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REVIEW ARTICLE

Peripheral and Central Glutamate Dyshomeostasis in Neurodegenerative Disorders

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Abstract: Glutamate's role as the major excitatory neurotransmitter of the mammalian central nervous system requires that its brain concentrations be kept tightly-controlled. However, in hepatic encephalopathy resulting from liver dysfunction; disruption of central neurotransmission and elevation of brain glutamate levels have been observed. These had been associated with certain neurological changes. While neurological changes resulting from hepatic encephalopathy are believed to be transient, the discovery of alterations in liver enzymes in Alzheimer's disease and the role of glutamate and glutamate homeostasis in hepatic encephalopathy have piqued interests in the possible role of glutamate, and glutamate homeostasis in neurodegenerative diseases. Here, we discuss the evidence in support of the involvement of peripheral/central glutamate homeostasis in the development of neurodegenerative disorders, as well as, the implications of such interactions in the development of new therapies for neurodegenerative disorders.

Keywords: Gut-liver brain axis, glutamate receptors, sodium-dependent transporter, cystine-glutamate antiporter.

1. INTRODUCTION

Glutamate is an amino acid that plays crucial role in intermediary metabolism, and is also essential to the functioning of the central nervous system. Dietary sources include meat, cheese, and glutamate-containing food-seasonings like monosodium glutamate. In the body, glutamate can be viewed as being contained in two pools, a peripheral and a central one; both of which are relevant to its metabolic and brain excitatory roles. Glutamate's importance to general metabolism is exemplified through its role in linking the metabolism of carbohydrates and amino acids *via* the tricarboxylic acid cycle, and by acting as a substrate or co-substrate in different enzymatic reactions [1, 2].

In peripheral organs like the liver, glutamate is central to amino acid metabolism, through the transdeamination of a large number of amino acids, or the synthesis of glutamate from the catabolism of amino acids like glutamine, proline, arginine and histidine. Hence, the glutamate that is found in this peripheral pool is usually derived from the diet, peripheral glutamine metabolism and/or synthesized by gut bacteria [3-6].

Almost six decades ago, the excitatory effect of glutamate on nerve cells was reported [7, 8]. Since this discovery, its role in brain metabolism, as an excitatory neurotransmitter (within normal range), and an excitotoxin (in excess) has been studied extensively [8-12]. Presently, it is known that in the vertebrate central nervous system (where as many as 40% of the synapses are glutamatergic), glutamate is not only the main excitatory neurotransmitter, but it is also an intermediate precursor of γ–amino-butyric acid (the main inhibitory neurotransmitter in the brain) [2, 12, 13]. In the brain, glutamate is one of the most abundant free amino acid, and in similarity with its peripheral effects, it also lies at the crossroad of multiple metabolic pathways [12, 14].

Despite having similar roles, it is generally believed that the central and the peripheral glutamate pools do not freely mix; otherwise, this would create a challenge for the regulation of glutamate levels in the brain. Crucial to this partitioning is the blood brain barrier that has been shown to have the ability to exclude most of the peripheral glutamate (plasma glutamate), suggesting that the brain glutamate levels are maintained by glutamate that is largely produced within the brain [15]. Under physiological conditions, this partitioning of activities in the central and peripheral pools is generally intact. However, in pathological conditions such as inflammation or in hyperammonaemia (arising from a number of diseases including liver failure), studies have shown the activation of cerebral enzymes such as glutamate dehydrogenase, and a resultant increase in extracellular glutamate concentration [16, 17]. This shows that while the peripheral and central glutamate pools may appear distinct, the regulatory systems can interact with each other, and a deficiency in the functions of one may lead to a loss of regulatory ability in the other. Also, the awareness of the link between excess brain glutamate and neuronal death raises questions as to the importance of the interactions between peripheral/central

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glutamate homeostasis (through the brain-gut--liver axis) and the development of neurodegenerative diseases.

While the neurological changes resulting from hepatic encephalopathy are believed to be transient, the reports of alterations in blood glutamate levels and/or liver enzymes in neurological disorders like autism, schizophrenia, cognitive impairment and Alzheimer's diseases [18-23] and suggestions that peripheral glutamate concentration correlated positively with central glutamate levels [20, 24] have piqued the interest of researchers on the possible roles of glutamate, and glutamate homeostasis in nervous system diseases (especially neurodegenerative diseases) and its import on the development of novel therapies. Here, we discuss evidence in support of the involvement of peripheral (plasma/liver) and central (brain) glutamate homeostasis in the development of brain disorders, as well as, the implications of such interactions in the development of new therapies.

1.1. Glutamate: A Historical Perspective

Glutamate, which is an important constituent of a large number of proteins is also one of the most abundant amino acids found in the human body [10]. Despite its importance to health and well-being, it is classified as a non-essential amino-acid because it can be synthesized endogenously. In 1866, scientist Karl Heinrich Ritthausen purified glutamic acid from gliaden, which is a protein component of wheat gluten, after which it was named [25, 26]. Recognition of the possible neurophysiological importance of glutamate was first documented about seven decades ago, when glutamate was noticed to occur in high concentrations in the brain. Subsequently, researchers would focus on the relationships between dietary glutamate in the possible treatment of seizure and learning disorders [27]. The possibility that glutamate could be a brain neurotransmitter was suggested by Hayashi following observations that injection of glutamate into the carotid arteries or brain tissue was associated with the development of seizures [28, 29]. Another indication that glutamate could be considered an excitatory neurotransmitter was suggested by Curtis *et al*. [7, 30] who examined the activities of amino acids (generally) and acidic amino acids (specifically) on toad spinal cord neurons; although formal confirmation and general acceptance of the brain neurotransmitter properties of glutamate would not occur for another two decades [27]. In the ensuing years, scientists continued to study glutamate's characteristics, thereby increasing our understanding of glutamate analogues, naturally occurring glutamate, glutamate receptors, the possible interactions of glutamate in the brain, as well as the different roles (other than its importance in intermediary metabolism) played by glutamate in the maintenance of health or the pathogenesis and treatment of disease [31-41]. Also, the systems that regulate brain glutamate levels are still being studied, and it is known that its metabolism depends largely on a number of reversible and irreversible reactions strictly controlled by over 107 regulator molecules [42]. Finally, in the last two decades of the 20th century, extensive work on glutamate homeostasis has led to the discovery and distribution of brain glutamate transporters, the identification and cloning of the excitatory amino acid transporters [43-47] and the development of subtype□specific glutamate transporter knockout mice [48-50]. All these findings have increased our understanding of the importance of glial glutamate transporters in glutamate homeostasis and the maintenance of brain function.

1.2. Glutamate in the Liver, Blood and Brain

Glutamate in the mammalian body is derived from both exogenous and endogenous sources. Exogenous sources of glutamate are largely derived from dietary proteins or food additives like monosodium glutamate [26, 51]. Glutamate makes up about 7% of proteins found in meat [26, 52], while proteins like ornithine aminotransferase contain significantly more [26]. Endogenouslyglutamate found in a number of organs, including liver and brain is derived from the catabolism of a number of amino acids [26, 53]. Blood glutamate is derived from dietary proteins and monosodium glutamate, catabolism of endogenous proteins, as well as from alimentary free L-glutamate, derived from degradation of luminal peptides [51, 54].

In the liver, glutamate is central to the metabolic processes in a number of ways; a) it plays a catalytic role in the transdeamination reactions of amino acids, b) it is an endpoint in the catabolism of a number of amino acids, including arginine, histidine, ornithine, proline, and glutamine, c) serves as a regulator for the urea cycle because it acts as a substrate alongside co-enzyme A for the synthesis of N-acetylglutamate a rate limiting enzyme and an allosteric activator of a key regulatory enzymes in the urea cycle [26, 55]. Present in the liver in large quantities and distributed unevenly within the hepatocyte lobules and zones are enzymes that are crucial for glutamate homeostasis. Some of these enzymes include glutaminase that catalyzes the deamidation of glutamine to glutamate to generate ammonia., alanine aminotransferase catalyzes the transfer of an amino group from alanine (donor) to the α-ketoglutarate (acceptor), resulting in the production of pyruvate and glutamate. Another very important enzyme is glutamate dehydrogenase (GDH), which catalyzes the reversible oxidative deamination of glutamate to α-ketoglutarate and ammonia, and helps to bridge the amino acid–to–glucose pathways. Here, we have reports that the activity of GDH especially is crucial for energy metabolism throughout the body, GDH has also been shown to aid in the maintenance of an equilibrium, by ensuring an appropriate ratio of ammonia and amino acids for urea synthesis in the periportal hepatocytes, as well as producing glutamate for glutamine synthesis, thus making it a crucial enzyme in glutamate homeostasis [6, 56]. Deficiency or alteration in the functioning of a number of enzymes like GDH has been linked to the development of hyperinsulinism or hyperammonaemia syndrome [6, 56].

Glutamate in the blood is derived mainly from dietary sources, but also from direct secretions from organs like the liver in which glutamate is synthesized into the blood (portal vein). Blood glutamate concentration is usually maintained at about 40 to 60 μM [57], while in the brain, extracellular

brain glutamate concentration ranges from around 25 to 90 nM [58, 59] with significantly higher concentrations (90.2 μM to about 20 μM) observed intracellularly [60, 61]. Studies have also demonstrated that under normal conditions, blood levels of glutamate far exceed brain or cerebrospinal fluid (CSF) levels, with this difference giving rise to what is now considered the intraparenchymal-blood glutamate concentration gradient [62, 63]. This gradient is however maintained through the integrity of the blood–brain barrier that limits the influx of blood glutamate, as well as the activity of endothelial glutamate transporters that have been shown to continually transport excess glutamate from the brain/CSF into the blood [64].

In the brain, a large percentage of available glutamate is synthesized from glucose and non glucose sources, following which it is stored in vesicles. Because glutamate does not move freely from plasma into the brain; due to the presence of the blood brain barrier, a large percentage of the brain requirement for glutamate is sourced from glutamate converted from glucose sourced from plasma. Plasma-derived glucose enters the brain through a family of glucose transporter molecules (GLUTs) which are present on astrocytes, endothelial cells and neurons [65, 66]. Through the glycogen synthesis, the glycolytic pathway and finally the tricarboxylic acid (TCA) cycle, glucose gets converted first to glycogen or pyruvate which enters the TCA cycle, following which ketoglutarate an intermediate of the cycle is used in glutamate synthesis (reactions which take place in the astrocyte).

Glutamate is the most abundant amino acid in the brain, far exceeding the concentration of a number of other amino acid and resulting in the existence of another gradient. Therefore to prevent excitotoxic injury, the brain glutamate concentration gradient must be kept at the barest minimum. And this is maintained by the actions of a number of enzymes including enzymes of glutamate synthesis/catabolism and glutamate transporters in specified cellular and sub-cellular compartments [2, 15, 63].

Overall, the critical role played by glutamate in the blood/liver, its extensive distribution in the brain, its role in the control of a number of physiological functions, and the implications of glutamate dyshomeostasis are evidences in support of glutamate's importance in the maintenance of brain/body health [67-69] and the development of disease [17, 70, 71].

1.3. Glutamate Biosynthesis and Metabolism

The biosynthesis of glutamate has been extensively studied and is believed to occur *via* two very crucial pathways for which the end point is conversion of 2-oxoglutarate (an intermediate in the citric acid cycle) to glutamate [72, 73]. The first pathway involves a reductive amination of 2-oxoglutarate (catalysed by glutamate dehydrogenase), using ammonium as nitrogen donor; while the other pathway which is also a reductive amination is catalysed by a flavin-dependent iron sulphur cluster protein (glutamate synthase), and involves the conversion 2-oxoglutarate using glutamine as the nitrogen donor [72].

The metabolism of glutamate is mostly intracellular, being involved in the metabolism of almost all other amino acid *via* transamination or glutamate dehydrogenase catalysed reactions [74-76]. In the liver glutamate metabolism occur mainly in the periportal hepatocytes where most of the required enzymes are found in large quantities [26, 76]. The breakdown of glutamate involves a number of reversible and irreversible reactions catalyzed by key enzymes that are also modulated by other regulatory factors [42]. In a reversal reaction involving the tricarboxylic acid cycle, the carbon from glutamate is converted to 2-oxoglutarate, a process which in some organisms is the major source of carbon for energy metabolism [73, 77]. Another important product and substrate in glutamate biosynthesis and metabolism is glutamine. Glutamine synthetase, which catalyses the adenosine-triphosphate dependent amidation of glutamate to glutamine [72] utilises ammonium as a source of nitrogen. Glutamate metabolism plays a vital role in biosynthesis of nucleic acids and proteins, through transamination reactions catalysed by transaminases; the amine group of glutamate is transferred to the 2-oxo precursors of several amino acids including aspartate, serine, alanine, leucine, valine, leucine, phenylalanine, tyrosine and isoleucine. Glutamate is also a nitrogen donor for the nitrogens in purines and pyrimidines [73].

In the central nervous system, the biosynthesis and metabolism of glutamate occurs in neurons and/or glial cells (with astrocytes playing a very important part) through reactions that are considered part of the glutamate-glutamine cycle. In the brain, the metabolism of glutamate is very complex and highly-compartmentalised [2, 15]. The neurotransmitter pools are strictly maintained by *de novo* synthesis of glutamine in the astrocytes (reactions catalysed by both pyruvate carboxylase and glutamine synthetase). Glutamate is then formed from glutamine through a deamidation reaction catalysed by the enzyme glutaminase, also yielding ammonia [2]. In the human, glutamate decarboxylase, an enzyme located only in the brain catalyses the major catabolic non oxidative decaboxylation of glutamate to γ-amino-butyric acid [76].

1.4. Glutamate Signalling

Glutamate, which is arguably the most important excitatory neurotransmitter in the central nervous system [12, 63] is synthesized in the neurons or glial cell; and is concentrated in the synaptic vesicles of the presynaptic terminal of glutamatergic neurons *via* the activity of vesicular glutamate transporters [63, 78]. Thereafter, it is released into the synaptic cleft when the neurons are stimulated [63]. Also present within the synaptic vesicle is glutamate that is generated within the vesicle itself from 2-oxoglutarate by a vesicle-associated aspartate tranferase [79]. Upon stimulation of the neurons, glutamate is released from the presynaptic terminals into the synaptic cleft (following the depolarization of the presynaptic membrane) where it mediates signal transduction by interacting with (metabotropic and ionotropic [α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainate, and N-methyl-D-aspartic acid (NMDA)] gluta-

mate receptors present on the pre- and post-synaptic membranes [63, 80, 81].

Once within the synaptic cleft, glutamate's fate is twofold, it is either taken up again by the presynaptic membrane or quickly cleared by astrocytes located around the synapse [63, 82]. Delays in glutamate clearance results in the excessive activation of glutamate receptors found on the post-synaptic membrane, causing glutamate excitotoxity, free-radical induced mitochondrial injury, destruction of the calcium ion buffer system and inhibition of phosphatidylcholine-specific phospholipase [83-85]. Excessively high levels of calcium and inflammatory mediators have also been reported to potentiate exocytosis-mediated release of glutamate from the synaptic terminals, with the development of an excitotoxicity cascade [86]. Studies have also shown that the presence of high levels of glutamate in the synaptic cleft causes the overactivation of ionotropic glutamate receptors, resulting in the deterioration of dendrites, postsynaptic spines and neuronal cell bodies [8, 87]. Glutamate is involved in neuronal development [88] as well as the modulation and maintenance of the diverse functions of the brain including emotionality, learning/memory and neuroinflammation [63, 89-92]. Therefore, homeostatic control and regulation of glutamate signalling is essential for normal brain functioning [93-95].

In the last twenty years, it has also become apparent that glutamate signalling occurs in non-neuronal tissues and organs as diverse as the pancreas, bone, skin, and lungs [96-99]. This was attributed to the presence of glutamate signalling mechanisms (vesicular release and receptor-mediated responses) in these organs similar to that found in the central nervous system [63]. These further buttresses the crucial role played by glutamate (either centrally or peripherally) in the maintenance of health and well-being.

1.5. Glutamate Homeostasis

Living organisms (from invertebrates to vertebrates) contain large intracellular pools of glutamate [73], due to employment of several biochemical pathways that ensure this. For instance, while only 6% of the codons in the *Escherichia coli* genome is involved in glutamate synthesis [73, 100], the concentration of glutamate in its cytosol far exceeds that of most other amino acids [101]. In humans, glutamate is one of the most abundant amino acids [10], and it is both derived from the diet and also synthesised in the body through a series of reactions and pathways, showing how important glutamate is to the maintenance of physiologic function. The vital roles played by glutamate in intermediary metabolism, glutamate signalling and excitatory neurotransmission, as well as the effects of glutamate dyshomeostasis (especially in the brain but also in a number of other organs) means that for the maintenance of health and well-being, a tight hold must be maintained on glutamate synthesis, metabolism and signalling.

Centrally, glutamate homeostasis refers to mechanisms that ensure a tight control of extrasynaptic glutamate concentrations which is essential for limiting the capacity of glutamatergic synapses to either potentiate or depotentiate [102]. In the blood, glutamate homeostasis is maintained by a number of complex poly-component mechanisms that include the activities of a number of enzymes secreted by the liver, and through the metabolic effects of some hormones such as insulin and glucagon [103]. Enzymes such as glutamate-pyruvate transaminase (GPT) and glutamate-oxaloacetate transaminase (GOT) and their respective co-substrates (pyruvate and oxaloacetate) ensure the conversion of glutamate into 2-ketoglutarate, aspartate and alanine [103, 104]. Reports from rodent studies have also demonstrated that intravenously-administered pyruvate or oxaloacetate decreased blood concentration of glutamate by up to 30 and 40% respectively, and by 60% when administered together [103, 104].

Glucose, insulin and glucagon have all also been reported to significantly decrease blood glutamate concentration [105]. The blood glutamate lowering effects of glucose is believed to be linked to its ability to stimulate insulin secretion ([105, 106]. Increase in insulin secretion in turn promotes glutamate efflux from plasma into skeletal muscle [103]. It has also been suggested that trough the actions at the AMPA receptors located in the pancreas a positive feedback mechanism exists between high blood glutamate concentration and the activation of insulin or glucagon secretion that aids in the return of glutamate towards normal levels [103].

Generally, synaptically-released brain neurotransmitters undergo uptake and metabolism, following which their precursors are released back to neurons [107-109]. In the brain, homoeostasis of glutamate (and a number of other amino acids) is maintained and regulated mainly through the activities of astrocytes that ensure up to 90% of extracellular glutamate removal [109]. Again, Hamilton and Attwell [110] had suggested that in addition to releasing glutamate precursors to neurons, astrocytes (through a process mediated by Ca^{2+}-dependent exocytosis) release small amounts of glutamate to adjacent neurons, to assist in synchronizing their firing. While the clearance of glutamate is achieved primarily by astrocytes, it is moderated by glutamate uptake transporters [108, 111]. The two main glutamate transporters involved in glutamate uptake are sodium-independent (chloride-dependent antiporters that ensure cystine/glutamate exchange) and sodium-dependent transporters also known as excitatory amino acid transporters (EAATs), which are responsible for the uptake of the larger percentage of extracellular glutamate [82, 111].

Sodium-independent transporters are expressed by a number of cells in the central nervous system, including astrocytes and microglia [108, 112-114]. The Na^{+} independent transporters are also responsible for the uptake of cystine, used in the synthesis of, glutathione. Although Na^{+}-independent transporters have almost similar affinity for glutamate as do the EAATs, their uptake of glutamate under physiological conditions is significantly lesser [108].

Excitatory amino acid transporters are a family of brain glutamate transporters made up of five members including EAAT 1 to 5 which are responsible for the uptake of the majority of the extracellular glutamate. The first two isoforms

EAAT-1 and 2 are also known as glutamate-aspartate transporter (GLAST) and glutamate transporter-1 (GLT-1), respectively [44, 45, 108]. A number of the EAATS are expressed in the endothelium of the blood-brain barrier as well as ubiquitously in the brain [103]. In the brain, they are also expressed in specific regions; for example EAAT1 is found in large quantities in the cerebellum while EAAT2 is expressed abundantly in the hippocampus and cerebral cortex. Critical to glutamate homeostasis is their expression on glial cells, particularly astrocytes [115]. Other transporter systems including vesicular glutamate transporters (which are intracellular transporters present only in neurons) and glutamate-cysteine exchangers (present in neurons and glia) have been reported to also transport glutamate [61, 116-118].

Finally, in the brain, there have been reports of alternative mechanisms of glutamate homeostasis. Studies have demonstrated the presence of a unidirectional movement of glutamate from the brain into the blood, a process that is facilitated by the presence of glutamate transporters (EAAT1, EAAT2 and EAAT3) on the blood brain barrier [64, 119-121]. Also present on the abluminal side of the membrane are glutamine transporters that take up glutamine. This then allows for the efflux of glutamate from the brain to the blood [63, 103, 119-121].

1.5.1. Mechanism of Regulation of Glutamate Homeostasis in the Brain

Years of research have shown that a number of factors including stress, oxidative stress, excitotoxicity and neuroinflammation are distinct but important hallmarks of several neurological disorders; while neurodegeneration and cell death are usually the common end- points of these pathological processes. However, in recent times, studies are beginning to demonstrate that glutamate dyshomeostasis in a key feature in the progression of a number of these disorders [122-129].

In the mammalian brain, a tight control of extracellular glutamate levels is maintained, especially, in the light of the possible dire consequences of continued or unregulated presence of glutamate at the brain synapses. A number of mechanisms assist in maintaining the normal glutamate gradient between the intracellular and extracellular compartment of the brain in health [66]. These mechanisms include, regulating the quantity of glutamate that moves from the peripheral pool (plasma) to the central pool (central nervous system), homeostatic synaptic plasticity at the level of the neurons, the uptake of glutamate from the extracellular space by glutamate transporters following release into the synaptic cleft, and the metabolic clearance of glutamate through the glutamine-glutamate –γ-amino butyric acid cycle [66].

Glutamate that is derived from plasma does not cross into the brain readily due to the blood-brain-barrier. For every one gram of brain tissue, it is estimated that only about 0.67 nmol of plasma glutamate enters per minute [66, 130], a rate that is significantly less than reported with a number of other amino acids including valine, glutamine and arginine [130]. In neurons and glial cells, homeostatic synaptic plasticity (believed to occur in both the pre and post-synaptic terminals) has been described as a mechanism through which glutamate synaptic activity is maintained at appropriate levels. Reports show that the inhibition of postsynaptic glutamate receptor activity such as the increase in the activity at the AMPA receptor (that occurs with tetrodotoxin induced blockade of action potential) alters glutamate levels and release from presynaptic terminals [80, 93]. Genes, transcription activity, and signalling molecules have also been shown to be important mediators of homeostatic synaptic plasticity [94, 95, 131, 132]

The inability to degrade glutamate in the extracellular space necessitates the use of a combination of mechanisms that involve diffusion and uptake using glutamate transporters to rid the extracellular space of the released glutamate [133, 134]. Excitatory amino acid transporters (EAATs) especially EAAT1 and 2 which are the most abundant modulate glutamate levels and prevent neurotransmitter spill over *via* their ability to bind and take up glutamate from the extracellular space, by employing an electrochemical sodium/potassium gradient across the plasma membrane and transporting it into astrocytes and microglia. This important function is regulated extensively at the levels of gene expression, cell-surface trafficking of protein, and post-transcriptional splicing [66, 135].

Once in the astrocytes, glutamate can be channelled through a number of metabolic end points including release back into the extracellular space, re-entry into the TCA cycle, or the enzymatic conversion to glutamine through a reaction catalysed by glutamine synthetase (which is found in significant quantities in the brain and liver). This glutamine-glutamate GABA cycle ensures the continued central nervous system supply of glutamate and/or GABA from glutamine, and vice-versa [66]. Although opinions differ regarding the relative degrees of involvement of cellular components of the brain in the regulation of glutamate homeostasis, it is clear that both neurons and astrocytes play key roles [66, 134].

In the mammalian brain, a carefully-regulated transporter-mediated system is believed to be critical for optimal synaptic transmission [136]. However, while it is generally known that there are regional differences in the glutamate--mediated plasticity and excitotoxic thresholds in the brain. Recent evidence is also beginning to point in the direction of regional differences in glutamate dynamics and that non-GLT-1 transporters contribute significantly to glutamate clearance in the hippocampus, cortex, and striatum [136]. Again, different regions of the brain have been observed to exhibit varying degrees of efficiency in the clearance of extracellular glutamate, with a region such as the hippocampus being more efficient than others such as the striatum and cerebral cortex [136]. This could also reflect the relative susceptibility of these regions to excitotoxic damage. However, the overall implications of this degree of heterogeneity (in glutamate regulation in the brain) in the pathogenesis or management of neurodegenerative disorders would continue to be an interesting research area.

1.5.2. Regulators of Glutamate Homeostasis

1.5.2.1. Genetic and Transcriptional Regulation of Glutamate Homeostasis

There have been suggestions that imbalances in glutamate homeostasis could cause changes in neuroplasticity and aberrant potentiation of glutamate transmission, resulting in impairment of communication between different regions of the brain; thereby, leading to disease [124, 125].This has increased the search for genetic markers, transcriptional factors or molecular mechanisms responsible for the regulation of different aspects of glutamate homeostasis. As mentioned earlier, a notable feature of glutamate homeostasis in the brain is the paucity of enzymes to adequately degrade glutamate. Therefore, the maintenance of extracellular levels of glutamate within normal limits is largely dependent on glutamate transporters, exchangers, and receptors which are directly involved in the release and reuptake of glutamate [137, 138]. There have been reports that alterations in the genetic and/or transcriptional regulation of enzymes or key aspects of glutamate homeostasis or glutamate signalling pathways could affect the modulation of brain function [129]. This would suggest that genes and/or transcription factors are crucial to the maintenance of glutamate homeostasis and by extension normal functioning of the brain; making them logical targets in the development of new therapeutic strategies [124, 129, 139-142].

In the liver and brain, enzymes are critical to the synthesis, metabolism and homeostatic control of glutamate concentration. A number of these enzymes such as GDH, glutamate synthase and glutamate synthetase are encoded for by genes, and also have their activities allosterically regulated [143, 144]. For example, glutamate dehydrogenase is encoded by a single GLUD1 gene that is expressed widely in the liver. In humans and some other primates, a second GLUD 2 gene has been reported to be expressed in the brain and kidney [144, 145]. Mutations in the human GLUD 2 gene has been associated with the development of nigrastriatal degenerations in hemizygous males [146], while mutations or defects in the genes encoding a number of these enzymes have also been linked to inborn errors of metabolism [147, 148]

In the brain glutamate transporters and receptors are also crucial to the maintenance of its homeostasis. The translational and/or transcriptional regulation of glutamate receptor expression had also been reported. In the brain, the up- or down-regulation of different subunits of the glutamate receptor has been observed to occur with respect to disease development, disease progression, or treatment. The promoter regions of a number of these subunits have also been reported to share transcriptional start sites that are subject to manipulation. There have also been suggestions that fragments of neuron-specific glutamate receptor promoters could become useful therapeutic targets for neurons in the brain through the development of gene-targeting constructs.

In the adult nervous system, glutamate transporters (especially GLT-1) are present in large numbers, functioning as regulators of glutamate concentration at glutamate receptors. Also, there have been reports that in addition to this, they also modulate excitatory post-synaptic currents at other synapses [149]. Loss or decreased levels of glutamate transporters (GLT-1), glutamate transporter proteins and/or their messenger ribonucleic acids (mRNAs) have been observed in animal models of some neurodegenerative diseases including Alzheimer's disease and amyotrophic lateral sclerosis [118, 123, 149-152]. The regulation of glutamate transporters occur through a number of mechanisms such as mRNA maturation and stabilization, trafficking to and from the plasma membrane, transcription and post-translational modifications [115, 149]. Studies have shown that the expression of glutamate transporter protein or mRNA can be influenced by a variety of factors including steroids/steroid hormones (oestrogen, Tamoxien), glucocorticoids (dexamethasone), growth factors (glial cell line-derived neurotrophic factor, epidermal growth factor, basic fibroblast growth factor, insulin-like growth factor-1) and chronic stress [149, 153-157]. These factors could act by activating specific receptors, growth factors and/or neurotrophic factors. Oesrogens and other steroids activate G protein-coupled receptors or nuclear receptors (ERα and ERß resulting) in an oestrogen-dependent induction of transforming growth factor-α [149, 154, 157, 158]. Growth factors themselves have been reported to specifically influence glutamate transporter expression through the activation of nuclear factor kappa B (NFκB); using a number of pathways including phosphatidylinositol-4,5-bisphosphate 3 kinase/Akt (PI3K/Akt), Ras/Mitogen-extracellular signal regulated kinase (Ras/MEK) [157, 159, 160]. The activation of a variety of transcription factors including NFκB, N-myc and YY1 have also been shown to either increase or suppress the expression of glutamate transporters [149].

Alterations in the transcriptional regulation of neurotransmitter cycling resulting in the impairment of the glutamate/-GABA/glutamine cycle have also been linked with the development of neurologic disease including seizures [129, 161, 162]. Studies had shown that *repo* (a major glia developmental determinant in the adult fly), can trigger the expression of genes involved in neurotransmitter recycling during glia differentiation; with down regulation of genes during larval stages associated with the development of motor defects [129, 161, 162]. Mazaud *et al*. [129] using microRNA-based screening in adult *Drosophila* glia, observed that continued expression of *repo* was essential in adult glia for the transcriptional regulation of neurotransmitter recycling in both male and female flies. With the transient loss of *repo* occurring partly due to the impairment of the glutamate/GABA/glutamine cycle resulting in a sudden shortening of lifespan, the development of motor deficits, and an increased seizure threshold [129].

A number of studies have also demonstrated that apart from modulations at the level of the glutamate transporters and receptors, other glutamate markers such as the cystine-glutamate exchanger (xc-) (mainly expressed on asroglial cells) and its regular subunit xCT are important regulators of homeostatic control in the glutamate synapse [124, 163, 164]. The regulator xCT has been shown to mediate non-

vesicular glutamate release from microglia and astrocytes. It also regulates the one for one exchange of cysteine and glutamate, thereby ensuring the maintenance of glutamate concentration at physiological levels [124]. These sites have also been suggested to be potential targets for the development of novel antidepressant therapies [139, 140, 165].

1.6.2. Gastrointestinal Tract-brain Axis and Glutamate Homeostasis

In the last three decades, reports from clinical observations and preclinical studies have linked peripheral organ--cantered diseases, such as acute and chronic liver failure with behavioural changes in the central nervous system [17, 70, 167-171]. Around this same period, there have been suggestions that glutamate excitotoxicity similar to that observed in the brain could occur in organs such as the bone, lung, skin and pancreas as a result of high blood levels of glutamate [172]. In 2017, Bai *et al* [57] reported evidence of traumatic brain injury-induced acute lung injury that occurred as a result of dramatic increase in blood glutamate levels that could be linked to increases in brain levels of glutamate [57]. More recently, scientific evidence is also beginning to establish the links between impairment of the liver's metabolic functions and the pathogenesis of neurodegenerative disorders including Alzheimer's disease [173]. The existence of a bi-directional relationship between the gastrointestinal tract and the brain known as the gut-brain axis arose from studies that had demonstrated the presence of a possible multidimensional interaction between the gastrointestinal tract organs and/or their microbiome and the brain (gut-brain axis, gut microbiome-brain axis, gut-liver axis and a gut-liver-brain axis), with significant influence on brain function/structure through their ability to modulate endocrine, neurocrine and immunologic signalling pathways [174].

The occurrence of neuroinflammation (as evidenced by activation of micoglia, and increased synthesis of proinflammatory cytokines within the brain) in patients with liver failure specifically hepatic encephalopathy lead to suggestions of the presence of a liver-brain interaction Further studies in subjects with liver failure revealed that the liver-brain signalling mechanisms include a) the direct effects of systemic inflammation, accumulation of ammonia, and lactate, alteration of the BBB permeability and microglia activation leading to a recruitment of monocytes [175]. Knowledge of the extensive involvement of glutamate in body mechanisms either peripherally or centrally suggests that the gut-liver, gut-brain and liver-brain interactions would directly or indirectly impact glutamate concentration and glutamate homeostasis. The results of a number of studies demonstrating the influences of the gut liver-brain axis on neuroinflammation, addiction, and neurodegenerative diseases raise questions as to the extent of the relationship between the brain and other organs and its importance in the maintenance of health and prevention of central nervous system disease

The ability of the gut microbiome to modulate amino acid metabolism (including glutamate), neurotransmitter signalling, levels of inflammatory markers and the maintenance of the integrity of the blood brain barrier have been touted as possible pathways by which glutamate dyshomeostasis could occur [176, 177]. Specific alterations in the gut microbial diversity resulting in systemic inflammation, derangements in ammonia metabolism have been linked to neuronal and astrocytic dysfunction in patients with cirrhosis [176]. There have also been reports suggesting that inflammatory mediators are also able to regulate the extracellular concentration of glutamate through their effects on glial cells including microglia, astrocytes, and oligodendrocytes [177]

2. GLUTAMATE DYSHOMEOSTASIS AND DISEASE

Glutamate performs many diverse functions in the body including activities as a signalling molecule during brain development, brain neurotransmitter, energy source, building block for proteins and glutathione and the precursor for the inhibitory neurotransmitter GABA [178-181]. Thus, the maintenance of glutamate homeostasis would be crucial for brain and body health [149].

Glutamate dyshomeostasis describes the absence of a balance between synaptic and extra-synaptic levels of glutamate in the brain or the loss of glutamate-glutamine-ammonia balance in the periphery. There is evidence linking deficiencies of enzymes involved in glutamate biosynthesis or metabolism to the development of a number of systemic disorders including hyperammonemia, gyrate atrophy, haemolytic anaemia, 5-oxoprolinuria and γ-hydoxybutyric aciduria [42]. In the central nervous system disruptions in the homeostasis of glutamate has been implicated in the development of a number diseases including the development of seizures and neurodegenerative diseases like amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease and Huntington's disease [81, 123-129]. Also increasingly research has linked glial cell dysfunction to schizophrenia, depression and bipolar disorders also the development of addictive behaviours including drug seeking behaviours and relapse have been associated with glutamate dyshomeostasis]124, 125, 182-186]. Dysregulation of astrocytic glutamate homeostasis due to membralin deficiency had also been associated with the development of motor neuron disease including amyotrophic lateral sclerosis [81]. While impaired glutamate uptake by glutamate transporters have also been associated with the pathogenesis of some neurodegenerative disorders including Alzheimer's disease Parkinson's and Huntington's disease [123, 127]. More recently alterations in the glutamine-glutamate-GABA cycle in drosphilla have been linked with impaired motor activity and the development of seizures [129].

The array of diseases that have been associated with different aspects of glutamate homeostasis has led to suggestions that a reduction in the basal levels of glutamate in different regions of the brain [187] could be responsible for a decrease in the tone of the inhibitory presynaptic metabotropic glutamate receptors, leading to an increase in excitatory transmission [124] and finally glutamate excitotoxicity. The importance of glutamate dyshomeostasis in the pathogenesis of brain disease has also been affirmed by information garnered from the study of hepatic encephalopathy.

Hepatic encephalopathy which encompasses a wide range of alterations in normal brain function due to acute or chronic liver failure was one of the first indications that brain glutamate dyshomeostasis could result from peripheral disease. In the last two decades a number of studies have been able to demonstrate that with regards to the development of hepatic encephalopathy, the accumulations of a number of compounds topmost of all ammonia and neurotransmitter dysfunction such as glutamate dyshomeostasis were crucial [17, 70, 166, 171]. An increased level of brain ammonia is deemed excitotoxic *via* its association with increased synaptic release of glutamate in the brain [171]. The astrocytes that are found in the brain are the main site for ammonia detoxification; an increased ammonia level raises the amount of glutamine within astrocytes [188]. Hence, increased brain ammonia levels can induce functional changes in astrocytes, leading to increased levels of intracellular glutamine, which is a metabolic substrate for neuronal glutamate synthesis [189]. It is also possible that increased levels of glutamine within the astrocytes may also lead to osmotic shift of water into these cells, contributing to brain oedema and astrocyte swelling [190]; however, this notion remains to be validated. Also, in hepatic encephalopathy, biochemical changes that had been documented to occur within the astrocytes include alterations in: astrocyte-specific proteins like glial fibrillary acidic protein (GFAP), enzymes such as monoamine oxidase and glutamine synthetase, activation of mitogen activated protein kinases and transcriptional factors such as NF-κB and p53 [191, 192]. Amongst other effects, these changes affect the synaptic availability of neurotransmitters such as glutamate and dopamine, both of which have been implicated in the pathogenesis of neuron degeneration. Hence, while primary changes in the structural or functional integrity of neurons are not the reasons for neurological changes seen in hepatic encephaolopathy; a deficiency of the structural, metabolic and nutritional support offered by astrocytes could explain why conditions that are related to hepatic encephaolopathy may lead to neuron death. Since such conditions can lead to chronic functional and metabolic stress in neurons, by the use of mechanisms such as NMDA receptor-mediated excitotoxicity, oxidative stress, lactic acidosis, and increased production of pro-inflammatory cytokines [166].

Overall, while we currently understand how crucial maintaining glutamate homeostasis is to body and brain health, the possible benefits of pharmacologic or genetic manipulations of key enzymes or pathways involved in glutamate synthesis and/or metabolism; especially, as they relate to brain function like cognition, memory, mood, addiction, appetite and the development or treatment of neurodegenerative diseases are emerging areas of research..

2.1. Glutamate Dyshomeostasis and Neurodegenerative Disorders

The neurotoxic effects of glutamate (either derived endogenously or from dietary sources) were first recognised more than four decades ago [193]. However, to date, a number of studies from our laboratory have reported both the beneficial and neurotoxic effects of exogenous glutamate [3-5, 194-201] in rodents (Swiss mice). In the search for a better understanding of the pathogenesis of a number of neurodegenerative diseases, researchers have demonstrated that dyshomeostasis of endogenous glutamate and the resultant spillage of glutamate into extrasynaptic sites cause long-term depression, neuronal degeneration, and excitotoxicity [202-206]. This shows an intimate link between glutamate homeostasis (or the loss of it) and neurodegenerative disorders.

The term glutamate excitotoxicity was coined by Olney [207] to describe neuronal injury and cell death observed in the retina and large areas of the brain [207]. However, in the ensuing years, research has demonstrated several mechanisms including decreased expression of glutamate transporters, excessive activation of glutamate receptors, interaction with the system X_c^- subunit of the cysteine-glutamate transporter [8, 149, 157, 208, 209] through which glutamate excitoxicity could induce cell injury and neuronal death. Also, while it is generally accepted that the entry of glutamate from the blood is limited to areas of the brain outside the blood-brain barrier, during periods of brain development (when the BBB is not fully formed) or following the loss of BBB integrity as a result of injury (from trauma or swelling) or toxic metabolites like neuroinflammatory cytokines, it is possible for glutamate to enter outside these defined zones.

Interests in the possible relationship between peripheral and central glutamate concentration, and the possible roles of its dyshomeostasis in the development of brain disorders have arisen from reports: that a direct correlation exists between peripheral and central glutamate concentration, that peripheral glutamate dyshomeostasis (as occurs in liver failure) could result in encephalopathy, and that there is a rise in peripheral glutamate concentration in brain disorders such as autism and schizophrenia [22, 210].

In the brain, excitatory glutamatergic neurotransmission that occurs through the actions of ionotropic glutamate receptors, such as the N-methyl-D-aspartate (NMDA) receptor, has been shown to be critical for synaptic plasticity and neuron survival. However, excessive activity at the NMDA receptors resulting in excitotoxicity and cell death has been proposed as underlying mechanism for the development of neurodegenerative diseases such as Alzheimer's disease [211, 212].

The demonstration of glutamate receptors in the peripheral tissues, such as the stomach, liver, pancreas and intestines [213], the role of the gut-brain axis in the maintenance of brain health [174, 214-216], reports that alteration of glutamatergic receptor activity in the gastrointestinal tract may influence brain functions including mood, behaviour and stress response and result in the development of brain disorders [217], as well as studies linking blood ammonia with the development of neurodegenerative diseases [218, 219] increase the need to evaluate the possible bidirectional relationship between peripheral and central glutamate homeostasis/dyshomeostasis in the maintenance of brain health and the development of disease.

In neurodegenerative diseases like Alzheimer's disease (AD), a growing body of knowledge suggests the involvement of numerous potential drivers of neurodegeneration in the brain [220-223]. Oxidative stress, very low levels of reduced glutathione, and mitochondrial dysfunction are among the culprits in the onset and progression of AD pathology [224-228]. In addition to these, there have been questions regarding the peripheral origins of neurodegenerative diseases, especially AD [229] and, to a lesser extent Parkinson's disease (PD). This has arisen from scientific evidence of peripheral inflammation (tumour necrosis factor-alpha (TNF-α), interleukins (IL-1β, IL-6, IL-12, and IL-18), immune abnormalities and epigenetic dysregulation of macrophages (differential DNA methylation) and T cells (increased expression of microRNA-155) in patients with AD [230-234] and PD [235-237] compared to age and sex-matched controls. There have also been reports that these alterations in blood cytokines and inflammatory makers could significantly impact brain function and structure [238-241]. The validity of these claims is further strengthened by studies linking peripheral inflammation with alterations in brain glutamate levels and the development of excitotoxicity, at least in mood disorders [177, 203, 216, 242, 243]. Studies have demonstrated the ability of inflammatory cytokines to decrease the expression of glutamate transporters on astrocytes as well as cause an increase astrocytic glutamate release [122, 243-245], with the glutamate having the capacity for preferential access to the extrasynaptic *N*-methyl-D-aspartate receptors, resulting in a reduction in brain-derived neurotrophic factor and excitotoxicity [242, 246]. Cancer researchers have also demonstrated that increased peripheral immune response that occurs in lung cancers causes a dysregulation of peripheral glutamine-glutamate metabolism resulting in decrease in the activity of GDH and an increase in glutamate decarboxylase (GAD) activity, consequently leading to cognitive deficits (a marker of poor prognosis) in the patients [247].

Although, there is little or no direct evidence of peripheral glutamate dyshomeostasis causing neurodegenerative disease; evidence of peripheral glutamate dyshomeostasis in the development of hepatic encephalopathy (a complication of liver failure) and cognitive deficits that occur as a complication of cancer progression and/or therapy are pointers to the importance of peripheral glutamate homeostasis in the development of neurologic diseases. Also, there is the ability of inflammatory or immune cytokines to alter glutamate homeostasis either directly or through their ability to influence transcription of mRNA or protein of key regulators of glutamate homeostasis, leading to alterations in the blood brain barrier, which allows unmitigated access of blood glutamate to the brain. This unmitigated access perpetuates the vicious cycle of glutamate excitotoxicity and neurodegeneration. It is therefore important that efforts aimed at combating the onset and progression of neurodegenerative disorders should include the search for more therapeutic agents that are targeted at maintaining glutamate homeostasis both peripherally and centrally.

2.2. Glutamate Homeostasis as Therapeutic Targets in Neurodegenerative Diseases

Decades-long progressive loss of subpopulations of neurons in specific brain regions are characteristic features of neurodegenerative diseases [248]. Despite this knowledge, there continues to be an increasing worldwide prevalence of AD and PD which are the two most-common neurodegenerative diseases [249-253].

So far, despite certain undeniable advances in therapeutics, the search for drugs for treatment of neurodegenerative disorders has yielded only limited viable management options for patients. Sadly, in the last five decades, no new major drugs have been discovered for PD; neither is there any new therapeutic breakthrough for AD [251, 254]. It is also particularly worthy of note that the currently-available drugs are limited in their ability to curb disease progression. The absence of effective treatment and the failure a number of potential therapies during clinical trials are probable pointers to an incomplete understanding of pathogenesis, which emphasises the need to continually seek new drug target for neurodegenerative diseases. Factors like oxidative stress have been suggested as central targets in the pathology of neurodegenerative diseases [248, 254, 255]; however, there have been little or no success when drugs are directed at mitigating neurodegenerative diseases *via* this pathway. More recently, expanding knowledge on the possible involvement of glutamate dyshomeostasis in the development of neurodegenerative diseases is directing attention to the possible effect of targeting key regulators of glutamate homeostasis in the drug development for neurodegenerative diseases. The key regulators of glutamate homeostasis include enzymes responsible for glutamate synthesis/metabolism, transporters (glutamate and non-glutamate), glutamate receptors, and astrocytes. The activities of these regulators are further modulated by genes and transcription factors.

2.2.1. Glutamate Synthesis and Metabolism Enzymes as Therapeutic Targets

Glutamate dehydrogenase (GDH) is a key enzyme involved in glutamate metabolism. It is therefore believed that the regulation of glutamate metabolism *via* GDH may be a promising therapeutic approach for managing neurodegenerative disorders. A loss of regulation of GDH activity in the central nervous system is said to be highly-correlated with neurological disorders. Along this line, studies that were conducted using mutant mice and allosteric drugs showed that a deficiency or an overexpression of GDH activity in the brain influences the onset of disorders such Parkinson's disease, Alzheimer's disease, temporal lobe epilepsy, and spinocerebellar atrophy *via* its effect on whole body energy metabolism [256]. In experimental stroke where excitotoxicity is the main pathophysiology, mice that overexpressed GDH had smaller ischaemic lesions than mice with normal GDH expression. Also, GDH activators improve lesions *in vivo* and this occurs by increasing α-ketoglutarate levels. Again, when neurons are exposed to an *in vitro* insult, an enhanced GDH activity leads to increased ATP level; thereby

increasing neuronal mitochondrial activity and reducing the risk of excitotoxicity during a period of energy crisis [256].

Therefore, it is apparent that modulation of GDH activity during conditions of neuronal stress can help to maintain mitochondrial integrity, and prevent neuronal metabolic failure that leads to neuron death [256, 257]. Therapeutic agents that are targeted towards achieving this would be valuable in preventing neurodegeneration.

2.2.2. Glutamate Transporters as Therapeutic Targets

Sodium-dependent glutamate transporters (SLC1A1-3, 6, 7 or excitatory amino acid transporters EAAT1-5) which are known to play crucial roles in the maintenance and regulation of brain glutamatergic neurotransmission [127, 258-260] have also become potential targets for drug discovery [261]. EAAT1-5 transporters are involved in the rapid binding and buffering of glutamate, ultimately removing glutamate from the synaptic cleft, thereby protecting against excess presence and. potentially cytotoxic extracellular glutamate levels. This transporter system also conveys the bound glutamate into cells, for recycling and reuse [259, 260]. Increased efficiency at glutamatergic synapses can be achieved by using agents that modulate EAATs such as selective EAAT inhibitors which has the potential to improve transmission at glutamatergic synapses and provide therapeutic benefit under some conditions [259, 260]. In essence, a more detailed understanding of the roles of EAAT2 in health and disease would pave the way for the development of new selective modulators of EAAT2 function. Along this line, recent research using computational methods for identification of specific EAAT2 inhibitors has led to the identification of selective class of EAAT2 inhibitors which may be pharmacological tools for further exploration of the possibility of developing EAAT2-based pharmacotherapy [260], that may be applicable to neurological disorders and maybe more specifically neurodegenerative disorders.

The regulation of glutamate transporter-1 (GLT-1) is critical to the homeostasis of the glutamatergic system. Also, GLT-1 downregulation is commonly associated with several neurological diseases such as HD, AD, Parkinson's disease and ALS [262]. Therefore, some therapeutic strategies have been aimed towards upregulaion of glutamate transporters such as GT-1. One of such is the use of the synthetic glucocorticosteroid dexamethasone which had been shown to be a transcriptional enhancer of GLT-1 through glucocorticoid receptors (GR) and receptor subtypes that are expressed in primary astrocytes [263]. *In-vitro* experiments had shown dexamethasone's ability to elevate GLT-1 transcription, protein levels and activity in cortical and striatal astrocytes [155, 264]. However, when used as a single agent, dexamethasone was unable to increase GLT-1 protein levels in cerebellar and midbrain astrocytes; but in combination with a DNA methyltransferase inhibitor, it increased GLT-1 expression in cerebellar glia [155]. Despite promising results from a number of the aforementioned studies, the exact role of dexamethasone in combating specific neurodegenerative disorders is yet to be determined, and this might be as a result of an incomplete understanding of the many factors that contribute to their aetiology.

The β-lactam antibiotic ceftriaxone had also been shown to be increase GLT-1 expression possibly through a mechanism that involves elevation of the transcription of GLT-1 in astrocytes *via* the nuclear factor-κB (NF-κB) signaling pathway [265]. However, a number of other factors may be involved as ceftriaxone treatment failed to upregulate GLT-1 or modulate glutamate uptake in striatal astrocytes when growth factor is withdrawn [266]. More recently, it was suggested that ceftriaxone might indirectly upregulate GLT-1 by upregulation of an antioxidant defense system [267]. Ceftriaxone's ability to upregulate GLT-1 expression had been demonstrated in models of HD [268], genetic mouse model of epilepsy [269] and the 6-hydroxydopamine model of PD [270]. It also decreased neurodegeneration in the MPTP model of PD [271] and the G93A mouse model of ALS [272]. However, it failed to show efficacy during Stage 3 trials in ALS [273].

Adverse effects such as impaired synaptic plasticity in the hippocampus, impaired memory recognition [274, 275], and impairment of neuronal circuits leading to a reduction in EEG theta power in the frontal and parietal cortex [276] are also critical issues of concern. However, what is not clear is whether these adverse effects are as a consequence of increased glutamate transporter protein expression, or they are due to activation of other pathways. Also, further research must be conducted to establish the actual mechanism of action of ceftriaxone in this regards, as direct targeting of GLT-1 transcription process is probably essential for it to be an appropriate glutamate modulation agent.

The neuroprotective agent riluzole had also been shown to dose-dependently increase Na^+-dependent glutamate uptake in synaptosomes; however, the mechanism by this occurs is unknown [266]. In a study using striatal astrocyte cultures, riluzole was shown to upregulate both GLT-1 protein levels and activity [277]. However, riluzole was also able to decrease ipsiversive rotation (without affecting GLT-1 expression) following amphetamine challenge in 6-OH-DA-treated animals, a phenomenon that suggests preservation of the dopaminergic system [278].

Specific genes can be delivered into cells using adeno-associated virus (AAV), and can be expressed under specific promoters; and this approach allows the delivery of normal copies of a gene in the attempt to manage genetic disorders [279]. This way, attempts have been made to increase the cellular expression of GLT-1 by using vehicles that are capable of intracellular delivery of genes that code for the protein.

Intraspinal delivery of AAV8-Gfa2-GLT1 had been associated with an increase in astrocytic GLT-1 protein expression [280]. However, overexpression of GLT-1 through AAV8-GLT1 administration had proven deleterious in certain contexts such as cervical-contusion spinal cord injury (SCI) where it appeared to cause more death of neurons [280], even though it is still possible for it to have some other bene-

fits [281]. With time, it is possible that we will get to understand the likely roles of AAV therapies in neurodegenerative diseases better, especially when we consider the fact that this approach may offer obvious advantages (such as specificity) over the use of drugs in the modulation of GLT-1 expression.

Finally, it is now known that Hsp90β overexpression causes a reduction in GLT-1 protein levels; however, knocking down Hsp90β increases GLT-1 expression but does not affect GLT-1 mRNA, a situation that suggests Hsp90β plays a role in the regulation of GLT-1 post-transcription. Therefore, Hsp90β could also be a promising new target that may also be responsible for GLT-1 dysfunction in neurological disorders [282-284].

2.2.3. Glutamate Receptors as Therapeutic Targets

In neurodegenerative disorders such as PD, it had been suggested that the ability of ionotropic and metabotropic glutamate receptors to modulate neurotransmission throughout the basal ganglia makes them potential targets for reversing the effects of altered neurotransmission [285, 286]. To buttress this, studies had shown the primary motor symptoms of PD, as well as unwanted effects of dopamine replacement therapy, could be reversed or prevented through the modulation of glutamate receptor activity [287]. Also, there have been reports suggesting that glutamate receptor ligands may slow down disease progression through their ability to delay progressive neuron loss [285, 286, 288, 289]. For the ionotropic receptors, ligands at both NMDA and AMPA receptors have been examined; however, it is likely that pharmacological modulation of metabotropic glutamate receptors (mGluRs) may be more suited for PD treatment due to the ability of mGluRs to fine-tune neurotransmission [285]. Both antagonists and activators of different subtypes of mGluRs have shown promise in several animal models of PD by reversing motor deficits and providing protection against neurodegeneration [285].

2.2.4. Astrocytes as Therapeutic Targets

Recent knowledge has increased our understanding of the importance of astrocytes in maintaining proper glutamate homoestasis, neuronal health and function [254]. In the past, neurodegenerative disease drug development programs targeted only neurons [254]. However, astrocytes also play a very important role in the regulation of glutamate homeostasis. Studies targeting astrocytes as potential therapies have suggested the culturing and characterisation of healthy astrocytes followed by their transplantation into the brains of persons with neurodegenerative disorders where they are either used to replace dying astrocytes or to aid the survival of existing neurons [254]. *In vivo* and *in vitro* studies have been used to demonstrate the benefits of astrocyte transplantation in diseases such as amyotrophic lateral sclerosis (ALS). In a mouse model of ALS, the direct transplantation of human (h)iPSC-derived neural progenitor cells furthered the life-span of the mice [290]. Also, following SCI, axonal regeneration and functional recovery was promoted following transplantation of mouse or human astrocytes derived from glial-restricted progenitors [291]. In other studies involving spinal cord lesion, injected mesenchymal stem cells into the spinal cord migrated to the lesioned area to differentiate into astrocytes and exert neuroprotection by reducing microglial activation and normalizing GLT-1 levels [292]. Other modalities include cell grafting strategies that have been successfully employed in models of neurodegenerative disorders such as PD and ALS, and also HD [293].

The role of astrocytes in maintaining brain glutamate homeostasis cannot be overemphasized and the astocytic glutamate transporters are crucial for this. Also, a decline in levels of GLT-1 in different models of neurodegenerative diseases, such as AD, ALS and HD, suggests a correlation between reactive gliosis, loss of glutamate homeostasis, and accumulation of excitotoxic levels of glutamate [272]. Structural or functional inadequacies of astrocytic glutamate transporters had been seen in sporadic forms of ALS and HD patients [294, 295].

Currently, it had become obvious that therapies that target restoration or preservation of astrocyte function are likely to become viable options in the regulation of glutamate transport and modulation of the onset or course of a number of neurodegenerative disorders. However, there are not yet many pharmacological agents that are useful in this area.

CONCLUSION

Research has continued to uncover the links between glutamate dyshomeostasis and neurodegenerative disorders. However, beyond this, the possibility of targeting cells and cellular/molecular entities that are involved in glutamate synthesis, turnover and actions, and using various manipulative strategies to modulate them for optimisation of glutamatergic neurotransmission is being explored. The expansion of knowledge on the roles of glutamate and the possibility of exploring glutamate-based pathways for neurodegenerative disorders management might put us on course for better preventive and management strategies/options. Also, glutamate-based therapies might present themselves as the much-needed options for a breakthrough in the understanding and management of neurodegenerative disorders. As research leads us along this path, time will tell if our true destination is in sight.

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