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Review

Biogenic Amines in Gliomas: A Comprehensive Literature Review

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Abstract

Gliomas are primary brain tumors that are believed to originate from neuroglial cells or progenitor cells and are the most common neoplasms affecting the central nervous system (CNS). Gliomas can be categorized into two main groups based on the WHO classification system: low-grade gliomas and high-grade gliomas. Unfortunately, high-grade gliomas have a poor prognosis despite significant research efforts dedicated to discovering more effective treatments. Biogenic amines are organic compounds found in food, plants, and animals. They are produced through the chemical decarboxylation of amino acids. Interestingly, some biogenic amines are known for their toxic and carcinogenic properties. However, the full role of biogenic amines in gliomas has not been fully explored. In this review, we aim to investigate the known roles of biogenic amines in glioma development, diagnostics, and potential future treatment applications.

Keywords: glioma; biogenic amines; amino acids

1. Introduction

Amino acids are crucial building blocks of proteins. They contain an amino group and a carboxylic acid group and have an important role in the regulation of gene expression [1]. Amino acids can be categorized into three groups: essential amino acids, non-essential amino acids, and conditionally essential amino acids. Essential amino acids cannot be synthesized by the human body and must be obtained from the diet. These essential amino acids include phenylalanine, valine, tryptophan, threonine, isoleucine, methionine, histidine, leucine, and lysine [2]. Alternatively, non-essential amino acids, such as aspartic acid, arginine, alanine, asparagine, glycine, glutamic acid, glutamine, serine, proline, citrulline, and tyrosine, can be produced by the body and are synthesized using essential amino acids. However, there is a subset of amino acids known as conditionally essential amino acids, also referred to as semi-essential amino acids, which are typically considered non-essential. However, during specific pathological conditions or physiological periods of growth, such as pregnancy or adolescent growth, the body may not be able to produce them in sufficient quantities. Consequently, they become essential amino acids during these circumstances. Examples of conditionally essential amino acids include arginine, glycine, glutamine, ornithine, proline, taurine, cysteine, and tyrosine [2].

In this review, we will discuss some of the amino acids and the current understanding of how certain amino acids are connected to cancer, with a particular focus on gliomas. By doing so, we seek to shed light on the potential implications of these amino acids for cancer treatment.

2. Glycine

Glycine is a conditionally essential amino acid biosynthesized in the body from serine. Glycine plays a role in the body's production of DNA, hemoglobin, and collagen, and in the process of energy release, while also having a crucial role as a precursor to proteins. Additionally, glycine is an important component of protein synthesis, although it is typically only found in relatively low quantities within most proteins. Collagen, on the other hand, is a unique protein that contains an unusually high proportion of glycine, accounting for roughly 35% of its composition [3]. In higher eukaryotes, the biosynthesis of delta-aminolevulinic acid—a crucial precursor for porphyrins that is necessary for hemoglobin and cytochromes—involves the enzymatic action of ALA synthase on glycine and succinyl–CoA. Glycine serves dual roles as a neurotransmitter in the central nervous system (CNS). Its function as an excitatory neurotransmitter involves enhancing the effects of glutamate at N-methyl-D-aspartate (NMDA) receptors [4]. Conversely, glycine can also act as an inhibitory neurotransmitter, primarily in the spinal cord, brainstem, and retina. Activation of glycine receptors leads to the influx of chloride ions through ionotropic receptors, resulting in the generation of an inhibitory postsynaptic potential (IPSP) in the neuron.

Glycine has been linked to many cancers. For example, in a study that was conducted on fecal metabolomics, a glycine derivative named tryptophyl–glycine, which is a dipeptide formed from L-tryptophan and glycine residues, and is associated with a high risk of developing colorectal cancer (CRC). However, this association may be explained by increased levels of cell division, cell death, and pro-

tein degradation. Conversely, N-2-furoyl-glycine, which is a xenobiotic found in cigarette smoke and coffee and is obtained by the formal condensation of the glycine amino group with 2-furoic acid, was found to be inversely related to colorectal cancer [5]. Thus, fecal metabolomics has the potential to emerge as an advantageous novel tool for researching CRC and various other diseases [5].

On a different note, glycine may have a protective role against the development of pancreatic cancer. Luu *et al.* [6] found that the risk of pancreatic cancer was reduced in individuals with elevated levels of glycine in serum collected more than 10 years before the diagnosis of cancer; however, notably, the study did not specify the subtype of pancreatic cancer. The protective role of glycine against pancreatic cancer might be explained by the glycine conjugation of bile acids; ursodeoxycholic acid (UCDA), a secondary bile acid formed by intestinal microbiota, is usually conjugated with glycine, which increases the hydrophilicity that ultimately leads to the decreased cytotoxicity and membranolytic properties found in bile acid. Considering the beneficial influence of serine and glycine, the interplay among an individual's genetic profile, nutritional status, and dietary patterns offers a promising evidence-based framework for devising personalized nutrition strategies. This approach can be thoroughly examined to explore its potential in preventing pancreatic cancer through targeted interventions.

Glycine accumulation was linked to the increased survival of brain cancer cells within ischemic zones of gliomas. Normally, SHMT2 (serine hydroxymethyltransferase 2), which is a mitochondrial enzyme, converts serine to glycine in the proliferating cells. Glycine decarboxylase (GLDC) prevents the accumulation of glycine and its conversion to amino acetate and methylglyoxal, which are toxic metabolites. In cases of brain gliomas, GLDC is inhibited, while SHMT 2 continues to convert serine to glycine. This leads to the accumulation of glycine and its deleterious effects on the cells [7].

3. Serine

Serine is a non-essential amino acid, which is synthesized by humans. It has a role in the metabolism of fats and fatty acids, muscle growth, and sustaining a healthy immune system [8]. Serine exists in two forms: L-serine and D-serine. L-serine is commonly found in vertebrate proteins and serves as a precursor for other amino acids, such as glycine and cysteine [9]. Notably, L-serine plays a role in neurotransmission by serving as a precursor for glycine and D-serine, both of which are involved in regulating excitatory glutamatergic transmission [10]. D-serine specifically promotes long-term potentiation by modulating N-methyl-D-aspartate (NMDA) receptors. In addition to its aforementioned functions, serine also plays a vital role in supplying one-carbon units for the tetrahydrofolate (THF) cycle, which is involved in biosynthetic pathways, such as nucleic acid metabolism. Furthermore, serine is considered a precursor in the thymidine synthesis pathway [11].

Serine has many associations with cancers. For example, researchers found that higher levels of serine had a protective effect against the development of pancreatic cancer [6]. One explanation for this was the cancer-protective effects of the by-products generated from serine biosynthesis, such as α-ketoglutarate, which serve as cofactors of the dioxygenases involved in regulating genes. Moreover, serine was found to increase the growth of CRC cells and their resistance to 5-fluorouracil [12].

High levels of serine improved the survival of glioblastoma cells in stressful conditions, and serine deprivation led to a reduction in cell growth and increased cell death in hypoxia [13]. Moreover, 3-phosphoglycerate dehydrogenase (PHGDH), an enzyme that catalyzes the rate-limiting step in serine synthesis, is a major contributor to brain metastasis; thus, its inhibition may provide a potential treatment to avoid brain metastasis in various cancers [14]. Consequently, a research investigation was conducted to evaluate the impact of NCT503, a potent and specific inhibitor of PHGDH, in augmenting the efficacy of temozolomide, an established alkylating agent utilized in the treatment of glioblastoma. The study yielded promising results, thereby indicating the potential of this combination therapy as a viable approach to managing glioblastoma [15].

4. Fumaric Acid

Fumaric acid, a dicarboxylic acid, has an essential role in the Krebs tricarboxylic acid (TCA) cycle by serving as a precursor to L-malate. The formation of fumaric acid is catalyzed by succinate dehydrogenase via the oxidative conversion of succinic acid [16]. Fumaric acid undergoes a reversible enzymatic reaction into malic acid, which is catalyzed by fumarate hydratase, a known tumor suppressor. When fumarate hydratase is depleted, fumaric acid accumulates abnormally, resulting in malignant transformation and tumor progression. This accumulation activates a sequence of oncogenic cascades, including the upregulation of transcription factors, which promote the epithelial-to-mesenchymal transition and facilitate cell transformation [17]. In summary, fumarate plays a role in enhancing the expression of specific transcription factors that drive cellular changes and contribute to tumor development. Furthermore, fumaric acid holds relevance in fumarase deficiency, which is an inherited disorder of metabolism [18].

Dimethyl fumarate, which is a methyl ester of fumaric acid, has been studied as a potential treatment for glioblastoma due to its neuroprotective and antitumor effects [19]. However, more studies are needed to determine whether this drug can be beneficial in the treatment of glioblastoma.

5. Threonine

Threonine is an essential amino acid, which is important in the CNS, porphyrin metabolism, fat metabolism, and preventing fat buildup in the liver [20]. Interestingly, in most currently available infant formulas, threonine content is approximately 20% higher than that found in human milk. Thus, premature infants who consume these formulas have plasma threonine concentrations up to twice as high as those fed with human milk. The presented data indicate that this increase in plasma threonine levels leads to elevated brain glycine levels, which affects the balance of neurotransmitters in the brain. Consequently, these findings suggest potential implications for brain development in the early stages of postnatal life [21].

Protein serine/threonine kinase (STK), which phosphorylates the serine or threonine hydroxyl group, has been linked to various cancers. For example, STK 24 was found to inhibit gastric cancer metastasis [22]. Moreover, it was found that STK31 expression may be affected by the human papillomavirus (HPV16) oncogene E7 in cervical cancer through a methylation-mediated mechanism, while aberrant methylation of the STK31 promotor/exon 1 region may induce cervical cancer development. Therefore, STK31 may be a cellular target gene for the HPV-16 oncogene E7 [23]. Moreover, STK31 levels were found to be higher in colorectal cancer tissues, making STK31 a useful non-invasive biomarker in the diagnosis of CRC [24].

6. Glutamine

Glutamine is a non-essential amino acid, which is found in all organisms and is mainly produced by skeletal muscles [25]. It has a role in the production of excitatory and inhibitory neurotransmitters (glutamate and GABA) [26]. Glutamine metabolism is considered one of the methods that cancer cells use for survival and growth [27,28]. Therefore, targeting glutamine metabolism has been studied as a promising treatment for cancers. For example, Kim *et al.* [29] found that inhibiting glutamine uptake can decrease SKOV3-TR cell resistance to paclitaxel, thereby providing a potential therapy for paclitaxel resistance in ovarian cancer. Similarly, inhibition of glutamine uptake was found to improve the inhibitory effects of cetuximab on gastric cancer [30].

Glutamine metabolism has been involved in many metabolic pathways in brain cancer cells, such as macromolecule synthesis, energy production, epigenetic regulation, and redox homeostasis [31]. Moreover, a notable discovery emerged from examining brain tissue samples collected from glioma patients prior to chemotherapy or radiation therapy, during surgical resection or excision. These samples exhibited elevated levels of glutamine, suggesting a correlation between glutamine concentration and the unfavorable prognosis of gliomas. Consequently, glutamine is a promising prospective biomarker for monitoring glioma progression.

Due to the crucial role of glutamine in regulating cellular functions and its association with poor prognosis, drugs that inhibit glutamine transporters, such as SLC1A5, were found to inhibit lung cancer growth *in vitro* and *in vivo* [32]. Hence, targeting glutamine transporters may provide a promising strategy for developing a new treatment for cancers and, particularly, gliomas.

7. Glutamate

Glutamate, or glutamic acid, is a non-essential alpha-amino acid, which is present in all living organisms, including bacteria, plants, and animals. It plays a vital role in eliminating excess or waste nitrogen from the body. Additionally, glutamate is the predominant fast excitatory neurotransmitter in the nervous system, and its receptors are widely distributed in neuronal and glial membranes. The main two types of glutamate receptors are ionotropic receptors and metabotropic receptors, which are ligand-gated ion channels and G-protein coupled receptors, respectively [33].

In addition to their presence in the CNS, glutamate receptors have been identified in peripheral organs and have been implicated in cancer development. A notable instance is the expression of metabotropic glutamate receptor 4 (mGluR4) in the colon epithelium, where its signaling has been associated with an unfavorable prognosis in colorectal cancer [34].

The synthesis and release of glutamate from glioma cells were discovered to occur through the system x_c^-cystine–glutamate transporter, as a byproduct of glutathione synthesis. This glutamate release contributes to the aggressive characteristics of gliomas, by enhancing their malignant behavior. The excess extracellular glutamate is facilitated by the system x_c^- transporter and provides a survival advantage by promoting resistance to apoptosis and stimulating the proliferation and invasion of glioma cells [35]. Indeed, the invasive features of gliomas, which are facilitated by the release of glutamate, pose a notable challenge to the effective management of the disease.

Numerous drugs focusing on glutamate and its receptors are currently under investigation for treating gliomas, including perampanel, which acts as an antagonist of the α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) glutamate receptor. Initially developed as an anticonvulsant for drug-resistant epilepsy, associated with gliomas, perampanel has demonstrated additional properties as an antitumor agent. Studies have revealed that perampanel reduces extracellular glutamate levels and diminishes glucose uptake in glioblastoma cell cultures. These findings highlight its potential as an antitumor treatment in addition to its anticonvulsant effects [36]. Moreover, a study was performed to investigate the role of managing newly diagnosed glioblastoma patients with radiation (RT), temozolomide (TMZ), and talampanel, an AMPA antagonist. The results showed that patients treated with RT+TMZ

and talampanel had significantly longer survival rates than patients treated with RT+TMZ alone [37].

The expression of SLC7A11/xCT, an antiporter responsible for importing cystine in exchange for glutamate, was correlated with unfavorable prognoses and drug resistance in cancer cases. Notably, SLC7A11 has been implicated in cisplatin resistance in gastric cancer [38], temozolomide resistance in glioma [39], and gemcitabine resistance in pancreatic cancer [40]. Intriguingly, SLC7A11 has been detected in 50% of glioma patients, and its upregulation has been associated with accelerated glioma cell growth, increased glutamate toxicity, seizure induction, and reduced overall survival [41]. Consequently, targeting SLC7A11 presents a potential therapeutic approach for the treatment of cancers and particularly gliomas.

8. Tryptophan

Tryptophan is an essential alpha-amino acid, meaning that it must be obtained from the diet. As humans age, the amount of tryptophan and proteins the human body requires reduces: adults need a daily intake of at least 3 mg/kg. Tryptophan can be found in wheat germ [42] and acts as a precursor for both serotonin and melatonin. Vitamin B6, niacin, and glutathione are required for the metabolism of tryptophan into serotonin. Furthermore, niacin (vitamin B3) is an important metabolite of tryptophan that originates from the catabolism of kynurenine and quinolinic acid, which are products of tryptophan degradation. Several conditions and diseases are characterized by tryptophan deficiencies [43]. For example, malabsorption of fructose leads to improper absorption of tryptophan in the intestine. This reduces the levels of tryptophan in the blood, which may cause depression. Tryptophan plays a role in "feast-induced" drowsiness. Carbohydrate-rich meals stimulate insulin secretion, which enhances the uptake of large neutral branched-chain amino acids (BCAAs) into muscle. This results in an increased tryptophan to BCAA ratio in the bloodstream, leading to greater uptake of tryptophan across the blood–brain barrier and into the cerebrospinal fluid. In the cerebrospinal fluid, tryptophan is converted into serotonin, and then, melatonin, which promotes sleep. Tryptophan's conversion to serotonin suggests that consuming tryptophan or its precursor, 5-HTP may improve symptoms of depression by raising serotonin levels in the brain.

The intake of purified tryptophan leads to an elevation in serotonin levels in the brain, whereas the consumption of tryptophan-containing foods does not have the same effect. The reason for this is that the same transport system responsible for carrying tryptophan across the blood–brain barrier also transports various other amino acids found in protein-rich foods. In specific circumstances, tryptophan has the potential to act as both a neurotoxin and a metabotoxin [44].

Kynurenine, a tryptophan metabolite, was found to both promote glioma growth and invasiveness and suppress antitumor immunity. The metabolism of tryptophan into kynurenine by the enzymes indoleamine-2,3-dioxygenase (IDO) and tryptophan-2,3-dioxygenase (TDO) is considered a crucial microenvironmental factor in glioma; therefore, therapeutic targeting of IDO and TDO are considered potential treatment candidates for patients with malignant glioma [45].

9. N,N-Dimethylarginine

N,N-dimethylarginine, also known as asymmetric dimethylarginine, is a natural product that is considered an arginine derivative. It is found in the blood and has an inhibitory effect on the production of nitric oxide [46]. High levels of asymmetric dimethylarginine were found in patients with breast cancer and lung cancer compared to healthy individuals [47,48]. Further, asymmetric dimethylarginine was found to promote gastric cancer migration and invasion [49].

A research investigation was conducted to explore the role of asymmetric dimethylarginine in the suppression of nitric oxide, which is a critical regulator of angiogenesis in CNS tumors [50]. The study specifically examined the impact of dimethylarginine dimethylaminohydrolase I (DDAH I), an enzyme responsible for metabolizing asymmetric dimethylarginine, on the rat C6 glioma cell line. The results demonstrated that higher DDAH I expressions led to increased nitric oxide synthesis, ultimately, leading to enhanced tumor growth.

10. Homoarginine

Homoarginine is a natural product derived from lysine, which has a role as a human and xenobiotic metabolite [51]. Homoarginine deficiency is associated with an increased risk of fatal cardiovascular events [52]. Low levels of homoarginine, which is a cardiac biomarker, have also been associated with an increased risk of cardiovascular events [52]. Patients with breast cancer receiving chemotherapy were found to have lower levels of homoarginine, which again indicates an increased risk of cardiovascular events [53]. Conversely, tamoxifen use in breast cancer patients has been associated with increased levels of homoarginine, thereby reflecting its protective effects on the heart. Limited studies have explored the potential involvement of homoarginine in cancer in general and in gliomas, in particular. Some research suggests that homoarginine may play a role in regulating nitric oxide synthesis, which has implications for angiogenesis and tumor growth. However, the existing studies have primarily focused on cardiovascular diseases rather than cancer.

11. Lidocaine

Lidocaine is used as a local anesthetic and an antiarrhythmic. It stabilizes the neuronal membrane by inhibiting voltage-gated sodium channels [54]. Many studies have described the role of lidocaine in the management of many

cancers. For example, it was observed that lidocaine can exert anticancer effects on breast, gastric, bladder, colorectal, cervical, and epithelial ovarian cancers by inhibiting certain pathways involved in the growth of these cancers [55–59]. Moreover, a retrospective study, which included patients undergoing pancreatectomy, found that intraoperative intravenous use of lidocaine was associated with prolonged overall survival rates [60].

Lidocaine was shown to have a role in inhibiting glioma cell proliferation: Leng *et al*. [61,62] found that lidocaine inhibited the proliferation of glioma cells by suppressing transient receptor potential melastatin 7 channels (TRPM7), which upon activation led to the proliferation, migration, and invasion of malignant glioma cells.

12. Peptides

A peptide is a short chain of two to fifty amino acids connected by peptide bonds. Peptides are crucial for a range of fundamental physiological processes and are involved in numerous biochemical reactions [63]. Dipeptides are peptides composed of two amino acids.

gamma-Glutamylglutamine, also known as L-γ-glutamyl-L-glutamine or bis-g-glutamylamine, is a dipeptide that belongs to the class of organic compounds known as glutamine and derivatives [64]. gamma-Glutamylglutamine is found in foods, such as anatidae, chicken, and domestic pigs, thereby making it a potential biomarker in the consumption of these foods. gamma-Glutamylglutamine is associated with several diseases, including Crohn's disease, schizophrenia, iron deficiency, and hyperammonemia.

Previous data indicated that gamma-Glutamylglutamine has few associations with cancers. Yet, a few articles have described the importance of gamma-Glutamylglutamine in the treatment of human cancers. For example, poly(l-γ-glutamylglutamine) was found to be effective in increasing doxorubicin uptake, prolonging its retention, and reducing its efflux by drug-induced resistant human breast cancer cells; thus, highlighting it as a promising strategy for overcoming the resistance to antitumor drugs [65].

Similarly, researchers found that targeting nucleolin—a receptor that is highly expressed in glioblastoma U87 MG cells and neovascular endothelial cells—using an aptamer AS1411-functionalized poly(l-γ-glutamylglutamine)-paclitaxel (PGG-PTX) nanoconjugates drug delivery system presented the best anti-glioblastoma effect, prolonging the median survival time and inducing apoptosis in most tumor cells *in vivo*, compared to the other analyzed groups, thereby making it a promising targeting delivery strategy for glioblastoma therapy [66].

In addition to dipeptides, oligopeptides are peptides comprising two to twelve amino acids. Bradykinin, an oligopeptide, is a vasoactive kinin that is involved in a wide range of biological processes, including in blood pressure regulation, and is considered a potent vasodilator. Bradykinin was found to stimulate cancer cell growth along with facilitating tumor invasion and migration [67]. Therefore, several studies were conducted to identify antagonists of bradykinin with potential anticancer effects. For example, the inhibition of the bradykinin B1 receptor by novel inhibitors reduced the malignant progression of hepatocellular carcinoma, which may provide a potential treatment for this cancer [68]. Furthermore, bradykinin was shown to promote the proliferation, migration, and invasion of cervical cancer cells. Thus, antagonizing the bradykinin B2 receptor has the opposite effect on the B1 receptor [69].

Bradykinin promotes glioma cell migration and invasion by acting on the bradykinin B2 receptors. Consequently, targeting B2 receptors can be considered a potential treatment for gliomas in the future [70].

13. Conclusions

Brain tumors necessitate ongoing research and revolutionary treatments. Biogenic amines, involved in diverse physiological functions, are implicated in these tumors. Although the exact relationship remains unclear, further investigation can potentially identify new diagnostic and therapeutic approaches. Studies on metabolic pathways can provide insights into the roles of metabolites in tumor pathogenesis. Animal models and *in vitro* experiments support biogenic amines as potential therapeutic targets. Thus, continued exploration is crucial to advance understanding, identify biomarkers, and develop personalized treatment strategies, to potentially continue to improve patient outcomes.

Author Contributions

Conception, drafting, and approval of final version of manuscript: AA and OA. Both listed authors participated in the writing of the manuscript and have read and approved the final version.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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