REVIEW ARTICLE

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Could glutamate be a diagnostic marker in neurological and psychiatric diseases?

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Abstract

Introduction and Objective. Glutamate plays a role in the pathogenesis of numerous neurological disorders, including Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, migraine, and stroke. Additionally, it is implicated in the aetiology of psychiatric disorders, such as schizophrenia, depression, and bipolar affective disorder. As it can be simply identified in bodily fluids, fluctuations in its levels may serve as a potential indicator of pathological processes. The aim of the study was to determine whether fluctuations in glutamate concentrations could be beneficial in predicting and monitoring the progression of the mentioned diseases.

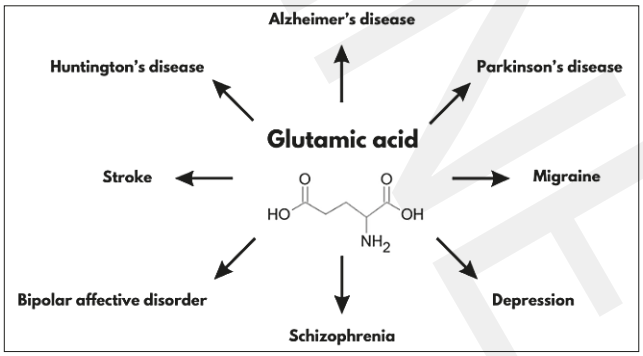
Review Methods. A literature search was conducted in the PubMed database using the following algorithm: (glutamate) AND (blood/plasma/serum/nerve tissue) AND (neurodegeneration/Alzheimer/Parkinson/migraine/stroke/psychiatric/depression/schizophrenia). More than 80% of the identified publications were published in 2017 or later.

Brief description of the state of knowledge. The majority of studies cited revealed a clear difference in glutamate concentrations between the control group and the study group. In the majority of cases of neurodegenerative diseases, blood glutamate concentrations demonstrated a downward trend. Conversely, in psychiatric diseases, stroke and migraine, they exhibited an upward trend.

Summary. Damage to the blood-brain barrier, which regulates glutamate transfer from nerve tissue to blood, appears to significantly affect glutamate levels in both blood and nerve tissue during disease. Altered blood glutamate concentration could serve as a diagnostic marker, although meta-analysis is needed to define clinically applicable ranges.

Key words

stroke, psychiatric diseases, migraine, biomarker, neurodegenerative diseases, glutamate, diagnosis marker



Graphical abstract

INTRODUCTION AND OBJECTIVE

Glutamate function in the body. Glutamic acid is one of twenty protein amino acids, categorised as an endogenous amino acid. Glutamate and its derivatives play a significant role in numerous biochemical processes, acting as a connecting factor between pathways such as the Krebs cycle, the urea cycle and others. Glutamate is the subject of a number of biochemical reactions, including decarboxylation, deamidation, amidation, and transamination. It can be synthesized from glucose through the malate-aspartate shuttle following glycolysis [1]. Table 1 illustrates the various reactions that glutamate undergoes, its location within the body, and the enzymes involved in these processes.

Glutamate is a fundamental component of numerous proteins, including haemoglobin and myoglobin. The negative charge of this amino acid is responsible for maintaining the correct tertiary structure of the protein. Furthermore, the gamma-carboxylation of glutamate with vitamin K contributes to the maintenance of normal blood haemostasis. This process is known as the vitamin K cycle and results in the production of active clotting factors that strongly bind calcium ions. Glutamate is an indispensable component of glutathione, a vital antioxidant. Additionally, it functions as a signalling molecule in the beta-cells of the pancreas, regulating the release of insulin. Following the consumption of protein-rich food, it is responsible for the perception of a meaty taste, commonly referred to as 'umami'. Furthermore, within the stomach, it interacts with the afferent vagus nerve endings, which stimulates the limbic system and hypothalamus [2].

Glutamate in the nervous system and role of blood-brain barrier. Glutamate fulfills a number of significant roles at the cellular level. It is stored in vesicles in the synapses of glutamatergic neurons and released into the synaptic cleft

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upon nerve stimulation [3]. Indeed, it is one of the most important excitatory amino acids within the nervous system. It is well documented that elevated levels of glutamate within the synaptic gap can induce excitotoxic effects, precipitated by the excessive activation of N-methyl-D-aspartate (NMDA) receptors located on the cell membrane. Consequently, a significant influx of extracellular calcium is triggered, resulting in the release of Ca^{2+} from intracellular stores. This, in turn, precipitates a further escalation in the cytosolic free Ca^{2+} concentration, leading to mitochondrial damage, oxidative stress, and ultimately, cell death [4].

Glutamate is the precursor for the formation of γ-aminobutyric acid (GABA), the principal inhibitory neurotransmitter within the central nervous system. The process of GABA formation is catalysed by glutamate decarboxylase [2]. It is postulated that abnormalities in the glutamate/GABA ratio in the central nervous system (CNS) could be a contributing factor in the development of a number of neurological and psychiatric diseases, including Alzheimer's disease, epilepsy, stroke, traumatic brain injury, depression, schizophrenia and autism [5]. Recent studies have demonstrated that appropriate plasma glutamate levels are essential for the optimal functioning of the gut microbiome which, in turn, is crucial for maintaining normal body weight and even has a beneficial protective function against the onset of certain neurological diseases [6, 7].

The blood-brain barrier (BBB) is a structure formed by brain microvessel endothelial cells, pericytes, and astrocytes, supported by microglia and neurons. The blood-brain barrier isolates the brain and limits the diffusion of many nutrients, including glucose and amino acids, which are essential for metabolism. Therefore, other routes are required by which these components can enter the neural tissue. The function is fulfilled by membrane transporters belonging to the Solute Carrier family (SLC). These proteins enable the transport of various molecules, including carbohydrates, amino acids, fatty acids, hormones, nucleotides and vitamins. The differential distribution of these transporters on both sides of the BBB is associated with differences in the preferential transport of substances from the blood to the brain or *vice versa*, as some of these proteins may be predominantly distributed on the luminal, abluminal, or evenly on both sides of the membrane [8]. In turn, neurotransmitters such as glutamate or glycine are unable to pass from the blood into the brain. However, the transport of glutamate from neural tissue into the blood is possible and occurs primarily via Na^{+} dependent glutamate transporters, known as excitatory amino acid transporters (EAATs). These mechanisms are considered to protect neural tissue from excitotoxicity [9,10]. Glutamate is predominantly synthesised in neural tissue through a process of transamination, whereby essential amino acids (which exhibit high permeability to the blood-brain barrier) and alpha-ketoglutarate are utilised as substrates. A second pathway for synthesising glutamate involves the action of ammonium ion-binding glutamate dehydrogenase [10]. In certain instances, such as in cases of neurodegerative diseases and traumatic brain injury, there is a disruption of the mechanisms that regulate glutamate concentration in the nerve tissue, which can result in the migration of glutamate across the BBB into the blood [11].

Techniques for measuring glutamate concentrations. Glutamate concentrations are higher in plasma at 5–100 μM/L and in whole blood at 150–300 μM/L, compared to in the CSF – 0,5–2 μM/L and urine – 3,3–18,4 μM/L, and it is uncertain whether plasma concentrations correlate with CSF concentrations [12]. In contrast, glutamate concentration in the brain tissue oscillates around 10,000–12,000 μM/kg. This significant difference between body fluids and nerve tissue is provided by the blood-brain barrier (BBB). The integrity of the BBB is a natural limiter of the pathological fluctuations in the levels of extracellular fluids and plasma [11].

Glutamate may be identified through instrumental analysis in a number of bodily fluids, most notably cerebrospinal fluid (CSF), blood serum, plasma and urine. Current technologies being used to measure glutamate concentration include laboratory-based methods such as high performance liquid chromatography (HPLC), gas chromatography-mass spectrometry (GCMS) and enzymatic or non-enzymatic electrochemical techinques. The development of new non-enzymatic methods based on cobalt compounds, nickel compounds and carbon nanotubes is particularly promising due to their high sensitivity, greater stability and relatively low cost [12]. The direct testing of glutamate concentrations in nerve tissue is a challenging process. While proton magnetic resonance spectroscopy represents a viable approach, this method is costly and not widely accessible [13]. A biomarker is classically defined as a characteristic that is objectively measured and assessed as an indicator of normal and pathogenic processes or pharmacological response to a therapeutic intervention [14].

Given that glutamate can be detected in body fluids by the methods mentioned above, it can also act as a potential biomarker of pathological and disease processes. The aim of this study is to investigate whether glutamate can be used as a marker for selected disease entities and, if so, to what extent.

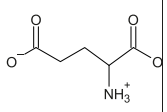
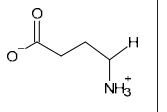
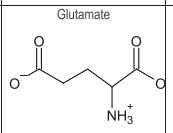
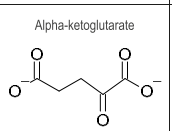
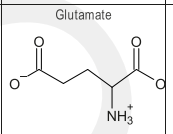
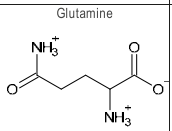
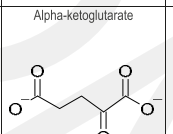
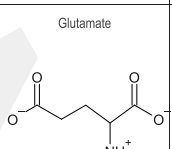
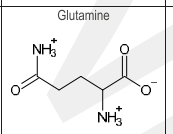
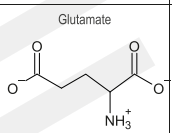
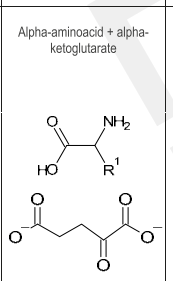
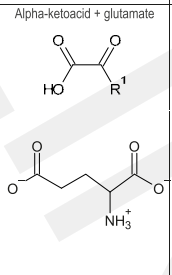
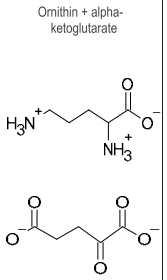
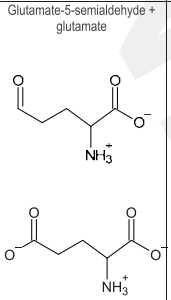
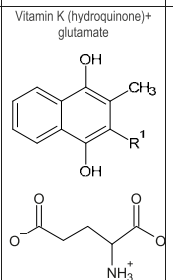
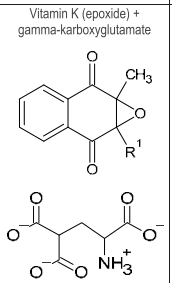
REVIEW METHODS

The review was based on scientific publications acquired via search strategy using the key words: 'glutamate', 'marker', 'diagnosis marker', 'biomarker', 'blood', 'plasma', 'serum', 'nerve tissue', 'blood-brain barier', 'neurodegeneration', 'Alzheimer', ''Parkinson', 'migraine', 'stroke', 'psychiatric', 'depression', 'schizophrenia'. The search was performed using the database PubMed. The publications selected included meta-analyses, reviews, controlled trials and research articles. Finally 68 publications were selected, 54 of which (79%) were published in 2017, or later, while 12 (21%) had been published before 2017.

NEURODEGENERATIVE DISEASES

Glutamate plays an important role in the pathomechanism of neurodegenerative diseases. Excess of this neurotransmitter leads to excitotoxicity, i.e. an increase in receptor excitation. In Alzheimer's disease, these include both presynaptic and postsynaptic glutamatergic receptors NMDA, Kainate, AMPA (ionotropic receptors) and mGluR1 and mGluR5, mGluR2 and mGluR3 and mGluR4,6,8 (metabotropic receptors). Ionotropic glutamate receptors contain an ion channel that is directly activated upon glutamate binding, whereas metabotropic glutamate receptors activate ion channels by coupling to G-protein signalling systems, either

Table 1. The most important reactions of glutamate [1]

Reaction type	Substrate	Product	Enzyme	Localization
Non-oxidative decarboxylation	Glutamate 	Gamma-aminobutyric acid 	Glutamate decarboxylase (EC 4.1.1.15)	Only in the brain
Oxidative deamination	Glutamate 	Alpha-ketoglutarate 	Glutamate dehydrogenase (EC 1.4.1.3)	Mainly liver and kidney
Amidation	Glutamate 	Glutamine 	Glutamine synthetase (EC 6.3.1.2)	Brain, Perivenous hepatocyte, Myocyte, Adipocyte
Oxidative amination	Alpha-ketoglutarate 	Glutamate 	Glutamate dehydrogenase (EC 1.4.1.3)	Mainly liver and kidney
Deamidation	Glutamine 	Glutamate 	Glutaminase (EC 3.5.1.2)	Liver Kidney Brain Enterocytes
Transamination	Alpha-aminoacid + alpha-ketoglutarate 	Alpha-ketoacid + glutamate 	Glutamate aminotransferase (EC 2.6.1.15)	All tissues
Transamination	Ornithin + alpha-ketoglutarate 	Glutamate-5-semialdehyde + glutamate 	Ornithine aminotransferase (EC 2.6.1.13)	All tissues (in particular perivenous hepatocytes)
Gamma-karboxylation	Vitamin K (hydroquinone)+ glutamate 	Vitamin K (epoxide) + gamma-karboxyglutamate 	Gamma-glutamyl carboxylase EC (4.1.1.90)	Liver, Bone

indirectly through the secondary messenger pathways or directly through the βγ subunits of the G-protein [2]. The activation of ionotropic glutamate receptors generally results in an influx of calcium ions from the extracellular space into neurons. Conversely, the activation of metabotropic glutamate receptors leads to the release of calcium from intracellular stores, such as the sarcoplasmic reticulum. Of unique importance are the ionotropic N-methyl-D-aspartate receptors (NMDARs), which have the highest permeability to Ca^{2+} ions. It has been shown that high levels of calcium ion influx from the extracellular space into neurons, which exceeds the regulatory mechanisms of the cell, can lead to neurotransmission dysfunction and thus initiation of neurodegenerative processes. In addition, numerous studies show that amyloid β (Aβ) induces changes in glutamate availability and modulation of NMDAR channel function correlating with neurotoxicity and degeneration in Alzheimer's disease, which fits with the spectrum of clinical symptoms observed in patients. Among other things, the glutamate uptake and recycling system, as well as the integrity of the presynaptic neurotransmitter release mechanism, is impaired in Alzheimer's disease [15,16].

The glutamate uptake and recycling system, also known as the glutamate-glutamine cycle, is the process by which glutamate is efficiently removed from the synaptic gap by astrocytes, then converted via the enzyme glutamine synthetase to glutamine and re-transported to neurons, where it is converted by the enzyme phospho-activated glutamine back to glutamate. This mechanism is essential for maintaining effective glutamatergic neurotransmission and protecting the brain from excitotoxicity [17]. There are also numerous reports of microglia influencing excessive glutamatergic neurotransmission mainly through the AMPA receptor and presynaptic mGlu2/mGlu3 [16]. Based on a study in which N-acetylaspartate (NAA) was significantly decreased in the posterior cingulate nerve and bilateral hippocampus in patients with Alzheimer's disease, using proton magnetic resonance spectroscopy (HMRS) to assess glutamatergic activity, it can be concluded that NAA has diagnostic potential [18]. It should be noted that in the HMRS study, the NAA signal was read in conjunction with N-acetylaspartylglutamate (NAAG), which acts as a neuromodulator of glutamatergic synapses by activating mGluR3, thereby influencing the reduced glutamate release by feedback [19,20]. Furthermore, in a pilot study that also assessed metabolic changes and microstructure in different brain areas, reduced glutamate levels in the left hippocampus and N-acetylaspartate levels in the posterior cingulate cortex were observed in eight subjects with mild cognitive impairment and nine with Alzheimer's disease, compared to 16 healthy elderly subjects [21]. Similar conclusions were reached by the authors of this study when comparing participants with mild cognitive impairment of an amnesic nature to participants without such impairment [22]. Also of interest are reports showing a reduction in glutamate concentrations in perchloric acid brain extracts taken post-mortem from Alzheimer's patients carrying the E3 allele of apolipoprotein E (Apo-E) compared to brains from healthy individuals, suggesting the potential nature of glutamate as a biomarker in this disease [23]. A study by Buard et al. shows that lower glutamate concentrations correlated with cognitive impairment in people with Parkinson's disease, indicating that glutamate may be a potential indicator of cognitive impairment in patients. Metabolic and neurodegenerative

changes were assessed using HMRS [24]. A study conducted by Fiandac et al. evaluated the presence of selected blood metabolites in patients diagnosed with Parkinson's disease and traumatic brain injury. It was observed that the concentration of glutamate present in the blood was significantly lower in patients with Parkinson's disease, while patients with traumatic brain injury exhibited increased blood glutamate concentrations in comparison to the control group [25]. However, a meta-analysis evaluating the presence of potential biomarkers of Parkinson's disease in blood and cerebrospinal fluid indicated that reduced glutamate levels in cerebrospinal fluid were evident in patients with the disease, whereas blood glutamate levels were not significantly different from those of the control group [26].

Also in genetic neurodegenerative Huntington's disease, in which the main symptoms are the so-called chorea movements, dementia and personality disorders, decreased glutamate and N-acetylaspartate levels were found in both patients and animal models, as imaged by HMRS. There was also a study using glutamate chemical exchange saturation transfer imaging (gluCEST), which has been shown to be a biomarker for Huntington's disease. This compared brain glutamate levels in Ki140CAG mice (a mouse model of knock-in disease expressing a chimeric mouse/human exon 1 containing 140 CAG repeats inserted into the mouse Htt gene) with wild-type control littermates. A reduced gluCEST contrast, analogous to physiological glutamate concentrations, was observed in most of the brain in heterozygous mice, and even lower in homozygous mice, indicative of faster disease progression. In addition, the use of the HMRS method in this study showed similar results, which supports the efficacy of gluCEST [27]. Conversely, studies of selected biomarkers in amyotrophic lateral sclerosis (ALS) have shown that, in contrast to the other neurodegenerative diseases, glutamate levels in both plasma and cerebrospinal fluid increase with disease progression [28].

Migraine. Migraine is a frequent clinical problem encountered by neurologists. It is estimated that approximately 15% of the global population experiences migraine [29]. Research suggests that there is a link between glutamate and the development of migraine. Its effects on the trigeminovascular system may increase the risk of spreading depression in the cerebral cortex, which plays a significant role in the pathophysiology of migraine [30]. Studies have found that migraine sufferers have higher concentrations of this compound in not only in body fluids: plasma and cerebrospinal fluid, but also in platelets [31]. Some studies have observed an increase in blood glutamate concentrations in individuals with both chronic and episodic migraine compared to a control group. Glutamate levels were not found to be associated with the class of preventive treatment medication used for migraine [32,33]. However, among those who achieved target treatment outcomes, there was a notable reduction in plasma glutamate levels [34]. Consequently, glutamate, in conjunction with calcitonin gene-related peptide (CGRP), is identified as a promising marker, particularly in the context of chronic migraine. Furthermore, higher glutamate levels have been documented in migraine with aura compared to those without aura [31].

Stroke. Elevated glutamate levels have a link between acute conditions as well as chronic neurological diseases. Researchers have discovered an extremely important correlation between plasma glutamate levels and ischaemic stroke or post-stroke depression. Based on a study with post-stroke patients and in an animal model to identify a drug that reduces blood glutamate levels, they postulated that an elevated blood glutamate parameter may indicate an increased risk of stroke. Furthermore, this study suggests that lowering the concentration of this substance will also result in a decrease of the parameter in the brain [35]. Another study included a group of people who had experienced an episode of ischemic stroke – all subjects had elevated plasma glutamate parameters, and in patients who additionally suffered from depression, this parameter scored even higher. The researchers concluded that at a certain concentration of this compound, the occurrence of post-stroke complications could be predicted. In addition, it was noted that glutamate levels correlated with the extent of brain infarction, the severity of the course of the disease and the degree of functional disability [36,37]. Li at al. investigated the potential association between the presence of plasma free amino acids and the risk of developing cardiovascular diseases, such as myocardial infarction or stroke, in patients with type 2 diabetes. Following the testing of the plasma of 741 patients and the subsequent application of appropriate statistical analysis, it was determined that of the more than 20 plasma free amino acids, only glutamate exhibited a positive correlation with the occurrence of stroke. Conversely, no correlation was observed for coronary heart disease. The observed risk association between the presence of free glutamate in plasma and stroke appears to be attributable to its role in thrombogenesis and platelet activation [38]. One clinical trial evaluated the plasma levels of selected neurotransmitters in post-stroke patients in the context of adverse stroke events. Of the four amino acids (glutamic acid, aspartic acid, GABA and glycine), an increase in the concentration of the first three and a decrease in glycine was associated with an elevated risk of adverse events, including major disability or death. Moreover, the highest odds ratio was observed for glutamic acid (2.03; 95% CI: 1.59, 2.59; P-trend < 0.001) [39].

PSYCHIATRIC DISORDERS

Glutamate in psychiatric illnesses. The current review presents three psychiatric illnesses – schizophrenia, bipolar affective disorder and depression. The largest part of the review is devoted to schizophrenia because of the more significant impact of glutamatergic dysfunction on the course of the illness than in bipolar affective disorder and depression, and the wide range of literature that has focused on the search for glutamatergic treatments that could affect the negative symptoms of schizophrenia.

Schizophrenia. For almost half a century, the understanding of the pathophysiology of schizophrenia was dominated by the dopaminergic hypothesis. However, dopamine receptor blockers in the brain of typical and atypical antipsychotics, except for clozapine, were not effective in treating negative symptoms and cognitive impairment, which are prognostic indicators and disability in schizophrenia [40,41]. For this reason, it was unlikely that only dysfunction of the dopaminergic system would affect the core features of

schizophrenia. In the 1980s, it was observed that the use of ketamine and phencyclidine, which are incompetent NMDA antagonists, in anaesthesia produces schizophrenia-like symptoms, including not only psychotic symptoms and thought disorders, but also negative and cognitive symptoms in healthy people, and that ketamine- or phencyclidine-induced psychosis is clinically difficult to distinguish from primary psychosis in schizophrenia [42]. In contrast, genome-wide association studies conducted this century have shown that of the more than 100 schizophrenia risk genes, approximately 30% encode proteins located at the glutamatergic synapse and inhibit glutamate neurotransmission, particularly at the NMDA receptor [40, 43].

Based on the above, NMDA receptor hypofunction is increasingly recognised as an important pathomechanism in schizophrenia. However, to date, it has not been possible to identify patients with significant NMDA receptor hypofunction who would respond to glutamatergic treatment [42]. It is noteworthy that NMDA receptor hypofunction may be indirectly related to glutamatergic system overactivity. Therefore, acute provocation with a pharmacological NMDA receptor blocker, e.g. low-dose ketamine, mimics the broad symptomatology of schizophrenia and results in increased glutamate levels in both animals and humans. In rodents, acute provocation with ketamine caused a paradoxical increase in extracellular frontal glutamate, as well as dopamine. A similar increase in prefrontal glutamate was documented in healthy volunteers with proton magnetic resonance spectroscopy (1H-MRS). In addition, a characteristic small increase in striatal glutamate at a very early stage of the disease even before the inclusion of antipsychotic treatment has been documented with 1H-MRS [44].

In the studies analysed in this review, patients diagnosed with schizophrenia had higher mean blood glutamate concentrations compared to healthy subjects. In addition, patients with chronic schizophrenia had higher levels of glutamate concentrations than patients with recent onset of schizophrenia [45–47] (Table 2).

Bipolar affective disorder (BD). During the course of bipolar affective disorder, dysfunction is observed in the dopaminergic, noradrenergic and glutamatergic systems. Different combinations in neurotransmitter signalling elicit different functional brain states that manifest in different combinations of arousal or inhibition in psychomotility, affectivity and thinking, resulting in manic, depressive and mixed BD states [48]. Abundant evidence suggests that in BD, glutamatergic neurotransmission is severely impaired in different brain regions, leading to changes in synaptic signal transmission [49]. In the study results cited, it can be seen that people with BD have higher serum glutamate levels than healthy individuals [50, 51] (Tab. 2). Furthermore, in a systematic review and meta-analysis of studies on proton magnetic resonance spectroscopy in bipolar disorder analysed 40 studies involving 1,135 patients with BD and 964 healthy controls (HC), patients with BD had significantly elevated levels of glutamate+glutamine and glutamine in the anterior cingulate cortex, compared to HC. It was also shown that adult BD patients had significantly higher glutamate and glutamine levels than adult HC patients. However, no such relationship was shown in the paediatric population [13].

Depression, including post-stroke depression. The studies analysed show significantly higher glutamate levels in depressed patients compared to healthy individuals [7, 52] (Tab. 2). There is increasing evidence that glutamatergic signalling may be involved in the pathophysiology of depression. Disregulation between the main excitatory glutamatergic and inhibitory gamma-aminobutyric acid neurotransmission results in cellular damage called 'excitotoxicity', which is thought to be one of the causes of depression [53]. Transcriptomic studies, together with genomic studies, also point to GABA and glutamate dysfunction, as well as immune mechanisms linked to the use of novel fast-acting agents that target the glutamate and GABA systems, thereby increasing treatment efficacy [54]. Of note is the emergence of post-stroke depression (PSD), whose incidence ranges from 11 – 41% over two years and is associated with high mortality [55]. Unfortunately, there is no unified mechanism to explain PSD, which currently includes dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, increased inflammatory factors, reduced monoamine levels, glutamate-mediated excitotoxicity, and an abnormal neurotrophic response [55]. To date, it has been observed that there is a strong association between plasma glutamate levels on admission to hospital and the development of PSD within three months [56].

DISCUSSION

As evidenced by the cited studies, changes in glutamate concentration have been observed in individuals with neurological and psychiatric diseases. It can thus be concluded that glutamate plays an important role in the pathogenesis of these conditions. The most common method for measuring glutamate concentration in the body is through a blood test. However, due to the presence of the blood-brain barrier, changes in glutamate levels in the blood cannot accurately reflect changes in the CNS. In cases where BBB dysfunction occurs, such as in neurological diseases or brain injuries, e.g. stroke, glutamate can diffuse into the bloodstream, suggesting that glutamate may serve as a potential biomarker for these condition [11]. However, despite the high concentration of glutamate in neural tissue (10,000–12,000 μmol/L), only a small percentage (0.5–2 μmol/L) is in the extracellular space and may be involved in crossing the BBB [57]. Additionally, as previously stated, glutamate is not only involved in neurological processes but also plays a role in other physiological functions. Consequently, elevated blood glutamate concentration may indicate the presence of pathology in other organs, such as in the case of non-alcoholic fatty liver disease (NAFLD) [58]. Moreover, plasma glutamate concentration is susceptible to alteration by a multitude of additional factors, including obesity [59], diet [60], sport [61], or even gut microbiome [7].

Neurodegenerative diseases. Despite the lack of comprehensive understanding regarding the relationship between blood glutamate concentration and cerebrospinal fluid concentration, it is noteworthy that in the majority of cases associated with neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease, glutamate concentrations in body fluids and nerve tissue tend to be reduced [21–25, 62]. The probable cause of the reduction in

Table 2. Changes in glutamate levels in different diseases [26,37,45-47,50-52,56,62-65]

Disease entity	Research topic	Type of work	Years of research	Patients	Control	Results	Blood glutamate (Glu) levels (mean)
Migraine	van Dongen RM, Zielman R, Noga M, Dekkers OM, Hankemeier T, van den Maagdenberg AM, Terwindt GM, Ferrari MD. Migraine biomarkers in cerebrospinal fluid: A systematic review and meta-analysis. *Cephalalgia*. Jan. 2017, 37(1):49-63, [64].	A systematic review and meta-analysis (40 studies)	1960–2001	385 patients with episodic(interictal/ictal) migraine	196 healthy people	In patients with episodic ictal migraine elevated blood glutamate levels were observed, while in the second group of patients with episodic interictal migraine the overall difference was not statistically significant.	Episodic migraine-interictal: SMD*: 1.08 95% CI-0.07, 2.22 Episodic migraine- ictal: SMD*:2.01,95% CI:1.27, 2.75 *-standardised mean differences
Migraine	Campos F, Sobrino T, Pérez-Mato M, Rodríguez-Osorio X, Leira R, Blanco M, Mirelman D, Castillo J. Glutamate oxaloacetate transaminase: a new key in the dysregulation of glutamate in migraine patients. *Cephalalgia*. Oct. 2013, 33(14):1148-54 [65]	Original research	June 2007–November 2009	45 patients with migraine (with and without aura)	16 healthy people	Migraine patients had significantly elevated blood glutamate levels, compared to controls.	Control: 15.2± 2.9 vs. 18.7± 3.8U/l Migraine: -interictal: 153.7± 68.6 vs. 121.5± 59.2μM -ictal: 145.1±90.5 vs. 137.2± 96.2μM
Stroke	Cheng SY, Zhao YD, Li J, Chen XY, Wang RD, Zeng JW. Plasma levels of glutamate during stroke is associated with development of post-stroke depression. Psychoneuroendocrinology. 2014 Sept; 47:126-35 [37]	Original research	November 2011–September 2013	209 patients with acute ischemic stroke	120 healthy people	Blood glutamate levels were significantly elevated during acute stroke, compared with the control group. In addition, time-dependent changes in glutamate concentrations were observed.	Control: 25—75 μM Acute ischemic stroke: 130—258 μM 0-8h:104 (75—187) μM 8-16h: 202(142—269) μM 16-24h:227 (159—296) μM 24-48h:125(90—207) μM
Alzheimer's disease (AD)	Chang CH, Lin CH, Liu CY, Huang CS, Chen SJ, Lin WC, Yang HT, Lane HY. ' for detecting mild cognitive impairment and Alzheimer's disease: Machine learning approaches. J Psychopharmacol. 2021 Mar; 35(3):265-272 [56]	Original research	no inormation about it	21 patients with mild cognitive impairment (MCI) and 133 patients with AD	31 healthy controls (HC)	MCI and AD groups had lower plasma d-glutamate levels, compared to healthy controls.	Alzheimer's disease – 785.10 ± 720.06 ng/ml, HC – 1620.08 ± 548.80 ng/ml
Alzheimer's disease	Lin CH, Yang HT, Chiu CC, Lane HY. Blood levels of D-amino acid oxidase vs. D-amino acids in reflecting cognitive aging. Sci Rep. 2017 Nov 1; 7(1):14849 [62]	Original research	no inormation about it	77 patients with amnestic MCI, 128 patients with mild AD and 76 patients with moderate to severe AD	116 healthy controls	D-glutamate levels fell step-by- step from healthy elderly, MCI, mild AD, to later-phase AD. On the other hand, L-glutamate levels was higher in individuals with MCI, mild AD, or moderate-severe AD, than in healthy elderly.	D-glutamate levels: patients with MCI – 1097.8 ± 284.0 ng/mL, mild AD – 1031.9 ± 775.8 ng/mL, moderate-severe AD – 598.3 ± 551.9 ng/mL, healthy elderly – 1620.4 ± 558.2 ng/mL
Parkinson's disease (PD)	Jiménez-Jiménez FJ, Alonso-Navarro H, García-Martín E, Agúndez JAG. Cerebrospinal and blood levels of amino acids as potential biomarkers for Parkinson's disease: review and meta-analysis. Eur J Neurol. 2020 Nov; 27(11):2336-2347 [26]	Meta-analysis (10 studies)	1966–2020	366 patients with PD	259 healthy controls	Patients with Parkinson's disease were found to have reduced levels of glutamate in the cerebrospinal fluid, compared to a healthy age- and gender-matched group. Plasma glutamate levels were similar in Parkinson's disease patients and controls.	The latest study: glutamate levels in CSF: Parkinson's disease - 1.5 no unit, HC-1.9 no unit
Amyotrophic lateral sclerosis (ALS)	Andreadou E, Kapaki E, Kokotis P, Paraskevas GP, Katsaros N, Libitaki G, Petropoulou O, Zis V, Sfagos C, Vassilopoulos D. Plasma glutamate and glycine levels in patients with amyotrophic lateral sclerosis. *In Vivo*. 2008 Jan-Feb; 22(1):137-41 [63]	Original research	no information about it	65 patients with ALS	20 healthy controls	Plasma glutamate levels were increased in ALS, which was associated with longer disease duration and male gender. The increase was found only in the medullary subtype of the disease, while no significant increase was observed in the paretic subtype.	ALS - 38.4 (29.5–47.6) μM HC - 32.8 (22.3–41.6) μM

Disease entity	Research topic	Type of work	Years of research	Patients	Control	Results	Blood glutamate (Glu) levels (mean)
Schizophrenia	C. Madeira et al., "Blood Levels of Glutamate and Glutamine in Recent Onset and Chronic Schizophrenia," Front Psychiatry, vol. 9, 713, Jul. 2018 [45].	Original research	2006–2016	patients from two cohorts - 32 patients with recently diagnosed schizophrenia (less than five years after the onset of symptoms) and (56 and 67) patients with chronic schizophrenia	from two cohorts- 53 and 75, respectively	Patients with schizophrenia of recent onset showed an increased glutamine/glutamate ratio, while patients with chronic schizophrenia had a decreased glutamine/glutamate ratio compared to healthy control (HC)	First cohort: recent onset schizophrenia- 131.2 µmol/l; chronic schizophrenia- 254.6 µmol/l; HC- 201.5 µmol/l, 180.3 µmol/l; Second cohort:chronic schizofrenia- 470.0 µmol/l; HC- 264.5 µmol/l
Schizophrenia	S. A. Ivanova, A. S. Boyko, O. Yu. Fedorenko, N. M. Krotenko, A. V Semke, and N. A. Bokhan, 'Glutamate Concentration in the Serum of Patients with Schizophrenia', Procedia Chem, vol. 10, 80–85, Jul. 2014 [46].	Original research	no information about it	158 patients with paranoid schizophrenia	94 healthy people	Maximum glutamate concentrations were detected in patients with a duration of illness longer than ten years. Interestingly, no significant differences in serum glutamate levels were observed in patients with the leading positive or negative clinical symptoms	schizophrenia- 21.35 ± 5.5 nmol/µl; HC- (13.69 ± 5.25 nmol/µl;
Schizophrenia	Song, Jiali, et al. Peripheral glutamate levels in schizophrenia: evidence from a meta-analysis. Neuropsychobiology, 2014, 70.3: 133-141 [47]	Meta-analysis (10 studies)	1972-2007	320 schizophrenia patients	294 healthy controls	Significantly higher levels of glutamate revealed in patients with schizophrenia than in healthy controls in both models, i.e. where males and females were separate samples and when they were a combined sample; revealed no significant association between differences in glutamate levels and age, gender, ethnicity, medication, sample type (serum versus plasma), and whether patients were fasting	schizophrenia-33.4-57.000 µmol/l; HC- 19.5-28.000 µmol/l
Bipolar affective disorder	E. Pålsson et al., "Markers of glutamate signaling in cerebrospinal fluid and serum from patients with bipolar disorder and healthy controls," Eur Neuropsychopharmacol, vol. 25, No. 1, 133–140, Jul. 2015 [50].	Original research	no information about it	215 patients with bipolar affective disorder (ChAD). cerebrospinal fluid (CSF) was collected from 132 patients	112 healthy people. CSF was collected from 87 HC	Serum levels of glutamine, glycine, and d-serine were significantly higher in patients with bipolar disorder compared to controls, while l-serine levels were lower. The glutamine/glutamate ratio did not differ between groups. In cerebrospinal fluid, no statistically significant differences were observed between patients and controls	bipolar disorder- 58.4 µM; HC- 54
Bipolar affective disorder vs depression	Liao JW, Wang SS, Yang HH, Ma P, Li CR, Pan JY. Comparative analysis of serum glutamate and gamma-aminobutyric acid levels in patients with bipolar depressive disorder and major depression disorder]. Zhonghua Yi Xue Za Zhi. 2020 Jun 16;100(23):1800-1804. Chinese [51]	Original research	2018-2019	47 patients with depression and 45 with BD	41 healthy people	The serum Glu level and Glu/GABA ratio in depression and bipolar depression groups were higher than those of the healthy control group, while the GABA level were lower than those of healthy control group. However, Glu/GABA was higher in bipolar depression group than that in depression group.	depression-(36±7) mg/L; bipolar depression- (37±7) mg/L; HC (28±4) mg/L
Major depressive disorder (MDD)	Inoshita M, Umehara H, Watanabe SY, Nakataki M, Kinoshita M, Tomioka Y, Tajima A, Numata S, Ohmori T. Elevated peripheral blood glutamate levels in major depressive disorder. Neuropsychiatr Dis Treat. 2018 Apr 6; 14:945-953 [52]	Meta-analysis (11 studies)	1993-2018	529 patients	590 HC	Among the 11 studies, six reported elevated glutamate levels in MDD, while the other five studies did not find significant differences in glutamate levels between MDD patients and control subjects	Study 1: MDD- 191.86nmol/mL; HC- 21..58nmol/mL; S2: MDD:336 no unit; HC-265 no unit; S3: MDD- 86.05nmol/mL; HC-21.97 nmol/mL S4: MDD-155.66µmol/L; HC 134µmol/L; S5: MDD-94.0 nmol/mL; HC-59.6 nmol/mL; S6: MDD-44.1 µM/L; HC-39.3 µM/L etc.
Post-stroke depression (PSD)	Cheng SY, Zhao YD, Li J, Chen XY, Wang RD, Zeng JW. Plasma levels of glutamate during stroke is associated with development of post-stroke depression. Psychoneuroendocrinology. 2014 Sep;47:126-35 [37].	Original research	2011-2013	70 patients (33.5%) were diagnosed as having major depression at 3 month	139 post-stroke patients	Patients with major depression showed higher levels of plasma glutamate and lower glutamate oxaloacetate transaminase (GOT) at admission. In multivariate analyses, plasma glutamate and GOT were independent predictors of PSD at three months	major depression-299 (235-353) µM; control- 157 (108-206) µM

glutamate concentrations observed in neurodegenerative diseases is thought to be a direct depletion of glutamate-producing cells and a direct reduction in glutamate release into the blood. Alternatively, it may be the result of a compensatory reduction in serum glutamic acid levels in response to its deficiency in the brain [25]. In contrast, glutamate concentrations were elevated in ALS, suggesting that the participation of glutamate in the pathophysiology of this disease may be somewhat different [63] (Tab. 2).

Stroke and migraine. Conversely, elevated glutamate levels are likely to be associated with a rapid disruption to the blood-brain barrier and excessive release from neurons in a relatively short period of time, as observed in stroke [25, 39]. The findings of the studies that have evaluated the level of glutamic acid in migraine attacks indicate that the concentration of glutamic acid in the blood is elevated during migraine attacks [32, 34, 64, 65] (Tab. 2). Furthermore, a meta-analysis that investigated serological migraine chronic markers demonstrated that elevated glutamate levels in conjunction with CGRP appear to be a promising prognostic marker and a useful measure of migraine chronic treatment efficacy [32].

Psychiatric diseases. In schizophrenia, when comparing different cohorts of patients and healthy control subjects in different studies, differences between blood glutamate levels in patients and healthy subjects are apparent. However, when comparing the same groups, for example, of patients with schizophrenia, significant differences in glutamate concentrations are apparent. The above data confirm that glutamatergic dysfunction is associated with the pathology of schizophrenia, but this may vary from patient to patient. However, it is unclear at this time whether inter-individual variability in glutamate is greater in schizophrenia sufferers than in the general population [66]. Given the significant impairment in the functioning of people with schizophrenia, it seems of utmost importance to find biomarkers to make an accurate diagnosis and implement appropriate treatment. Regarding advances in biomarker research in psychosis, current symptom-based criteria already seem insufficient in clinical settings. Neuroimaging of glutamate/glutamine density changes seems to be a potential biomarker that requires further thorough research. On the other hand, when looking for biochemical/immunological markers in the diagnosis of psychosis, the appropriate timing of the accumulation of body fluids should be taken into account to minimise the influence of the stress axis on their concentrations [67]. People with BD have higher glutamate levels than healthy individuals. Such results can be observed in both blood and the frontal cortex as measured by 1H MRS. There are hypotheses that the elevated brain glutamate levels in bipolar disorder observed by 1H MRS with very high consistency, can be explained by an increase in anaplerosis mediated by pyruvate carboxylase, which is a mitochondrial enzyme and through which, in the brain, released glutamate neurotransmitter is replenished by the glutamate-glutamine neurotransmitter cycle and *de novo* glutamate synthesis through anaplerosis [68] (Tab. 2).

CONCLUSION

The main aim of this review was to show the significant role of glutamate in neurological and psychiatric diseases and to demonstrate its potential as a biomarker, an aim which the authors believe have achieved. However, it is realised that in order to attempt to establish a range of glutamate concentrations that could be clinically applicable, it would be necessary to perform a comprehensive meta-analysis, taking into account all the studies performed to date, depending on the type of method and the body fluid in which glutamate concentrations were measured in different disease entities, and depending on the demographics of the subjects.

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