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The kynurenine pathway in traumatic brain injuries and concussion

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Up to 10 million people per annum experience traumatic brain injury (TBI), 80–90% of which are categorized as mild. A hit to the brain can cause TBI, which can lead to secondary brain injuries within minutes to weeks after the initial injury through unknown mechanisms. However, it is assumed that neurochemical changes due to inflammation, excitotoxicity, reactive oxygen species, etc., that are triggered by TBI are associated with the emergence of secondary brain injuries. The kynurenine pathway (KP) is an important pathway that gets significantly overactivated during inflammation. Some KP metabolites such as QUIN have neurotoxic effects suggesting a possible mechanism through which TBI can cause secondary brain injury. That said, this review scrutinizes the potential association between KP and TBI. A more detailed understanding of the changes in KP metabolites during TBI is essential to prevent the onset or at least attenuate the severity of secondary brain injuries. Moreover, this information is crucial for the development of biomarker/s to probe the severity of TBI and predict the risk of secondary brain injuries. Overall, this review tries to fill the knowledge gap about the role of the KP in TBI and highlights the areas that need to be studied.

KEYWORDS

the kynurenine pathway, neuroinflammation, traumatic brain injury, quinolinic acid, inflammation

1. Introduction

Traumatic brain injury (TBI) is a major cause of disability and death worldwide which affects about 10 million people annually across all age groups (1). According to the Centers for Disease Control and Prevention (CDC), in 2019, more than 223,000 TBI-associated cases were hospitalized in the USA (2). Generally, TBI can be classified as mild, moderate, and severe according to the Glasgow Coma Scale (GCS) score and neurobehavioral characteristics after injury. The most TBIs reported are categorized as mild TBI or concussions (80–90% of cases) that are caused by a bump or blow to the head as well as by a strong hit to the body that leads to quick back and forth movements in the head and brain followed by bouncing the brain, chemical alteration in the brain, and damaging brain cells (3–5). TBI causes a wide range of symptoms including headache, dizziness, fatigue, vomiting, cognitive impairment, loss of concentration, memory deficits, loss of consciousness, and mood swings. TBI can also be classified based on the injury progression to primary and secondary injuries. Primary injury can be caused by immediate physical injury to the brain and may follow by contusion, concussion, and disruption of brain tissue. The secondary injury occurs due to the primary injury's biomolecular changes and pathophysiological consequences. The secondary injury may emerge from minutes to weeks after the initial injury and is known by cerebral oedema, hemorrhage, diffuse brain swelling, infection, and ischemia (6–8). The pathophysiology of TBI has

been investigated in several studies (9–11). Briefly, after primary brain injury, some neurochemical changes occur that lead to secondary injuries. Among them, releasing excitatory amino acids (e.g., glutamate) and generating reactive oxygen species (ROS) and nitric oxide are closely associated with brain cell injury. Increased calcium influx to the brain cells induced by excitatory amino acids could promote ROS generation in neurons. Excessive amounts of intracellular calcium and ROS induce nitric oxide release, leading to oxidative stress, lipid peroxidation, and the release of excitatory amino acids. Glutamate exerts its excitatory function in TBI through alterations in presynaptic and postsynaptic glutamate receptors (12, 13). Generally, glutamate receptors (i.e., amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors and N-methyl-D-aspartic acid (NMDA) receptors) promote the influx of calcium into the neuronal cells in TBI. It has been shown that employing NMDA receptor antagonists could improve TBI symptoms (14–16). One of the main pathophysiological processes which play critical roles in clinical and functional outcomes in TBI is inflammation. TBI promotes activation of resident microglia and peripheral neutrophil recruitment subsequently followed by infiltration of macrophages and lymphocytes as well as the release of inflammatory cytokines and chemokines (17, 18). One of the most important pathways activated during inflammation is the kynurenine pathway (KP). Under the inflammatory condition, KP metabolites could be involved in excitotoxicity through the production of neurotoxic compounds such as quinolinic acid (QUIN), kynurenine (KYN), and 3-hydroxykynurenine (3HK) (19–21). KP metabolites play different roles including neurotoxic, neuroprotective, and immunomodulatory activities contributing to various neuroinflammatory-associated diseases such as Alzheimer's disease (22, 23), amyotrophic lateral sclerosis (24), and multiple sclerosis (25, 26). In this review, we proposed that dysregulation of the KP could be a potential underlying mechanism of TBI-induced neurotoxicity.

Moreover, this review addresses the evidence supporting the involvement of the KP in TBI pathophysiology. This review discusses the role of KP metabolites in the development of secondary brain injuries. The first section describes the KP functions and regulations. This is followed by hypothesizing possible mechanisms of KP involvement in TBI supported by the body of evidence extracted from the literature. Understanding the possible association between the KP and TBI can be helpful in exploring biomarkers as well as new treatment targets.

2. The kynurenine pathway

The KP is the main route of tryptophan metabolism synthesizing nicotinamide adenosine dinucleotide (NAD⁺) as well as several neuroactive metabolites (27–29) (Figure 1). About 95% of tryptophan is metabolized to KYN through the KP by the activity of regulatory enzymes indoleamine 2,3-dioxygenase-1 (IDO1) and tryptophan dioxygenase (TDO2). While IDO1 is predominantly expressed in macrophages, microglia, astrocytes, and neuronal cells, TDO2 is primarily expressed in the liver (30, 31). Several inflammatory cytokines such as interferon-gamma (INF- γ), interleukin 1 β (IL-1 β), and tumor necrosis factor- α (TNF- α) induce the activity of IDO1 (21, 32). Conversion of

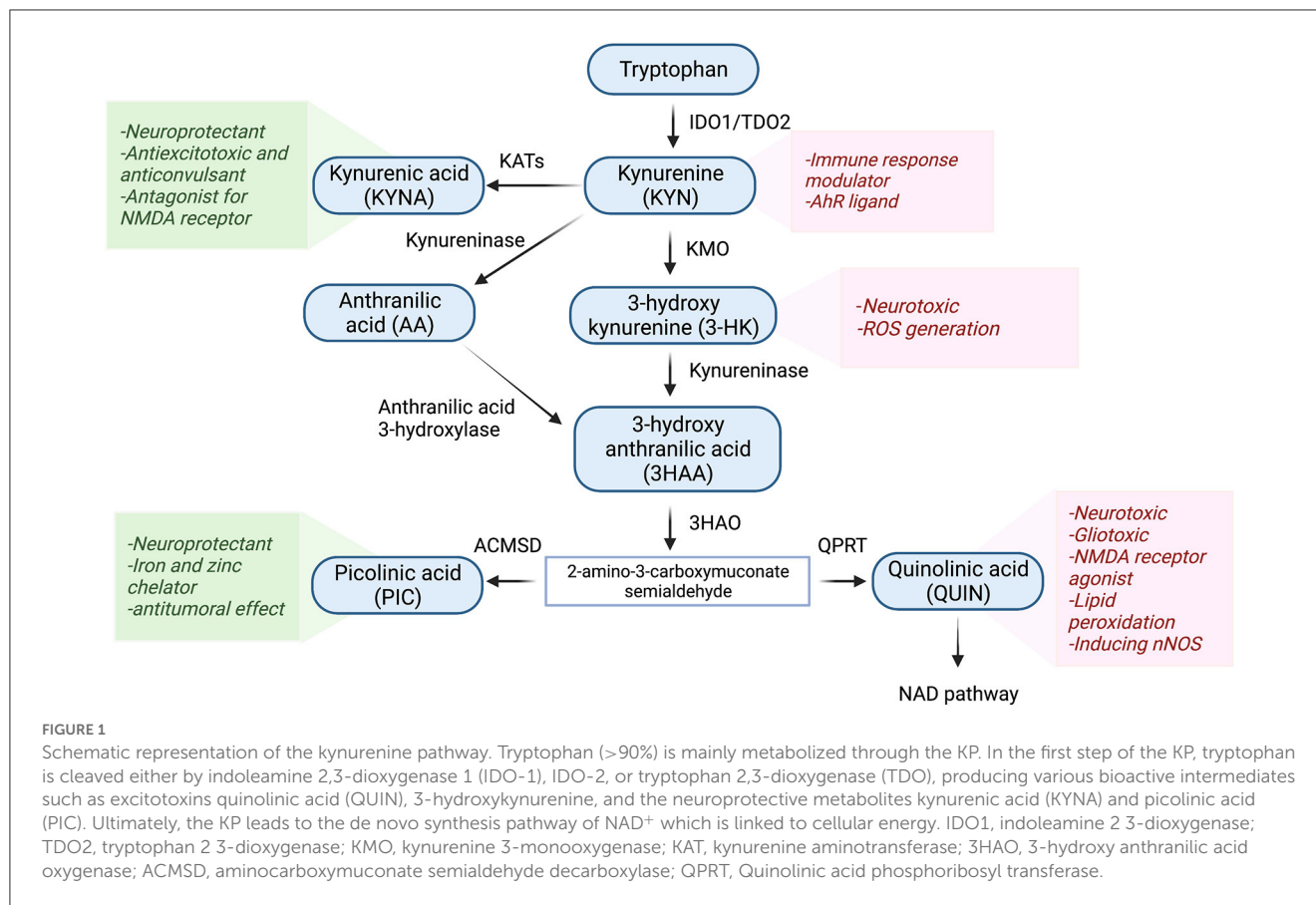
tryptophan to KYN follows by production of neuroprotective and neurotoxic metabolites. KYN is converted to kynurenine acid (KYNA) by kynurenine aminotransferases (KATs) or 3-HK through kynurenine-3-monooxygenase (KMO). The latter eventuates to the generation of the neurotoxic metabolite, QUIN. The KP has been identified in most cells, however, it is highly activated in monocytic cells under inflammatory circumstances (33). During the inflammation, activated macrophages and microglia produce QUIN which can further decrease KYNA by eliminating astrocytes. It has been demonstrated that 500–1,200 nM of QUIN induces apoptosis in human astrocytes (34, 35).

Among KP metabolites, KYNA and QUIN due to their polar properties and lack of transportation systems cannot cross the blood-brain barrier (BBB), while other KP metabolites cross the BBB through active transportation and passive diffusion (36, 37). Among the neuroactive KP metabolites, QUIN is assumed to be an important molecule in TBI. It has been documented that the level of QUIN is strongly elevated during inflammation (32, 38, 39). Moreover, QUIN can act as a glutamate agonist and activate the NMDA receptor which stimulates calcium influx into the neurons and ultimately promotes cell deaths (40, 41).

2.1. Involvement of the KP in TBI

In the early phase of brain injury, damage-associated molecular patterns (DAMPs) are released as primary inducers of the innate immune system. These molecules are recognized by Toll-Like Receptors (TLR) expressing cells such as macrophages, astrocytes, dendritic cells, and glial cells which results in infiltrating immune cells to the brain, triggering an inflammatory response, and releasing cytokines and chemokines (42–44). It is well known that IDO1/TDO2 (i.e., the first enzyme of the KP) is highly activated during the inflammation leading to an increase in levels of neurotoxic metabolites such as 3-HK and QUIN. In the central nervous system (CNS), most cells possess all the enzymes of the KP and can catabolise tryptophan, however, human neurons, astrocytes, and oligodendrocytes cannot produce QUIN. This neurotoxic metabolite is mainly synthesized by activated microglia and infiltrating macrophages (27). QUIN as an NMDA receptor antagonist can activate the receptor contributing to increased Ca²⁺ influx, inducing neuronal nitric oxide synthase (nNOS), and oxidative stress. Moreover, QUIN can increase glutamate release from the neuron and inhibits glutamate uptake by astrocytes resulting in glutamate accumulation, neurotoxicity, and cell death (41, 45, 46) (Figure 2).

Over the past decades, it has been established that inflammation, oxidative stress, and excitotoxicity play critical roles in TBI, however, the underlying mechanisms of secondary brain injury remain uncovered. Dysregulated KP and neuroinflammation have been identified in several CNS-associated diseases (e.g., Alzheimer's disease, amyotrophic lateral sclerosis, AIDS-dementia complex, and Parkinson's disease) (23, 24, 47, 48). Activation of the KP during the inflammation has raised the possibility of KP metabolites' involvement, particularly neurotoxic molecules such as QUIN, in secondary brain injury. One of the first studies investigating the KP dysregulation following TBI in humans



was conducted by Sinz et al. (49). They examined cerebrospinal fluid (CSF) in 39 patients (GCS < 8) during the first week of the injury. The levels of QUIN in patients significantly increased to 463 ± 128 nmol/L (5–50-fold), about nine times higher than the normal concentration of QUIN in CSF, 72–83 h after injury. Their results did not show any relevance between QUIN concentration in patients and GCS, age, gender, and treatment. Elevated levels of QUIN in human CSF were reported in further studies. For instance, Yan et al. (19) measured KP metabolites in CSF from 28 TBI patients with severe TBI (GCS \leq 8) from admission to 5 days after primary injury. Post-mortem brains were also collected to quantify the KP enzymes. Their results indicated an increase in the levels of KYN, KYNA and QUIN in CSF, while no significant changes were found in concentrations of tryptophan, AA, and 3-hydroxyanthranilic acid (3HAA). It is important to note that QUIN levels in patients' CSF were significantly higher than KYNA and KYN, suggesting elevated neurotoxicity in TBI cases.

Moreover, there was an inverse correlation between the levels of QUIN in CSF and the Glasgow Outcome Scale Extended (GOSE) score. Upregulating the IDO1 and kynureninase (KYNase) was also identified in the injured brains, supporting an increase in the levels of QUIN in CSF. It has been previously reported that the levels of pro-inflammatory molecules, particularly IL-6, IFN- γ , TNF- α , and GM-CSF, are significantly increased in TBI within early minutes of injury, suggesting an immediate inflammatory response (50). Both IFN- γ and TNF- α induce IDO1 and tryptophan degradation through the KP, contributing release of QUIN. The neurotoxic

activity of QUIN occurs through its interaction with NMDA receptors contributing to Ca²⁺ influx and oxidative stress that ultimately leads to ecotoxicity and cell death (41).

In a recent study, Zhang et al. (51) studied the expression of the two KP enzymes, kynureninase and kynurenine-3-monooxygenase (KMO) and kynureninase, in animal models. Blast-related traumatic brain injury was induced in rats using a shock tube and the expression levels of KMO and kynureninase were assessed using immunohistochemistry. They found that the expression of kynureninase and KMO significantly increased within a week in the hippocampus of the animals with TBI compared to the control. *In vitro* and *in vivo* studies showed that using Ro 61-8048 as a KMO inhibitor significantly decreased the apoptotic rate of neurons in the hippocampal CA1 area and improved the behavior of rats. However, benserazide hydrochloride (i.e., kynureninase inhibitor) treatment only showed protective effects *in vitro* (51). Decreased KYNA/QUIN and increased levels of QUIN in cases with sport-related concussion (SRC) have been reported previously (52).

Moreover, it has been reported that the concentration of QUIN in the plasma of football players with a prior concussion was higher than the control group even 10 months post-injury (53). It is inconsistent with the further study of Meier et al. (54) which reported that high school football players with a history of concussion had high levels of QUIN in serum up to 45 days after the injury in comparison to those who had no prior concussion, suggesting that a history of concussion may affect the KP metabolism toward QUIN production with a constant

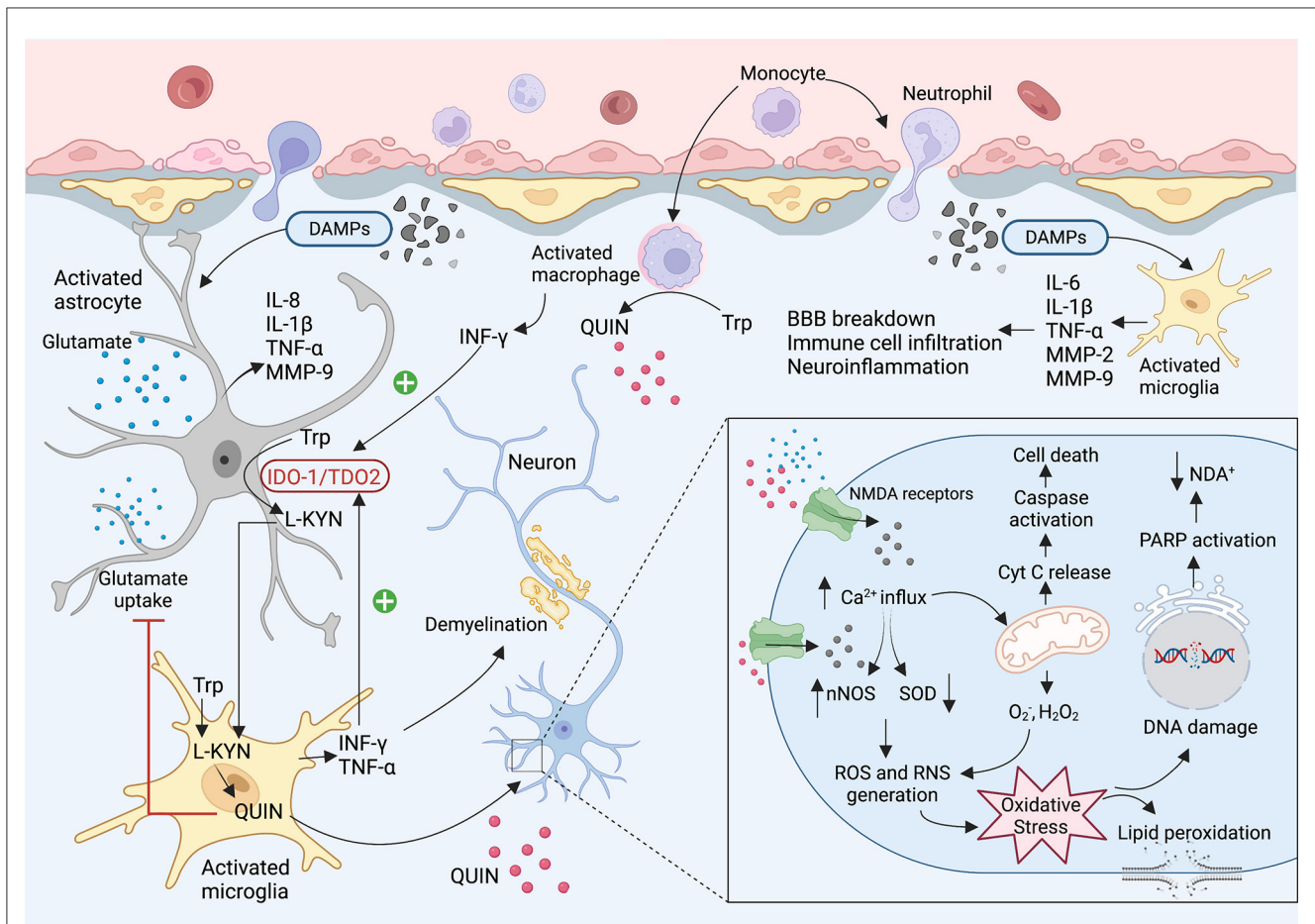


FIGURE 2

The KP involvement in the TBI and concussion. After brain injury, damaged tissues start to release DAMPs as an early stimulator of the resident cells. The DAMPs are recognized by activated microglia and astrocytes that lead to releasing several cytokines and chemokines. Elevated levels of $\text{INF-}\gamma$ and $\text{TNF-}\alpha$ activate the IDO1 leading to the production of KP neuroactive metabolites. Activated microglia and infiltrating macrophages are known as the main cells to produce QUIN in the brain. QUIN exerts its excitotoxicity through various mechanisms. QUIN is a glutamate agonist which can activate the NMDA receptor. Upon activation of NMDAR, a significant increase in intracellular Ca^{2+} influx occurs that leads to ROS and RNS generation, lipid peroxidation, mitochondrial dysfunction, DNA damage, and ultimately cell death.

elevated level even after days or months. In a recent study, Meier et al. (55) reported an association between KP metabolites and functional connectivity in football players with a history of concussion. Accordingly, a positive correlation was found between QUIN and connectivity strength in football players with acute injury and a history of concussion. At the same time this association was not observed in cases suffering acute injury without a prior concussion or healthy control group. Hypothetically, elevated levels of QUIN in individuals with concussion promote glutamatergic dysfunction that finally induces altered functional connectivity and psychiatric disorders (55). Table 1 summarizes the studies investigating the alterations of kynurenine pathway metabolites in TBI and SRC cases.

2.2. Involvement of the KP in TBI-associated psychiatric disorders

TBI could be accompanied with various symptoms that are associated with cognitive impairment (memory and concentration

problems) and psychiatric disorders (depression, anxiety, mood disorders) (56–58). Abnormally elevated levels of glutamate following TBI contribute to neuronal death and has been also linked to psychiatric conditions, cognitive impairment, and mood disorders (57–60). Since QUIN is known as an agonist for NMDA receptor, its increased levels under inflammatory conditions followed by severe TBI could over stimulate the NMDA receptor and induce neurotoxicity. Previous studies have reported that high levels of QUIN in blood and CSF could be associated with cytokine-induced depression and major depressive disorder (MDD) (61–63). On the other hand, increased levels of QUIN could be accompanied with either increasing or decreasing the levels of KYNA. Although KYNA is known as a neuroprotective metabolite and acts as antagonist for NMDA receptor, can induce glutamatergic hypofunction at higher levels leading to cognition impairment (64–66). In addition to the glutamatergic system, the cholinergic system has been involved in pathophysiology of TBI as well as further psychiatric complications. KYNA is also a non-competitive antagonist for $\alpha 7$ nicotinic acetylcholine receptors ($\alpha 7\text{nAChRs}$), ion channels widely expressed in central

TABLE 1 A summary of measurement of kynurenine pathway metabolites and enzymes in cases with TBI and SRC.

Type of injury	Sample origin	Patients/animal model	Metabolite/enzyme	Time of assessment	Results	References
TBI	CSF	39 patients (GCS<8)	QUIN	72–83 h post-injury	The levels of QUIN increased to 463±128 nmol/L (5–50-fold) compared to control	(49)
TBI	CSF, post-mortem brains	28 patients (GCS ≤ 8)	KYN, KYNA, QUIN, Trp, AA, 3-HAA	From admission to 5 days post-injury	- Increased levels of KYN, QUIN, KYNA - No significant changes in levels of Trp, AA, and 3-HAA - Upregulating IDO-1 and KYNase in brain tissue - Increased levels of IL-6, IFN-γ, TNF-α, and GM-CSF	(19)
SRC	Plasma	16 concussed cases	KYN, KYNA, QUIN	1 day, 1 week, 1-month post-injury	- Decreased KYNA/QUIN - increased levels of QUIN	(52)
SRC	Serum	59; High school football players	Trp, KYN, KYNA, QUIN, 3-HK	6 h, 24–48 h, 8–45 days post-injury	- Lower KYNA/QUIN in players with prior concussion - Increased KYNA/3-HK following concussion - Elevated QUIN levels in cases both acute and prior concussion	(54)
SRC	Serum	16 concussed cases without prior concussion, 21 concussed cases with prior concussion	Trp, KYN, KYNA, QUIN, 3-HK	1 day, 8 days 15 days, and 45 days post-injury	- QUIN levels were correlated with resting state fMRI in concussed participants with prior concussion	(55)
SRC	Hippocampal CA1 tissue	Rat	KMO and kynureminase	One week post injury	- Increased expression of kynureminase and KMO in the hippocampus of the animals - Ro 61-8048 as a KMO inhibitor decreased the apoptotic rate of neurons	(51)

nervous system that exert anti-inflammatory effects (67–69). Since cholinergic transmission mediated by α7nAChRs has critical roles in cognitive functions and anti-depressant effects, inhibition of α7nAChRs by KYNA could be associated with development of psychiatric disorders.

3. Clinical implications

Considering dysregulation of the KP in inflammatory diseases, KP enzymes can be considered as plausible therapeutic targets for alleviating the neuroinflammation, neuropathological, and psychiatric symptoms of TBI and concussion. Therapeutic approaches have designed to target the KP enzymes, particularly IDO-1, to prevent inflammation and depressogenic effects (70–72). Theoretically, inhibition of KMO or increasing the activity of KATs could be a potential approach to reduce the synthesis of neurotoxic metabolites and decrease the neuroinflammation after brain injury. Due to QUIN activates the NMDA receptor, the next approach was to examine whether blocking the NMDA receptor alleviates inflammation-mediated depression. Ketamine, an antagonist of the NMDA receptor, was considered for this purpose. It has gained attentions as one of the most important therapeutic drugs for treatment-resistant depression (73, 74). Both clinical and pre-clinical evidence have documented that ketamine increased KYNA and decreased QUIN and 3-HK, suggesting activation of KAT compared to KMO and shifting the KP toward synthesis of neuroprotective metabolites rather than neurotoxic compounds (74). KMO has been previously reported critical for inflammation-mediated depressogenic effects in rodents (75). KYNA analog 4-Chlorokynurenine (AV-101) is another antagonist of the NMDA receptor. 4-Chlorokynurenine could easily cross the BBB and convert to 7-Chlorokynurenic acid in the brain by astrocytes (76). A single treatment with 4-Chlorokynurenine showed a relatively similar dose-dependent and persistent anti-depressant activity to ketamine in male mice (76). However, clinical trials failed to prove any improvement in depression in human (ClinicalTrials.gov Identifier: NCT02484456; ClinicalTrials.gov Identifier: NCT03078322).

4. Conclusions

TBI patients suffer from high mortality and morbidity due to a lack of effective treatment. Despite substantial developments in understanding the pathophysiology of TBI, the underlying mechanisms of this disease remain unclear. Dysregulation of the KP during a wide range of inflammatory diseases including TBI has received remarkable attention. However, there are still limited evidence investigating KP metabolites in acute TBI and second brain injury. Although alterations in all KP metabolites may not be specific to TBI, some neurotoxic molecules such as QUIN might be a potential biomarker to monitor the second injury and its outcome during a time. According to the related studies, it could be presumed that TBI may selectively induce the KP toward the production of QUIN, a prominent excitotoxic metabolite of the pathway. A possible association between TBI and levels of QUIN have raised the possibility of using treatments to suppress the

KP enzymes to inhibit the neurotoxic effect of KP metabolites in secondary brain injury. One of the potential targets is KMO which converts KYN to 3-HK. Inhibiting KMO activity could decrease the levels of neurotoxic metabolites and increase KYNA production as a neuroprotective compound.

Author contributions

MD and GG contributed to conception of the manuscript. MD wrote the manuscript and prepared the figures. GG and BH read and edited the manuscript. All authors approved the submitted version.

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