Chapter

# Perspective Chapter: Neurotoxins and Erythrocytes - A Double-headed Arrow

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## Abstract

The prevalence of aggression has become an increasing problem that threatens lives, from suicidal ideation to homicide. Multiple factors contribute to such issue, including genetic, psychological, familial, economic, environmental, dietary habits, endocrine disturbances, psychiatric disorders, and neurological disturbances, making it resistant to control. If key targets can be identified, it might be possible to find a cure. To date, glutamate has been one culprit involved in aggression, instigated by inflammatory mediators and reactive oxygen species. Monosodium glutamate as well as omega-3 and-6 polyunsaturated fatty acids -components of our modern diet- modulate the inflammatory state, hence, affecting brain and blood glutamate, the latter is an essential neurotransmitter sharing in the antioxidant capacity of erythrocytes. Hence, the erythrocytic or blood glutamate assay, along with members of the inflammatory cascade, might be a cost-effective diagnostic and prognostic tool for aggressive behavior, especially feasible for assessing the efficacy of the intervening dietary and/or pharmacological measures to prevent such potentially devastating behavior.

**Keywords:** aggression, glutamate, monosodium glutamate, omega-3 fatty acids, omega-6 fatty acids

## 1. Introduction

Neurotransmitters in the brain are classified into inhibitory and excitatory. Each single neurotransmitter is a gear in an engine whose release is crucial for the brain's equilibrated machinery to proceed. The overflow of one neurotransmitter draws a cascade of events that disturb this discrete brain signaling, so does its deficiency. Accumulation of glutamate (Glu), the most abundant amino acid excitatory neurotransmitter, has been implicated in many neurological disorders, including aggressive behavior and the tendency to violence [1].

Exposure to ongoing or anticipated threatening events provokes a multitude of instinctive behavioral reactions, that enhance the ability to accommodate, survive, and sustain the stress, whether acute or chronic [2]. Among humans, stress-related behavior might be controlled relative to the magnitude of stress and its foreseen consequences; but in other cases, it might extend far beyond logic thinking and rational control, building up a crescendo aggressive attitude, that, instead of being a

reactive physiologic response, becomes an intuitive pathologic one, that, even, needs no impulse to ignite.

Since the brain is not totally segregated from the peripheral system, variations of blood Glu can mirror brain Glu turbulence, hence, blood assays have been suggested to diagnose and follow-up neurological diseases. Assaying blood Glu might offer a non-invasive, cost-effective, and quantitative way to assess aggression for a better control, comparing the potency and efficacy of various interventions that address this issue. Therefore, we can gather and analyze data, derived from blood assays of glutamate and inflammatory markers in cases exhibiting aggressive behaviors, to be invested for future implementation of treatment plans and optimum choice of medications, instead of a trial-and-error policy that wastes the time and delays improvements in which timing would be critical for the patient and his/her family, or surroundings.

## 2. Aggression

### 2.1 Types of aggression

Albeit some difficulty to differentiate between aggressive acts that are reactive and defensive and those that are intentionally destructive, yet psycho-socialists have defined aggression as a forceful physical or symbolic action that can be motivated (instrumental or proactive, and affective or reactive aggression), or deliberately damaging (aggression), whether directed to other person that does not wish to be harmed, living creature, the environment, or one's self, leading to physical or psychological harm [3]. So depending on the intent of the act, affective, reactive, defensive, or impulsive aggression is characterized, so that tough responses are not intended to harm. The opposite would be the predatory, premeditated, instrumental, proactive, or cognitive aggression when the intention is to hurt someone [4].

Not all aggressive reactions are physical, some can be psychological, verbal, sexual, social, or racial. The type causing actual physical harm is termed "violence" and is the extreme of aggression [5]. Nonphysical aggression is the more common to observe, yet the more difficult to track and punish, see examples [6, 7].

In terms of pharmacotherapeutics, we have the treatable secondary or medical aggression, related to psychologic disorders that respond to medications, including antipsychotics and antimanics, and the primary impulsive aggression that is addressed using other specific agents [8], although, in absence of psychopathology, seems resistant to manage [9].

### 2.2 Epidemiology of aggression

Two-million people are annually exposed to workplace violence, with 50% of cases falling among healthcare workers, and 7% of fatalities are ascribed to physical harm. Domestic violence affects 10 million people yearly in the United States, with an economic burden of more than 12 billion dollars per year. These estimates are expected to rise over the next 20 years [10].

Lifestyle changes during the coronavirus disease (COVID-19) pandemic, including the distress of getting infected [11], poor sleep quality, a higher prevalence of post-traumatic stress disorder among hospitalized patients [12], and the social isolation

of the recommended lockdown, increasing the incidence of domestic violence and abuse toward children, in case of a violent family member, with limited access to community-based support and assistance [13], provoked depression, anxiety, and suicidal behavior [14]. The evolving stressful life conditions that followed the COVID-19 lockdown triggered violent attitudes and mental health issues, consequent to unemployment, and financial instability, while struggling to satisfy the basic needs of life, being helpless to find new job opportunities, and losing the liberty to have interactive social conversations and relations, concurrent with the compounded feeling of loneliness, uncertainty, and trepidation, considering the "others" potential threats of disease transmission. Neurological symptoms during the pandemic were variable and included suicidal behavior, agitation, paranoid delusions, bizarre behavior, and weird posture [15, 16]. Assumptions were made about the involvement of encephalitis [17, 18] and medications used in the treatment protocol of COVID-19 such as steroids, chloroquine derivatives, and benzodiazepines [19].

### 2.3 Aggression as related to other medical issues

Among health problems, pain was the most significant medical issue that can lead to aggression. Reports advocated respiratory distress as a cause of aggression [20].

Neurological disorders can provoke aggression as in some cases of attention deficit and hyperactivity disorder, autism, epilepsy, and Alzheimer's disease (AD) [21].

Psychological issues complicated by secondary aggression include bipolar affective disorder, schizophrenia, major depression, general anxiety disorder, post-traumatic stress disorder, and antisocial personality [22]. Substance abuse and/or withdrawal was an undeniable culprit, especially alcohols and hallucinogens [23].

Anemia, one of the most prevalent worldwide [24], was involved in aggressive cases [25–27]. Furthermore, iron deficiency can contribute to mood and behavioral disturbances, owing to its crucial role as a co-enzyme for the production and release of neurotransmitters [28].

Iatrogenic aggression can be seen with medications such as dopaminergic agents [29], antidepressants [30], glucocorticoids, testosterone, and androgenic steroids [31].

### 2.4 Diagnosis and management of aggression

There is no consensus concerning laboratory or imaging tools to diagnose aggression. But assessments converge on reporting either the consequences or some etiological factors such as substance abuse, toxicological screening, or psychological disorder [10]. While most pharmacologic treatments have long converged on controlling the causative factors of aggression, now, addressing the deliberate hostile behavior as an isolated disorder is getting more attention.

Experimental dietary manipulation deterred 2-year aggression in a dog using a diet regimen whose plan was based on hematologic, biochemical, and imaging investigations [32].

Presumably, investigating key mediators of aggression might help control primary aggression, for which psychological assessments failed to find a clue. Researchers suggested neuronal mediators that might lower the aggression threshold, including, but not limited to, dopamine (DA), serotonin (5-HT), gamma-amino butyric acid (GABA) [33, 34], and glutamate (Glu) [35].

## 3. Glutamate

### 3.1 Glutamate as brain neurotransmitter

Glutamate (Glu) is a nonessential and most abundant free amino acid, excitatory neurotransmitter in the brain. It is released through the glutamate-cystine exchange system (xC-system) in exchange of cystine at a 1:1 ratio, also used for the synthesis of the brain antioxidant, glutathione (GSH). Its central existence is not limited to the synapse, but it projects to extra-synaptic sites through ionotropic (iGluRs) and metabotropic glutamate receptors (mGluRs) [36]. The ionotropic receptors comprise three types, N-methyl-D-aspartate (NMDA), 2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl) propanoic acid (AMPA), and kainate.

To establish a synaptic neurotransmission, glypicans, the synapse-forming proteins secreted by astrocytes, increase the number and activity of postsynaptic AMPA receptors, amplifying the electrical current to open the $Mg^{2+}$-gated NMDA receptors. In the brain, micromolar levels of glycine, an inhibitory neurotransmitter, are sufficient to saturate NMDA for full functioning [37]. The ionotropic receptors are connected to their intracellular second messengers, stargazine, D-serine, and nitric oxide synthase, by postsynaptic density proteins (PSD95) [38], controlled by the immune (glial) cells, astrocytes, and microglia [39].

Glu diffuses binds to mGluRs on the astrocytic surface, triggering the release of the chemokine, CXCL12/stromal cell-derived factor (CXCL12/SDF1) [40], implicated in preclinical models of anxiety [41], urging microglia to release small physiologic quantities of tumor necrosis factor-alpha (TNF-α) [42]. By binding to astrocytes, TNF-α regulates Glu clearance, to ensure a well-controlled neuronal excitation, by immune-to-glutamate signaling [43].

The glial cells, microglia, astrocytes, and oligodendrocytes, communicate on a large-scale [44], conveying transsynaptic information along large brain regions [45]. The net result would be a presynaptic Glu release propagated and reflected on Glu release and uptake at distant sites [46].

Astrocytes, of the fibrous type, nurture and protect the unmyelinated nodes of Ranvier, while oligodendrocytes exert the same function for myelin sheath and cells [47]. While astrocytes of the fibrous type expand the white matter of the brain, astrocytes of the protoplasmic type span the gray matter of the brain, branching multiple times to yield fine processes that encase blood vessels at one end, forming part of the blood–brain barrier (BBB) [48], while surrounding thousands of synapses forming "astrocytic cradles" [47], provided with plenty of Glu transporters, that mediate Glu clearance [38] and keep Glu from spilling over into the extra-synaptic space [49].

Glu is cleared by excitatory aminoacids transporters (EAAT) of the endothelium of cerebral blood vessels as well as by passive diffusion through BBB to the systemic circulation [50, 51]. The EAATs-mediated Glu uptake is impaired during immune activation (**Figure 1**) [52–58].

Interestingly, reducing plasma Glu accelerated its clearance from the brain to the blood. Pharmacologically, this can be accomplished by the administration of inducers of the Glu metabolizing enzymes, serum Glu oxaloacetate (SGOT), and serum Glu pyruvate transaminase (SGPT) [43]. Experimentally, this Glu scavenging policy was successful to counteract excitotoxicity in animal model of stroke [59].

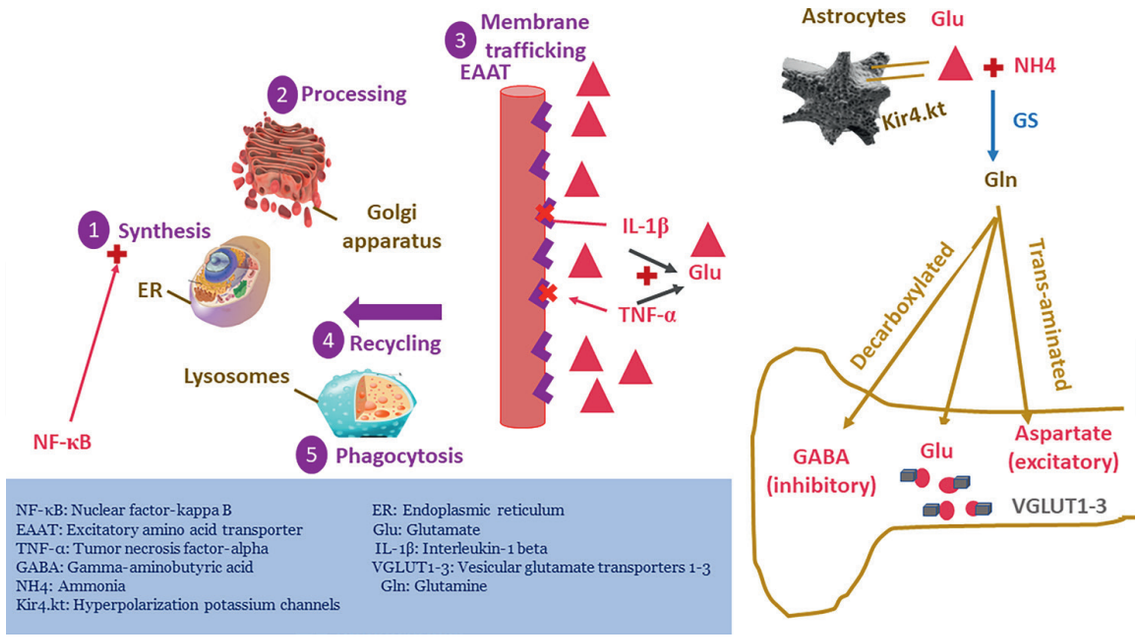


**Figure 1.**
*Glutamate clearance and immunomodulators. Glu is taken up by astrocytes, driven by Kir4.Kt, where both Glu and $NH_4$ yield the inert, Gln, by the action of GS. de novo Gln is transported to neurons either, to be re-converted to Glu, or to be transaminated to aspartate, or to be decarboxylated to GABA. Glu, synthesized from Gln, is packaged and stored in synaptic vesicles via VGLUT1–3. Membrane EAATs are synthesized in the endoplasmic reticulum and modified in the Golgi apparatus, before their expression on the surface. Their gene promoters are responsive to NF-κB. This is followed by their internalization either to recycle back to the surface or to be phagocytosed by lysosomes. EATTs are suppressed by TNF-α and IL-1β, rendering them insufficient for Glu clearance.*

## 3.2 Glutamate and aggression

An epigenetic mutation in the promoter region of *BEGAIN*, the gene expressing PSD95, involved in Glu receptors signaling, was identified in postmortem specimens of suicidal depressed patients [60]. A preclinical model of prenatal viral exposure incriminated in schizophrenia and autism spectrum disorders resulted in reduced PSD95, with overwhelming behavioral chaos [61].

Exposure to stress reduced a specific type of oligodendrocytes, NG+ cells, in laboratory animals [62], that share in glutamatergic and GABAergic synapse formation [63, 64], eventually impairing EAATs, with subsequent brain Glu overload [62].

A hypothalamic hamartoma (a congenital malformation) with excessive glutamic acid decarboxylase (GAD), enzyme involved in the synthesis of GABA from Glu, was accompanied by impulsive aggression, which improved after surgical resection of the deformity [65]. Glu has been targeted by various antiepileptic medications, many of which were successfully introduced in psychiatry to control psychopathologic aggression [66].

Experimental animals can be used to model both types of aggression, hyperarousal or defensive, and hypo-arousal or predatory, corresponding to the impulsive and proactive types in humans, respectively. In different species, from fish to humans, Glu was implicated in the hypothalamic elicit of impulsive aggression [67]. Despite the involvement of other neurotransmitters in aggression, such as DA and noradrenaline (NA), yet it seems that they operate through glutamatergic neurons. Preclinical research indicated that Glu might be the leading mediator of aggression, as identified in cats, rats, and hamsters [68, 69]. Genetic studies in mice linked the severity of aggressive traits to the Glu ionotropic receptor AMPA3 gene (Gria3) [70]. More

astonishing was that in mice subjected to social isolation and depicting aggressive behavior, NMDA subunits were highly expressed in the hippocampus, while down-regulated in the prefrontal cortex, the area of judgment and reasoning [71]. In human studies, the elevation of Glu in cerebrospinal fluid (CSF) was associated with impulsive aggression as well [1].

Nonetheless, the link between Glu and aggression is still confusing, noting the opposing effects of NMDA antagonists, when at the low dose they aggravate aggression, while at a high dose they soothe aggression [36]. Further work is also needed to track discrete Glu circuity in specific brain areas.

## 4. Blood glutamate and brain glutamate: a double-headed arrow

In erythrocytes, as in brain, a continuous Glu supply is required to synthesize the antioxidant, GSH, along with cysteine and glycine, by aid of the enzymes, glutamate cysteine ligase (GCL) and GS. As the erythrocytic cell membrane is impermeable to Glu [72], erythrocytes synthesize de novo Glu from either alpha-ketoglutarate using alanine aminotransferase (ALT), and aspartate aminotransferase (AST), or Gln using glutamine aminohydrolase (GA) [73]. As the oxidant, hydrogen peroxide ($H_2O_2$), traverses readily; in diseases with oxidative stress, erythrocytes capacity to synthesize more GSH is increased, using the endogenous Glu precursors, Gln and/or alpha-ketoglutarate, which exogenous supply was demonstrated to accelerate this process [74]. Recently, GA was proposed as one of the most powerful predictors of COVID-19 prognosis, based on case reports of critically—ill patients, indicating glutaminolysis and shift of glycolysis from anaerobic to aerobic, enriching Gln/Glu metabolic pathways, as was formerly detected in seizure disorders and inflammatory diseases [75].

Immune cells express Glu cognate receptors that regulate their functions. T-lymphocytes exhibit both iGluRs and mGluRs that respond to Glu in a dose-dependent way. In the nanomolar-micromolar range, Glu acts on ionotropic receptors, stimulating T-cells migration, and proliferation. In pathologic conditions, at high millimolar Glu concentration, metabotropic receptors are activated leading to suppression of T-cells proliferation, versus increased inflammatory cytokines release. By acting on mGluRs, Glu induces the apoptosis of memory and naïve B-lymphocytes [76].

In turn, iron deficiency anemia was involved in irreversible fetal brain alterations of excitatory and inhibitory neurotransmitter receptors. In a study [77], using an experimental model of stroke due to intracranial hemorrhage, several blood components modified the AMPA- and NMDA-mediated synaptic responses. While the whole blood inhibited the synaptic activity; diluted blood precipitated a prolonged epileptic NMDA synaptic activation; plasma and part of leukocytes evoked neuronal epileptiform discharges; and fraction of red blood cells, initially, stimulated the receptors, followed by their depression. In cerebral ischemia, brain Glu was found to rise [78], culminating into excitotoxicity [79].

Despite the inability of Glu to penetrate the BBB [80], the brain is not absolutely segregated from the effects of fluctuating blood Glu.

As a positive correlation has been reported between Glu levels in the blood and either CSF [81] or CNS [82], it was not surprising that, in 2018, Madeira et al. [83] assayed blood Glu and Gln in patients with recent onset and chronic schizophrenia to find that blood Gln/Glu ratio was increased with recent onset, versus decreased with long-standing disease. This complies with other studies reporting a low blood Glu with the first psychotic episode [84], versus high blood Glu in cases with chronic

schizophrenia [85]. This peripheral Glu change was previously mirrored in the brain by increased CSF Glu in chronic cases and a high Gln/Glu ratio in CSF of new-onset disorder [81].

In terms of pharmacological approach, typical antipsychotics were associated with lower blood Gln/Glu ratio than with atypical medications of the same category [83]. The inconsistent link between blood and brain Glu could be related to the altered eating behavior induced by either the atypical antipsychotics [86] and/or the disease itself [87].

## 5. Diet, glutamate, neuroinflammation, and neurotoxicity

### 5.1 Monosodium glutamate (MSG): a glutamate receptor agonist

Monosodium glutamate (MSG) is the sodium salt of *L*-glutamic acid. It is a natural dietary component found in dairy products as Roquefort and Parmesan cheese, and vegetables such as tomatoes, mushrooms, and broccoli. The unique taste of MSG, known as an essential component of the Asian cuisine, evoked its widespread use in restaurants and canned food all over the world to improve food palatability. The L-glutamic acid itself and its disodium salt have a milder taste. The average daily intake in humans ranges from 0.3 to 1.0 g [88].

Despite being generally recognized as safe (GRAS) by the food safety regulatory agencies, animal and human studies continue to raise concerns about its potential toxicity. In 2006, the European Food Safety Association (EFSA) included MSG in the list of food additives for which established acceptable daily intake (ADI) was reassessed to be 30 mg/kg, considering its no-observed adverse effect level (NOAEL) that is 3200 mg/kg.

Focusing on its neurotoxicity, MSG has been alleged of causing stroke, epilepsy, schizophrenia, anxiety, depression, and AD [89], all of which predispose to aggression. This food additive acts on Glu receptors, triggering an array of inflammatory events and oxidative stress [90], especially with chronic consumption of high doses [91]. By binding to hepatic Glu receptors, excess $NH_4$ ions are produced, with the secondary generation of reactive oxygen species (ROS), and eventual hepatotoxicity [92], impairing MSG metabolism, leading to its blood accumulation, and increasing the likelihood of neurotoxicity. Downregulating mGluRs and NMDA receptors was one of the protective mechanisms exerted by curcumin against MSG neurotoxicity [93].

Multiple experiments tracked the behavioral and neurochemical events associated with MSG [94–99]. Notably, extrapolating animal studies employing the systemic route of administration to human practice may flaw results interpretation, bypassing the usual metabolic breakdown of oral MSG ingested in food [100].

Interestingly, a positive link was detected between MSG and hemoglobin levels [101] and it was found to reduce the percentage of blood lymphocytes as well [102]. Moreover, the oxidative stress during MSG toxicity overwhelmed the Glu-derived antioxidants generated by erythrocytes [103].

### 5.2 Omega-3 (ω3) versus omega-6 (ω6) long-chain polyunsaturated fatty acids (LC-PUFA)

Polyunsaturated fatty acids (PUFA) are those containing two or more carbon double bonds, classified as omega-3, -6, and -9. Among long-chain polyunsaturated fatty acids (LC-PUFA), omega-3 (ω3), and omega-6 (ω6) can be discriminated. While

the literature recommended the addition of ω3 sources in the diet, they advised to limit the consumption of its nonidentical twin, ω6. A debatable issue was to whether focus on the relative ω6 to ω3 consumption, versus determining absolute figures for each [104].

Despite being essential FA, ω6 PUFA have a narrow therapeutic window, requiring a rational dietary consumption to establish physiologic, rather than deleterious effects [105]. The major dietary ω6 is linoleic acid (LA), converted to other ω6 products as γ-linolenic acid and dihomo-γ-linolenic acid, and from which arachidonic acid (AA) is derived, yielding pro-inflammatory molecules and ROS. Rich sources of LA are vegetable oils such as corn, sunflower, soy, and canola oils, while AA is present in meat and eggs mainly [106]. The recommended daily intake of LA in adult men is 17 g/day, to be further reduced for adult women to 12 g/day [107].

On the other side, the major component of ω-3 PUFA is the alpha-linolenic acid (ALA), contained in chia seeds, black walnuts, and soybean oil, and converted in the liver to docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and decosapentaenoic acid (DPA) [108, 109]; the latter is a potential reservoir for DHA and EPA [110]. The consumption of fatty fish, such as salmon, herring, sardines, mackerel, and cod liver oil, or the substitution with fish oil, as rich sources of ω3 PUFA, was adopted to improve neurological functions, especially that relevant synthesizing enzymes are lacking [111] and the plant-based sources containing ALA are insufficient for humans [112], due to the incomplete hepatic conversion to EPA and DHA [113].

The fatty acid composition of the brain consists of palmitate, AA, an ω6 PUFA, and DHA, as the major ω3 PUFA, other members of the latter group are present, but in very small quantities [114]. The brain depends on the uptake of ω3 PUFA from dietary or liver sources. Once absorbed from diet, ω3 PUFA are transported by lipoproteins and albumin to the blood stream [115]. In adult mice, blood and brain levels of ω3 PUFA (DHA and EPA) were dependent on dietary consumption [116]. Free fatty acid receptor (GPR40), which ligands include several medium and LC-FA, saturated or unsaturated, is ubiquitously expressed in the brain. If ω6 binds to GPR40, neurodegeneration follows. If the ligand is ω3, serum BDNF is increased with eventual synaptogenesis and neurogenesis [117].

Poor nutrition has long been declared as one of the risk factors to antisocial personality disorder in adulthood [118] and increased aggression during childhood and adolescence [119]. A defective supply of DHA from ω3-PUFA, an integral part of astrocytic cell membrane, caused an impaired Glu clearance, with subsequent altered behavior in adulthood [120]. Several human studies adopted ω3 PUFA to hinder aggression [121–127]. Omega-3 deficiency favors the production of inflammatory cytokines, disturbing Glu homeostasis (**Figure 2**) [43, 128–132]. Inflammation was linked to aggressive behavior in lower mammals and humans [133, 134]. There seems to be a bidirectional interaction, so that aggression by itself can precipitate oxidative stress, as was demonstrated in birds subjected to a violent interaction [135].

Despite studies claiming the benefits of ω3 PUFA in neurological disorders, a lack of consistency remains. Moreover, most studies addressed ω3 PUFA without discrimination between individual constituents. Scarce work investigated ω3 short-chain PUFA claiming their additional neurological benefits [136]; however, insufficient data exist at the current time.

In blood, erythrocytes content of ω3 PUFA is dependent on either exchange with plasma lipoproteins, in the case of EPA, or erythrocytic turnover, in the case of DHA and DPA [137]. Surprisingly, giving EPA supplementation, but not DPA, was reflected at the level of erythrocytes. Other blood components seem to have a special

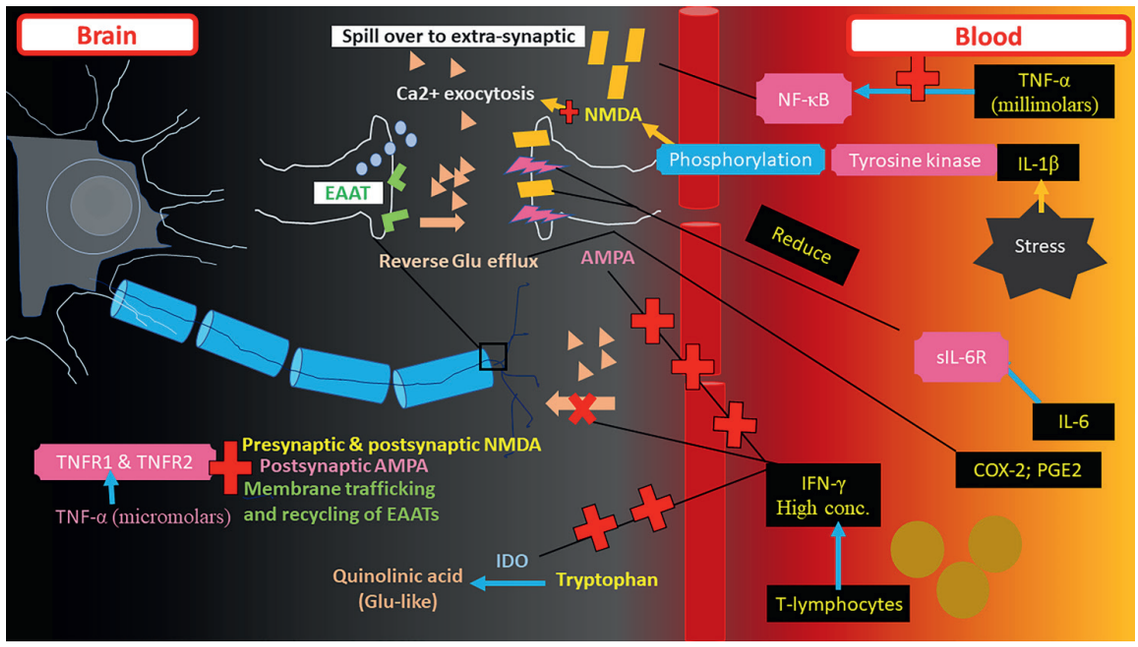


**Figure 2.**
*Glutamate and neuroinflammatory mediators. Among inflammatory cytokines, tumor necrosis factor-alpha (TNF-α) upregulates 2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl) propanoic acid (AMPA) receptors, on the expense of gamma-aminobutyric acid (GABA) downregulation. The rapid rise of TNF-α from micromolar to millimolar levels can lead to sustained nuclear factor-kappa B (NF-Kb) activation and neurotoxicity. A blunted TNF-α is not beneficial either, as by acting through its corresponding receptors (TNFR1 and TNFR2), it supports synaptic transmission by stimulating presynaptic N-methyl-D-aspartate (NMDA) and postsynaptic NMDA and AMPA activities, as well as assisting Glu transporters by regulating membrane trafficking of excitatory amino acid transporters (EAATs) and their recycling to the surface, added to conferring neuroprotection. Interleukin-1 beta (IL-1β), activated by stress, precipitates excitotoxicity by enhancing the postsynaptic NMDA pool and activity, by facilitating tyrosine kinase-mediated NMDA phosphorylation, increasing $Ca^{2+}$ permeability. Interferon-gamma (IFN-γ), released from T-lymphocytes at high concentrations, can impair the sequestration of Glu by EAAT, induces tryptophan catabolism through activation of IDO, generating Glu-like compounds as quinolinic acid and enhances AMPA-mediated neurotoxicity. Interleukin-6 (IL-6) acts on soluble IL-6 receptor (IL-6R) to abrogate presynaptic Glu release and reduce AMPA and NMDA activities. Cyclo-oxygenase-2 (COX-2) and prostaglandin E2 (PGE2) trigger the release of $Ca^{2+}$ from intracellular stores, causing reverse efflux of Glu by EAATs, followed by Glu spillover to bind to extra-synaptic NMDA.*

affinity to supplements of different ω3 PUFA members. Blood levels and response to supplementation are subjected to multiple factors, related to genetics, gender, interindividual variability ranging from an 82% decrease to a 5000% increase, and the type of supplement used [138–141].

Many years ago, low blood ω3 was detectable in impulsive offenders [142]. Blood levels of ω3 were negatively correlated to behavioral indices of aggression [143]. Blood samples were recommended when dealing with ω3 supplementation, being better predictors of aggression, that can discriminate responders from no- or low-responders and can tackle interactions with other nutrients [127]. Recently, a total daily dose of 960 mg DHA and EPA was provided to adult male prisoners in a correctional center as fish oil capsules reduced their aggression, most of them were nonaggressive at baseline [144]. In this trial, non-fasted blood samples were withdrawn, and plasma was separated from packed erythrocytes. Then, erythrocytes were prepared for fatty acid analysis [145]. Individual fatty acid analysis was done, then ω3 index was calculated as the sum of EPA and DHA, to be expressed as the mol percent of total erythrocyte fatty acids [146]. Participants with an index of 6% or higher were unlikely to benefit from the supplements due to a potential ceiling effect [147].

Unfortunately, results correlating blood levels of ω3 PUFA to the brain levels showed inconsistencies, limiting their applicability as surrogate biomarkers for brain disorders, at least for the time being. In fact, ω3 and ω6 PUFA complement to maintain constant levels of unsaturated membrane phospholipids, so that they compensate for each other [148].

## 6. Blood–brain bridge, rather than barrier

The brain is no more that sealed-off structure from the rest of the body, as detected in mice lacking immune cells and depicting difficulty in social behavior [149]. Instead of crossing the brain, immune cells signal through cytokines, so that knocking out cytokine receptors on the neurons can disturb social behavior in laboratory animals [150]. In turn, the brain areas involved in positive emotions and motivation can alter immune responses in inflammatory and oncogenic disorders [151]. Although, in healthy humans, limiting the amount of Glu that crosses the BBB [152] protects brain Glu levels from fluctuations of blood Glu [99]. Glutamate can breach such restrictive entry by enhancing the blood-brain permeability, while triggering cerebral vasodilatation [153].

In vascular injury of the brain, whether ischemic or hemorrhagic, the concomitant sizeable rise of blood and brain Glu occurs [154]. Such elevations were also noticed in many neurological disorders, including AD, epilepsy, and schizophrenia [155]. Following traumatic brain injury, the rise of brain Glu persists for months or even years thereafter. Such BBB disruption, not only allows blood Glu to reach the brain, but prevents the escape of cerebral Glu to the bloodstream.

In primary hypertension, the increased arterial content of Glu was linked to the higher Glu entry into the brain [156]. Similarly, systemic injection of Glu exacerbated brain damage [157]. Conversely, medications that lower blood Glu can assist Glu efflux from the brain [158]. So, restoring Glu level in both blood and brain to normal levels is required to reestablish the brain–blood Glu homeostasis. In their review, Gruenbaum et al. [159] highlighted the disruption of Glu efflux, breaking the integrity of the BBB, suggesting the feasibility of blood Glu scavengers in the treatment of depression following stroke.

One applied entity is the stress-induced aggression. During an anger attack, blood perfusion is increased, contrasted by cerebral hypoperfusion in between attacks, owing to stress-induce cerebral vasoconstriction [160]. Chronic stress causes disorganized BBB integrity, permitting the influx of mediators from peripheral blood, causing oxidative stress and neuroinflammation [161]. Altering the blood–brain Glu balance can excite excess Glu exit from the brain. To revert aggression and other subsequent psychological issues, oxaloacetate (OxAc) [162], the substrate of the enzyme glutamate-oxaloacetate transaminase 1 (GOT), that consumes Glu to render OxAc, was given to reduce blood Glu level.

## 7. Tips for erythrocyte glutamate assay in CNS disorders

In the brain, Glu is taken up from the extracellular to the intracellular domain of neurons and astrocytes by bidirectional transport mechanisms that, not only maintains low/high extracellular/intracellular levels, but also acts as a source of extracellular Glu when low [163], through stimulating Glu release [164]. Similarly,

the Glu active transport in erythrocytes maintains a high erythrocyte/plasma (E/P) concentration and a low plasma concentration.

In children with migraine, erythrocytic Glu was employed to mirror a centrally enhanced cellular uptake of this amino acid. In this setting, measuring plasma and erythrocytic Glu revealed a significant decrease in plasma, with a higher E/P concentration which was suggested as a reflection to mishandled CNS Glu turnover [165]. In contrast to the pediatric age group, adult migraineurs experienced elevated plasma and platelets Glu when measured during the attack-free periods [166]. Recently, stress, an aggression trigger, was documented to affect blood Glu levels [167].

A blood assay of Glu should be obtained after an overnight fast, to enhance specificity, avoiding misinterpretation due to nutritional factors, unless dietary management is planned. A preferable practice would be to monitor plasma Glu at the fixed time of the day, if multiple testing is needed, as plasma Glu might fluctuate along the day [168]. For better and more accurate interpretation, multiple factors that can modify blood Glu should be kept in mind, apart from nutritional status mentioned earlier, age, gender [169], body temperature [170], and even blood sampling sites seem confounding factors [171].

Normal Glu in plasma and whole blood is 50–100 and 150–300 μmol/l, respectively [59]. In the whole brain, Glu concentration is 12 μmol/g [172]. The free amino acids concentration can be calculated using whole blood and plasma concentrations [173].

The inverse relationship between plasma Glu and nitrogen hemostasis implicates that plasma urea and ammonia nitrogen should be assessed as well.

It is worthwhile to measure more than one inflammatory marker (C-RP, TNF-α, IL6, IFN-γ, and IL-1β) to identify patients who are likely to respond to Glu-targeted therapies, since inflammation seems an incident predisposing to Glu excitotoxicity. This was corroborated when the elevated inflammatory markers in blood predicted the favorable antidepressant response to the noncompetitive NMDA antagonist, ketamine [174]. Also, the administration of the inflammatory cytokine and interferon (IFN)-α induced a high plasma TNF-α [175]. Moreover, the higher plasma CRP level in depressed patients was correlated to a higher brain Glu [176]. As implicated in neuropsychiatric disorders, IL-6 promotes hepatic acute phase proteins, while processing neuroinflammation in the brain [177].

No study tracking the patients' behavior to neuropsychiatric medications or dietary manipulations has targeted both the blood level of Glu and the inflammatory markers. So, elaborative research work is indispensable to elucidate the benefits of blood assays in prediction and management panels.

## 8. Conclusions

Glutamate is one of the key mediators involved in aggressive behavior. In neuropsychiatric disorders, blood or erythrocytic Glu level mirrored brain Glu fluctuations. Anemia was demonstrated to affect brain Glu level, meanwhile precipitating aggression. Lowering blood Glu increased Glu clearance from the brain. Dietary manipulation was successful in controlling aggression, as inflammation and oxidative stress have been implicated in altered brain Glu and aggression. Hence, blood or erythrocytic assay of Glu might help the diagnosis and prognosis of aggression, as well as planning corresponding therapeutic strategies ranging from simple dietary manipulation, up to complex pharmacologic treatments. The more advances in the scientific research, knowledge, and testing techniques, the more explicit will be the

dynamics of behavioral issues, the more feasible and successful will be the diagnostic, preventive, and therapeutic interventions. Nonetheless, Glu is not the only culprit in aggression, other explored neurotransmitters and inflammatory markers can be assayed and targeted as well, to obtain a panel of laboratory markers and plan several therapeutic alternatives using these mediators, hoping to prevent an outraged ideation from proceeding to a devastating aggression.

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## Conflict of interest

The author declares no conflict of interest.

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