A. Use of acetylsalicylic acid as an allostatic modulator in the diets of growing Japanese quails exposed to heat stress. *J. Therm. Biol.* **2018**, *74*, 6–13. [CrossRef]
19. Javaid, M.; Haleem, A.; Khan, I.H.; Suman, R. Understanding the potential applications of Artificial Intelligence in Agriculture Sector. *Adv. Agrochem.* **2023**, *2*, 15–30. [CrossRef]
20. Arunrao, K.V.; Kannan, D.; Amutha, R.; Thiruvenkadan, A.K.; Yakubu, A. Production performance of four lines of Japanese quail reared under tropical climatic conditions of Tamil Nadu, India. *Front. Genet.* **2023**, *14*, 1128944. [CrossRef] [PubMed]
21. Goto, T.; Konno, S.; Konno, M. Establishment of Wild-Derived Strains of Japanese Quail (*Coturnix japonica*) in Field and Laboratory Experiments. *Biology* **2023**, *12*, 1080. [CrossRef]

22. Ida, B.; Kiendrebeogo, T.; Sanou, S. Technical-Economic Diagnosis and Development Prospects of Quail Farming in Burkina Faso. *Br. J. Multidiscip. Adv. Stud.* **2024**, *5*, 1–21. [CrossRef]
23. Ahmad, S.S.; Ahmad, K.; Lee, E.J.; Lee, Y.-H.; Choi, I. Implications of insulin-like growth factor-1 in skeletal muscle and various diseases. *Cells* **2020**, *9*, 1773. [CrossRef] [PubMed]
24. Bailes, J.; Soloviev, M. Insulin-like growth factor-1 (IGF-1) and its monitoring in medical diagnostic and in sports. *Biomolecules* **2021**, *11*, 217. [CrossRef] [PubMed]
25. Dehkhoda, F.; Lee, C.M.; Medina, J.; Brooks, A.J. The growth hormone receptor: Mechanism of receptor activation, cell signaling, and physiological aspects. *Front. Endocrinol.* **2018**, *9*, 35. [CrossRef]
26. Lee, W.-S.; Kim, J. Insulin-like growth factor-1 signaling in cardiac aging. *Biochim. Biophys. Acta Mol. Basis Dis.* **2018**, *1864*, 1931–1938. [CrossRef] [PubMed]
27. LeRoith, D.; Holly, J.M.; Forbes, B.E. Insulin-like growth factors: Ligands, binding proteins, and receptors. *Mol. Metab.* **2021**, *52*, 101245. [PubMed]
28. Yoshida, T.; Delafontaine, P. Mechanisms of IGF-1-mediated regulation of skeletal muscle hypertrophy and atrophy. *Cells* **2020**, *9*, 1970. [CrossRef]
29. Mohd Ali, N.; Mohd Yusof, H.; Long, K.; Yeap, S.K.; Ho, W.Y.; Beh, B.K.; Koh, S.P.; Abdullah, M.P.; Alitheen, N.B. Antioxidant and hepatoprotective effect of aqueous extract of germinated and fermented mung bean on ethanol-mediated liver damage. *Biomed. Res. Int.* **2013**, *2013*, 693613. [CrossRef] [PubMed]
30. Iorizzo, M.; Paventi, G.; Di Martino, C. Biosynthesis of Gamma-Aminobutyric Acid (GABA) by *Lactiplantibacillus plantarum* in fermented food production. *Curr. Issues Mol. Biol.* **2023**, *46*, 200–220. [CrossRef] [PubMed]
31. Liu, J.-M.; Fehér, C.; Cao, M.; Lu, F.; Jensen, P.R. Lactic acid bacteria: Microbial metabolism and expanding applications. *Front. Bioeng. Biotechnol.* **2021**, *9*, 794164. [CrossRef]
32. Wang, Q.; Liu, X.; Fu, J.; Wang, S.; Chen, Y.; Chang, K.; Li, H. Substrate sustained release-based high efficacy biosynthesis of GABA by Lactobacillus brevis NCL912. *Microb. Cell Fact.* **2018**, *17*, 80. [CrossRef]
33. Franciosi, E.; Carafa, I.; Nardin, T.; Schiavon, S.; Poznanski, E.; Cavazza, A.; Larcher, R.; Tuohy, K.M. Biodiversity and γ-aminobutyric acid production by lactic acid bacteria isolated from traditional alpine raw cow's milk cheeses. *Biomed. Res. Int.* **2015**, *2015*, 625740. [CrossRef]
34. Zhuang, K.; Jiang, Y.; Feng, X.; Li, L.; Dang, F.; Zhang, W.; Man, C. Transcriptomic response to GABA-producing Lactobacillus plantarum CGMCC 1.2437 T induced by L-MSG. *PLoS ONE* **2018**, *13*, e0199021. [CrossRef] [PubMed]
35. Lowe, D.P.; Arendt, E.K. The use and effects of lactic acid bacteria in malting and brewing with their relationships to antifungal activity, mycotoxins and gushing: A review. *J. Inst. Brew.* **2004**, *110*, 163–180. [CrossRef]
36. Aoki, H.; Uda, I.; Tagami, K.; Furuya, Y.; Endo, Y.; Fujimoto, K. The production of a new tempeh-like fermented soybean containing a high level of γ-aminobutyric acid by anaerobic incubation with Rhizopus. *Biosci. Biotechnol. Biochem* **2003**, *67*, 1018–1023. [CrossRef]
37. Yee, C.S.; Sohedein, M.N.A.; Suan, O.P.; Loen, A.W.W.; Abd Rahim, M.H.; Soumaya, S.; Ilham, Z.; Wan, W.A.A.Q.I. The production of functional γ-aminobutyric acid Malaysian soy sauce koji and moromi using the trio of Aspergillus oryzae NSK, Bacillus cereus KBC, and the newly identified Tetragenococcus halophilus KBC in liquid-state fermentation. *Future Foods* **2021**, *4*, 100055.
38. Devi, P.B.; Rajapuram, D.R.; Jayamanohar, J.; Verma, M.; Kavitake, D.; Avany, B.A.M.; Rani, P.U.; Ravi, R.; Shetty, P.H. Gamma-aminobutyric acid (GABA) production by potential probiotic strains of indigenous fermented foods origin and RSM based production optimization. *LWT* **2023**, *176*, 114511. [CrossRef]
39. Diez-Gutiérrez, L.; San Vicente, L.; Barrón, L.J.R.; del Carmen Villarán, M.; Chávarri, M. Gamma-aminobutyric acid and probiotics: Multiple health benefits and their future in the global functional food and nutraceuticals market. *J. Funct. Foods* **2020**, *64*, 103669. [CrossRef]
40. Pannerchelvan, S.; Rios-Solis, L.; Wong, F.W.F.; Zaidan, U.H.; Wasoh, H.; Mohamed, M.S.; Tan, J.S.; Mohamad, R.; Halim, M. Strategies for improvement of gamma-aminobutyric acid (GABA) biosynthesis via lactic acid bacteria (LAB) fermentation. *Food Funct.* **2023**, *14*, 3929–3948. [CrossRef]
41. Han, M.; Liao, W.-y.; Wu, S.-m.; Gong, X.; Bai, C. Use of Streptococcus thermophilus for the in situ production of γ-aminobutyric acid-enriched fermented milk. *J. Dairy Sci.* **2020**, *103*, 98–105. [CrossRef]
42. Alizadeh Behbahani, B.; Jooyandeh, H.; Falah, F.; Vasiee, A. Gamma-aminobutyric acid production by Lactobacillus brevis A3: Optimization of production, antioxidant potential, cell toxicity, and antimicrobial activity. *Food Sci. Nutr.* **2020**, *8*, 5330–5339. [CrossRef] [PubMed]
43. Cui, Y.; Miao, K.; Niyaphorn, S.; Qu, X. Production of gamma-aminobutyric acid from lactic acid bacteria: A systematic review. *Int. J. Mol. Sci.* **2020**, *21*, 995. [CrossRef]
44. Lim, H.S.; Cha, I.-T.; Roh, S.W.; Shin, H.-H.; Seo, M.-J. Enhanced production of gamma-aminobutyric acid by optimizing culture conditions of Lactobacillus brevis HYE1 isolated from kimchi, a Korean fermented food. *J. Microbiol. Biotechnol.* **2017**, *27*, 450–459. [CrossRef] [PubMed]

45. Diez-Gutiérrez, L.; Vicente, L.S.; Sáenz, J.; Esquivel, A.; Barron, L.J.R.; Chávarri, M. Biosynthesis of gamma-aminobutyric acid by Lactiplantibacillus plantarum K16 as an alternative to revalue agri-food by-products. *Sci. Rep.* **2022**, *12*, 18904. [CrossRef]
46. Song, N.-E.; Lee, D.-B.; Lee, S.-H.; Baik, S.-H. Preparation of high GABA-enriched yeast extract by non-Saccharomyces yeasts isolated from korean traditional fermented soybean product. *Microbiol. Biotechnol. Lett.* **2021**, *49*, 320–328. [CrossRef]
47. Lee, E.-J.; Lee, S.-P. Novel bioconversion of sodium glutamate to γ-amino butyric acid by co-culture of Lactobacillus plantarum K154 in Ceriporia lacerata culture broth. *Food Sci. Biotechnol.* **2014**, *23*, 1997–2005. [CrossRef]
48. Cai, H.; Li, X.; Li, D.; Liu, W.; Han, Y.; Xu, X.; Yang, P.; Meng, K. Optimization of gamma-aminobutyric acid production by Lactiplantibacillus plantarum FRT7 from Chinese Paocai. *Foods* **2023**, *12*, 3034. [CrossRef]
49. Fan, T.-T.; Chen, C.; Zeng, D.-W.; Wang, F.-L.; Xu, Z.-X.; Jin, M.-J.; Zou, Y.; Li, J.; Zhao, X.-Q. Stress-Driven Production of γ-Aminobutyric Acid Using Non-Conventional Yeast Strains Kluyveromyces marxianus JMY140K and Metschnikowia reukaufii JMY075. *J. Fungi* **2025**, *11*, 20. [CrossRef]
50. Han, S.-M.; Lee, J.-S. Production and its anti-hyperglycemic effects of γ-aminobutyric acid from the wild yeast strain Pichia silvicola UL6-1 and Sporobolomyces carnicolor 402-JB-1. *Mycobiology* **2017**, *45*, 199–203. [CrossRef]
51. Li, S.; Zhang, Y.; Li, X.; Yin, P.; Wang, T.; Li, Y.; Zhang, K.; Sheng, H.; Lu, S.; Ji, H. The effect of the ratio of gamma aminobutyric acid-producing Saccharomyces cerevisiae DL6–20 and Kluyveromyces marxianus B13–5 addition on cheese quality. *Front. Microbiol.* **2022**, *13*, 900394. [CrossRef]
52. Hajar-Azhari, S.; Wan-Mohtar, W.A.A.Q.I.; Ab Kadir, S.; Rahim, M.H.A.; Saari, N. Evaluation of a Malaysian soy sauce koji strain Aspergillus oryzae NSK for γ-aminobutyric acid (GABA) production using different native sugars. *Food Sci. Biotechnol.* **2018**, *27*, 479–488. [CrossRef] [PubMed]
53. Ab Kadir, S.; Wan-Mohtar, W.A.A.Q.I.; Mohammad, R.; Abdul Halim Lim, S.; Sabo Mohammed, A.; Saari, N. Evaluation of commercial soy sauce koji strains of Aspergillus oryzae for γ-aminobutyric acid (GABA) production. *J. Ind. Microbiol. Biotechnol.* **2016**, *43*, 1387–1395. [CrossRef]
54. Thongruck, K.; Maneerat, S. Enhanced production of gamma-aminobutyric acid (GABA) from Lactobacillus futsaii CS3 using agri-food industries by-products under batch and fed-batch fermentation. *Indian J. Microbiol.* **2023**, *63*, 467–482. [CrossRef]
55. Hepsomali, P.; Groeger, J.A.; Nishihira, J.; Scholey, A. Effects of oral gamma-aminobutyric acid (GABA) administration on stress and sleep in humans: A systematic review. *Front. Neurosci.* **2020**, *14*, 559962. [CrossRef] [PubMed]
56. Oketch-Rabah, H.A.; Madden, E.F.; Roe, A.L.; Betz, J.M. United States Pharmacopeia (USP) safety review of gamma-aminobutyric acid (GABA). *Nutrients* **2021**, *13*, 2742. [CrossRef]
57. Wan, Y.; Wang, Q.; Prud'homme, G.J. GABAergic system in the endocrine pancreas: A new target for diabetes treatment. *Diabetes Metab. Syndr. Obes. Targets Ther.* **2015**, *8*, 79–87.
58. Icer, M.A.; Sarikaya, B.; Kocyigit, E.; Atabilen, B.; Çelik, M.N.; Capasso, R.; Ağagündüz, D.; Budán, F. Contributions of Gamma-Aminobutyric Acid (GABA) Produced by Lactic Acid Bacteria on Food Quality and Human Health: Current Applications and Future Prospects. *Foods* **2024**, *13*, 2437. [CrossRef]
59. Kim, D.-H.; Dasagrandhi, C.; Park, S.-K.; Eom, S.-H.; Huh, M.-K.; Mok, J.-S.; Kim, Y.-M. Optimization of gamma-aminobutyric acid production using sea tangle extract by lactic acid bacterial fermentation. *LWT* **2018**, *90*, 636–642. [CrossRef]
60. Chong, S.; Ilham, Z.; Samsudin, N.; Soumaya, S.; Wan-Mohtar, W.A.A.-Q.I. Microbial consortia and up-to-date technologies in global soy sauce production: A review. *Int. Food Res. J.* **2023**, *30*, 1–24. [CrossRef]
61. Chang de Pinho, I.; Giorelli, G.; Oliveira Toledo, D. A narrative review examining the relationship between mental health, physical activity, and nutrition. *Discov. Psychol.* **2024**, *4*, 162. [CrossRef]
62. He, W.; Furukawa, K.; Toyomizu, M.; Nochi, T.; Bailey, C.A.; Wu, G. Interorgan metabolism, nutritional impacts, and safety of dietary L-glutamate and L-glutamine in poultry. *Adv. Exp. Med. Biol.* **2021**, *1332*, 107–128.
63. Kim, K.; Yoon, H. Gamma-aminobutyric acid signaling in damage response, metabolism, and disease. *Int. J. Mol. Sci.* **2023**, *24*, 4584. [CrossRef] [PubMed]
64. Cho, Y.-R.; Chang, J.-Y.; Chang, H.-C. Production of gamma-Aminobutyric Acid (GABA) by Lactobacillus buchneri isolated from Kimchi and its neuroprotective effect on neuronal cells. *J. Microbiol. Biotechnol.* **2007**, *17*, 104–109.
65. Mogor, F.; Kovács, T.; Lohinai, Z.; Dora, D. The enteric nervous system and the microenvironment of the gut: The translational aspects of the microbiome-gut-brain axis. *Appl. Sci.* **2021**, *11*, 12000. [CrossRef]
66. Auteri, M.; Zizzo, M.G.; Serio, R. GABA and GABA receptors in the gastrointestinal tract: From motility to inflammation. *Pharmacol. Res.* **2015**, *93*, 11–21. [CrossRef] [PubMed]
67. Pardridge, W.M. A historical review of brain drug delivery. *Pharmaceutics* **2022**, *14*, 1283. [CrossRef] [PubMed]
68. Cryan, J.F.; Dinan, T.G. Mind-altering microorganisms: The impact of the gut microbiota on brain and behaviour. *Nat. Rev. Neurosci.* **2012**, *13*, 701–712.
69. Pradhan, A. Nanoelectrochemical Analysis of Neurotransmitter Release in Cell Models of Alzheimer's Disease. Doctoral Thesis, University of Gothenburg, Göteborg, Sweden, 2024.

70. Niciu, M.J.; Kelmendi, B.; Sanacora, G. Overview of glutamatergic neurotransmission in the nervous system. *Pharmacol. Biochem. Behav.* **2012**, *100*, 656–664. [CrossRef]
71. Qian, X.; Zhao, X.; Yu, L.; Yin, Y.; Zhang, X.-D.; Wang, L.; Li, J.-X.; Zhu, Q.; Luo, J.-L. Current status of GABA receptor subtypes in analgesia. *Biomed. Pharmacother.* **2023**, *168*, 115800. [CrossRef] [PubMed]
72. Carter, C.R.; Kozuska, J.L.; Dunn, S.M. Insights into the structure and pharmacology of GABAA receptors. *Future Med. Chem.* **2010**, *2*, 859–875. [CrossRef] [PubMed]
73. Jazvinscak Jembrek, M.; Vlainic, J. GABA receptors: Pharmacological potential and pitfalls. *Curr. Pharm. Des.* **2015**, *21*, 4943–4959. [CrossRef]
74. Frangaj, A.; Fan, Q.R. Structural biology of GABAB receptor. *Neuropharmacology* **2018**, *136*, 68–79. [CrossRef] [PubMed]
75. Maruyama, I.N. Mechanisms of activation of receptor tyrosine kinases: Monomers or dimers. *Cells* **2014**, *3*, 304–330. [CrossRef]
76. Werner, H. The IGF1 signaling pathway: From basic concepts to therapeutic opportunities. *Int. J. Mol. Sci.* **2023**, *24*, 14882. [CrossRef]
77. Blum, W.F.; Alherbish, A.; Alsagheir, A.; El Awwa, A.; Kaplan, W.; Koledova, E.; Savage, M.O. The growth hormone–insulin-like growth factor-I axis in the diagnosis and treatment of growth disorders. *Endocr. Connect.* **2018**, *7*, R212–R222. [CrossRef] [PubMed]
78. Clemmons, D.R. The relative roles of growth hormone and IGF-1 in controlling insulin sensitivity. *J. Clin. Investig.* **2004**, *113*, 25–27. [CrossRef]
79. Arjunan, A.; Sah, D.K.; Woo, M.; Song, J. Identification of the molecular mechanism of insulin-like growth factor-1 (IGF-1): A promising therapeutic target for neurodegenerative diseases associated with metabolic syndrome. *Cell Biosci.* **2023**, *13*, 16. [CrossRef]
80. Ochoa-de la Paz, L.D.; Gulias-Cañizo, R.; Ruíz-Leyja, E.D.; Sánchez-Castillo, H.; Parodí, J. The role of GABA neurotransmitter in the human central nervous system, physiology, and pathophysiology. *Rev. Mex. Neurocienc.* **2021**, *22*, 67–76. [CrossRef]
81. Athapaththu, A.M.G.K.; Molagoda, I.M.N.; Jayasooriya, R.G.P.T.; Choi, Y.H.; Jeon, Y.-J.; Park, J.-H.; Lee, B.-J.; Kim, G.-Y. Gamma-aminobutyric acid (GABA) promotes growth in zebrafish larvae by inducing IGF-1 expression via GABAA and GABAB receptors. *Int. J. Mol. Sci.* **2021**, *22*, 11254. [CrossRef]
82. Yagoub, S.; Lippert, R.N. Insulin/IGF signaling in early brain development. In *Physiological Consequences of Brain Insulin Action*; CRC Press: Boca Raton, FL, USA, 2022; pp. 21–33.
83. Dixon, C.L.; Sah, P.; Keramidas, A.; Lynch, J.W.; Durisic, N. γ1-Containing GABA-A receptors cluster at synapses where they mediate slower synaptic currents than γ2-containing GABA-A receptors. *Front. Mol. Neurosci.* **2017**, *10*, 178. [CrossRef] [PubMed]
84. Mihic, S.J.; Harris, R.A. GABA and the GABAA receptor. *Alcohol Res. Health* **1997**, *21*, 127.
85. Terunuma, M. Diversity of structure and function of GABAB receptors: A complexity of GABAB-mediated signaling. *Proc. Jpn. Acad. Ser. B Phys. Biol. Sci.* **2018**, *94*, 390–411. [CrossRef] [PubMed]
86. Almutairi, S.; Sivadas, A.; Kwakowsky, A. The Effect of Oral GABA on the Nervous System: Potential for Therapeutic Intervention. *Nutraceuticals* **2024**, *4*, 241–259. [CrossRef]
87. Tang, X.; Jaenisch, R.; Sur, M. The role of GABAergic signalling in neurodevelopmental disorders. *Nat. Rev. Neurosci.* **2021**, *22*, 290–307. [CrossRef]
88. Réthelyi, J.M.; Vincze, K.; Schall, D.; Glennon, J.; Berkel, S. The role of insulin/IGF1 signalling in neurodevelopmental and neuropsychiatric disorders–evidence from human neuronal cell models. *Neurosci. Biobehav. Rev.* **2023**, *153*, 105330. [CrossRef]
89. Fathi, M.; Saeedyan, S.; Kaoosi, M. Gamma-amino butyric acid (GABA) supplementation alleviates dexamethasone treatment-induced oxidative stress and inflammation response in broiler chickens. *Stress* **2023**, *26*, 2185861. [CrossRef] [PubMed]
90. El-Naggar, K.; El-Kassas, S.; Abdo, S.E.; Kirrella, A.A. Role of gamma-aminobutyric acid in regulating feed intake in commercial broilers reared under normal and heat stress conditions. *J. Therm. Biol.* **2019**, *84*, 164–175. [CrossRef]
91. Ncho, C.M.; Jeong, C.; Gupta, V.; Goel, A. The effect of gamma-aminobutyric acid supplementation on growth performances, immune responses, and blood parameters of chickens reared under stressful environment: A meta-analysis. *Environ. Sci. Pollut. Res.* **2021**, *28*, 45019–45028. [CrossRef] [PubMed]
92. Al Wakeel, R.A.; Shukry, M.; Abdel Azeez, A.; Mahmoud, S.; Saad, M.F. Alleviation by gamma amino butyric acid supplementation of chronic heat stress-induced degenerative changes in jejunum in commercial broiler chickens. *Stress* **2017**, *20*, 562–572. [CrossRef] [PubMed]
93. Jeong, S.-B.; Kim, Y.B.; Lee, J.-W.; Kim, D.-H.; Moon, B.-H.; Chang, H.-H.; Choi, Y.-H.; Lee, K.-W. Role of dietary gamma-aminobutyric acid in broiler chickens raised under high stocking density. *Anim. Nutr.* **2020**, *6*, 293–304. [CrossRef]
94. Ncho, C.M.; Goel, A.; Gupta, V.; Jeong, C.-M.; Choi, Y.-H. Effect of in ovo feeding of γ-aminobutyric acid combined with embryonic thermal manipulation on hatchability, growth, and hepatic gene expression in broilers. *Anim Biosci.* **2022**, *36*, 284. [CrossRef]
95. Han, J.-K.; Oh, M.; Park, K.-T.; Joo, Y. Effects of gamma aminobutyric acid on performance, blood cell of broiler subjected to multi-stress environments. *Anim. Biosci.* **2023**, *36*, 248–255.

96. Zhu, Y.; Cheng, J.; Ren, M.; Yin, L.; Piao, X. Effect of γ-aminobutyric acid-producing Lactobacillus strain on laying performance, egg quality and serum enzyme activity in Hy-Line brown hens under heat stress. *Asian-Australas. J. Anim. Sci.* **2015**, *28*, 1006. [CrossRef]
97. Park, J.; Kim, I. Effects of dietary gamma-aminobutyric acid on egg production, egg quality, and blood profiles in layer hens. *Vet. Med.* **2015**, *60*, 629–634. [CrossRef]
98. Zhigang, S.; Sheikhahmadi, A.; Li, Z. Effect of dietary γ-aminobutyric acid on performance parameters and some plasma metabolites in Cherry Valley ducks under high ambient temperature. *Iran. J. Vet. Res.* **2013**, *14*, 283–290.
99. Peerboom, C.; Wierenga, C.J. The postnatal GABA shift: A developmental perspective. *Neurosci. Biobehav. Revs.* **2021**, *124*, 179–192. [CrossRef] [PubMed]
100. Sallard, E.; Letourneur, D.; Legendre, P. Electrophysiology of ionotropic GABA receptors. *Cell. Mol. Life Sci.* **2021**, *78*, 5341–5370. [CrossRef]
101. Dos Santos, W.O.; Wasinski, F.; Tavares, M.R.; Campos, A.M.; Elias, C.F.; List, E.O.; Kopchick, J.J.; Szawka, R.E.; Donato, J., Jr. Ablation of growth hormone receptor in GABAergic neurons leads to increased pulsatile growth hormone secretion. *Endocrinology* **2022**, *163*, bqac103. [CrossRef]
102. Devesa, J.; Devesa, P. Pituitary Growth Hormone Secretion and Cell Growth Hormone Production: Regulation of Their Secretion and Their Signaling Pathways. In *Growth Hormone-Impact and Insights in Human Beings*; IntechOpen: London, UK, 2023.
103. Masliukov, P.M. Changes of Signaling Pathways in Hypothalamic Neurons with Aging. *Curr. Issues Mol. Biol.* **2023**, *45*, 8289–8308. [CrossRef] [PubMed]
104. Albert-Gascó, H.; Ros-Bernal, F.; Castillo-Gómez, E.; Olucha-Bordonau, F.E. MAP/ERK signaling in developing cognitive and emotional function and its effect on pathological and neurodegenerative processes. *Int. J. Mol. Sci.* **2020**, *21*, 4471. [CrossRef]
105. Qian, L.; Zhu, Y.; Deng, C.; Liang, Z.; Chen, J.; Chen, Y.; Wang, X.; Liu, Y.; Tian, Y.; Yang, Y. Peroxisome proliferator-activated receptor gamma coactivator-1 (PGC-1) family in physiological and pathophysiological process and diseases. *Signal Transduct. Target. Ther.* **2024**, *9*, 50. [PubMed]
106. Colucci-D'Amato, L.; Speranza, L.; Volpicelli, F. Neurotrophic factor BDNF, physiological functions and therapeutic potential in depression, neurodegeneration and brain cancer. *Int. J. Mol. Sci.* **2020**, *21*, 7777. [CrossRef]
107. Bálint, F.; Csillag, V.; Vastagh, C.; Liposits, Z.; Farkas, I. Insulin-like growth factor 1 increases GABAergic neurotransmission to gnRH neurons via suppressing the retrograde tonic endocannabinoid signaling pathway in mice. *Neuroendocrinology* **2021**, *111*, 1219–1230. [CrossRef] [PubMed]
108. Huang, D.; Alexander, P.B.; Li, Q.-J.; Wang, X.-F. GABAergic signaling beyond synapses: An emerging target for cancer therapy. *Trends Cell Biol.* **2023**, *33*, 403–412. [CrossRef]
109. Negri, S.; Scolari, F.; Vismara, M.; Brunetti, V.; Faris, P.; Terribile, G.; Sancini, G.; Berra-Romani, R.; Moccia, F. $GABA_A$ and $GABA_B$ Receptors Mediate GABA-Induced Intracellular Ca^{2+} Signals in Human Brain Microvascular Endothelial Cells. *Cells* **2022**, *11*, 3860. [CrossRef] [PubMed]
110. Cui, T.; Schally, A.V. Growth hormone-releasing hormone (GHRH) and its agonists inhibit hepatic and tumoral secretion of IGF-1. *Oncotarget* **2018**, *9*, 28745. [CrossRef]
111. Guo, N.; Wang, X.; Xu, M.; Bai, J.; Yu, H.; Zhang, L. PI3K/AKT signaling pathway: Molecular mechanisms and therapeutic potential in depression. *Pharmacol. Res.* **2024**, *206*, 107300. [CrossRef] [PubMed]
112. Geffken, S.J.; Moon, S.; Smith, C.O.; Tang, S.; Lee, H.H.; Lewis, K.; Wong, C.W.; Huang, Y.; Huang, Q.; Zhao, Y.-T. Insulin and IGF-1 elicit robust transcriptional regulation to modulate autophagy in astrocytes. *Mol. Metab.* **2022**, *66*, 101647. [CrossRef]
113. Gajwani, N.; Rawat, K.; Sharma, A.; Rachamalla, M.; Jha, N.K.; Chopra, H.; Dhama, K.; Emran, T.B. IGF-1 and GLP-1 signaling: Potential therapeutic target for neurological disorders–correspondence. *Ann. Med. Surg.* **2023**, *85*, 61–63. [CrossRef]
114. Eyileten, C.; Sharif, L.; Wicik, Z.; Jakubik, D.; Jarosz-Popek, J.; Soplinska, A.; Postula, M.; Czlonkowska, A.; Kaplon-Cieslicka, A.; Mirowska-Guzel, D. The relation of the brain-derived neurotrophic factor with microRNAs in neurodegenerative diseases and ischemic stroke. *Mol. Neurobiol.* **2021**, *58*, 329–347. [CrossRef] [PubMed]
115. Lee, S.; Moniruzzaman, M.; Farris, N.; Min, T.; Bai, S.C. Interactive effect of dietary gamma-aminobutyric acid (GABA) and water temperature on growth performance, blood plasma indices, heat shock proteins and GABAergic gene expression in juvenile olive flounder Paralichthys olivaceus. *Metabolites* **2023**, *13*, 619. [CrossRef]
116. Al-Samerria, S.; Radovick, S. Exploring the therapeutic potential of targeting GH and IGF-1 in the management of obesity: Insights from the interplay between these hormones and metabolism. *Int. J. Mol. Sci.* **2023**, *24*, 9556. [CrossRef] [PubMed]
117. Arif, M.; Baty, R.S.; Althubaiti, E.H.; Ijaz, M.T.; Fayyaz, M.; Shafi, M.E.; Albaqami, N.M.; Alagawany, M.; Abd El-Hack, M.E.; Taha, A.E. The impact of betaine supplementation in quail diet on growth performance, blood chemistry, and carcass traits. *Saudi J. Biol. Sci.* **2022**, *29*, 1604–1610. [CrossRef]
118. Fujita, S.; Honda, K.; Yamaguchi, M.; Fukuzo, S.; Saneyasu, T.; Kamisoyama, H. Role of insulin-like growth factor-1 in the central regulation of feeding behavior in chicks. *Poult. Sci.* **2019**, *56*, 270–276. [CrossRef]

119. Shafik, B.M.; Kamel, E.R.; Mamdouh, M.; Elrafaay, S.; Nassan, M.A.; El-Bahy, S.M.; El-Tarabany, M.S.; Manaa, E.A. Performance, blood lipid profile, and the expression of growth hormone receptor (GHR) and insulin-like growth factor-1 (IGF-1) genes in purebred and crossbred quail lines. *Animals* **2022**, *12*, 1245. [CrossRef] [PubMed]
120. Farris, N.W.; Hamidoghli, A.; Bae, J.; Won, S.; Choi, W.; Biró, J.; Lee, S.; Bai, S.C. Dietary supplementation with γ-aminobutyric acid improves growth, digestive enzyme activity, non-specific immunity and disease resistance against Streptococcus iniae in juvenile olive flounder, Paralichthys olivaceus. *Animals* **2022**, *12*, 248. [CrossRef] [PubMed]
121. Kim, J.H.; Kim, S.J.; Lee, J.; Shin, C.H.; Seo, J.-Y. Factors affecting IGF-I level and correlation with growth response during growth hormone treatment in LG Growth Study. *PLoS ONE* **2021**, *16*, e0252283. [CrossRef] [PubMed]
122. Ncho, C.-M.; Goel, A.; Jeong, C.-M.; Youssouf, M.; Choi, Y.-H. In ovo injection of gaba can help body weight gain at hatch, increase chick weight to egg weight ratio, and improve broiler heat resistance. *Animals* **2021**, *11*, 1364. [CrossRef]

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