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Understanding the Roles of the Kynurenine Pathway in Multiple Sclerosis Progression

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Abstract: The kynurenine pathway (KP) is a major degradative pathway of tryptophan ultimately leading to the production of nicotinamide adenine dinucleotide (NAD⁺) and is also one of the major regulatory mechanisms of the immune response. The KP is known to be involved in several neuroinflammatory disorders including Alzheimer's disease, amyotrophic lateral sclerosis, AIDS dementia complex, Parkinson's disease, schizophrenia, Huntington's disease and brain tumours. However, the KP remains a relatively new topic for the field of multiple sclerosis (MS). Over the last 2–3 years, some evidence has progressively emerged suggesting that the KP is likely to be involved in the pathogenesis of autoimmune diseases especially MS. Some KP modulators are already in clinical trials for other inflammatory diseases and would potentially provide a new and important therapeutic strategy for MS patients. This review summarizes the known relationships between the KP and MS.

Keywords: kynurenine pathway, KP, multiple sclerosis, MS, pathogenesis

International Journal of Tryptophan Research 2010:3 157–167

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Introduction

Multiple Sclerosis

Multiple sclerosis (MS) is characterized by the formation of sclerotic plaques in various areas of the central nervous system (CNS). These plaques are the result of an inflammatory response most likely caused by activation of autoimmune Th-1 cell targeting oligodendrocytes and the myelin sheath together with activated monocytic cells. These highly immunologically active areas subsequently progress to form “scarring” plaques.¹ Symptoms and signs vary depending on the location and severity of the plaques.² MS is a complex disease that can exist in various clinical subtypes but generally has a relapsing-remitting (RRMS) course often developing into secondary progressive MS (SPMS). A less common subtype, primary progressive MS (PPMS) has no remissions from onset. It has been suggested that the adaptive immune system drives the early stages of MS and the innate immunity drives the progressive stage.³

In the next few sections, we will discuss how the KP interplays with both the adaptive (T-cells) and innate immunity (mainly macrophages and microglia) that have been associated with the detrimental effects in MS progression.

The kynurenine pathway (KP)

The KP is a metabolic pathway leading to the production of NAD⁺ from the degradation of the essential amino acid tryptophan (TRP).⁴ Over the last two decades the KP has been studied across various species and has been associated pathologically with several neurological diseases. Paradoxically, KP metabolites can exhibit both neuroprotective and neurotoxic properties.^{5,6} In this section we will briefly highlight some key metabolites and enzymes in the KP.

Indoleamine 2,3 Dioxygenase

Activation of the KP can be achieved through one of its first rate-limiting enzymes, indoleamine 2,3 dioxygenase (IDO)-1, tryptophan dioxygenase (TDO)^{7,8} and the recently discovered IDO-2.⁹ While little is known of the significance of IDO-2, extensive studies have been performed in understanding the role of IDO-1 in neuroinflammation.

IDO-1 is a key regulator of the immune response.¹⁰ Munn and co-workers showed that in the placenta, activation of IDO-1 was important in preventing rejection of the allogenic foetus.¹¹ The mechanism is most likely related to IDO-1 mediated catabolism of TRP leading to depletion of local TRP needed for adjacent maternal T-cell proliferation thereby causing T cell apoptosis.^{12–15} Our studies in conjunction with others have shown that human IDO-1 expression can be up regulated by many factors such as the interferons, tumour necrosis factor (TNF)- α , platelet activating factor (PAF), amyloid beta peptide 1–42, as well as the HIV-1 proteins Nef and Tat.^{16–20} More recently, studies using animal models have shown that the combination of TNF- α and IFN- γ play a key role in up regulation of IDO-1 in response to bacterial infection.²¹

Kynurenic acid (KYNA)

In the CNS, KYNA is synthesised from kynurenine by the enzymes kynurenine aminotransferases (KAT) I and II. Rodents have an additional enzyme KAT III, which has a similar gene structure to KAT I, and which can function as a compensatory enzyme in KAT II knockout mice.^{22,23} KAT III has not been detected in humans. KYNA is one of the early metabolites of the KP and is generally considered as a neuroprotective compound. KYNA is capable of blocking glutamate-induced excitotoxicity via its antagonistic effects on several subtypes of ionotropic glutamate receptors²⁴ such as N-methyl-D-aspartate (NMDA), kainate and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. KYNA has a higher affinity for the glycine site of the NMDA receptors than glutamate.²⁵ More importantly in the context of the KP, it can also effectively attenuate the excitotoxicity of the downstream KP metabolite, quinolinic acid (QUIN).²⁶ Despite the antagonistic properties of KYNA towards QUIN, during disease the concentrations of KYNA are usually too low to make this clinically significant. Lekieffre and co-workers demonstrated that it required three times more KYNA to antagonize the excitotoxic effect exerted by the same amount of QUIN.²⁷ Furthermore, it has been repeatedly shown that levels of KYNA are decreased in several major neurological diseases including amyotrophic lateral sclerosis (ALS), HIV-dementia, chronic brain injury and even MS²⁸ suggesting that the neuroprotective role



of KYNA had been compromised in these diseases. Ironically, KYNA in some circumstances may be detrimental. High levels of KYNA have been associated with other disorders such as schizophrenia²⁹ and epilepsy.³⁰ Depending of its relative concentrations, KYNA seems to have a Janus's face within the CNS that still needs to be studied and clarified.

3-Hydroxykynurenine (3-HK)

3-HK is increasingly being considered for its role in neurotoxicity. Elevations in 3-HK levels have been found to be associated with numerous neurological diseases including Huntington disease,³¹ HIV dementia³² and Parkinson's disease³³ The pathogenetic nature of this association was initially suggested by 3-HK's ability to mediate cytotoxicity in a neuronal cell line.^{34,35} However, the concentrations were supra-physiological leading to its dismissal as a neurotoxin.³⁶ Nonetheless, it is now known that 3-HK can generate ROS leading to neuronal cell death at pathophysiological concentrations.³⁷ Furthermore, 3-HK acts synergistically with QUIN to mediate excitotoxic damage.³⁸

Quinolinic Acid (QUIN)

QUIN is likely to be one of the most significant KP metabolites in terms of biological activity. It is an agonist of the NMDA receptor and as such is considered an endogenous excitotoxin.³⁹ In physiological conditions, QUIN is a crucial substrate for production of a key molecule for cell survival, NAD⁺. We showed that at physiological concentrations (50 nM), QUIN facilitates the production of NAD⁺ in both human primary astrocytes and neurons which is crucial for energy homeostasis and cellular repair.⁴⁰ However, elevated QUIN concentrations have been found in several major neuroinflammatory diseases such as Alzheimer's disease, Parkinson's disease, HIV dementia and more recently in ALS.⁴¹⁻⁴³ The exact roles of QUIN in these various neurological diseases have not been fully defined but several mechanisms for QUIN-induced cell toxicity have been identified:⁴⁴ 1) QUIN can activate NMDA receptors in pathophysiological concentrations that results in excitotoxicity;⁴⁵ 2) QUIN is capable of increasing the release of glutamate by neurons and decreasing glutamate uptake by astrocytes and can also inhibit astroglial glutamine synthetase⁴⁶ consequently leading to

the accumulation of glutamate in the microenvironment and excitotoxicity;^{47,48} 3) QUIN can kill astrocytes resulting in neurotoxicity because of the loss of astrocytic detoxifying function 4) QUIN is associated with lipid peroxidation. Some studies have also shown that QUIN can potentiate oxidative stress through generating and working synergistically with ROS in the mitochondria.⁴⁹ This leads to lipid peroxidation and energy depletion that ultimately results in cell death.⁴⁹⁻⁵¹ 5) More recently, we have demonstrated that QUIN can induce tau hyperphosphorylation in human neurons that is likely to contribute to microtubular dysfunction with consequent neuronal dysfunction.⁵²

Direct Evidence of KP Involvement in MS

Tryptophan degradation and KP activation in MS

The first evidence dated back to the early eighties, when Manaco A. reported a decrease in TRP in the plasma and CSF of MS patients.⁵³ Then Fuchs and co-workers⁵⁴ suggested that the KP may be involved in MS based on the correlation of the adaptive immune system and KP activation. This was later not supported by a study showing no significant difference in TRP concentration in serum and CSF of MS patients compared to controls.⁵⁵ However, with a better understanding of the KP and the development of more efficient methods to quantify the KP metabolites and KP enzyme expression, its involvement in MS has been re-evaluated. More recent studies have shown that patients with chronic MS have low TRP concentrations in serum and CSF suggesting activation of the KP.^{56,57}

Abnormality in KP metabolism in MS

Other evidence comes from analysis of human MS *ex vivo* samples. Rejdak et al showed that the levels of KYNA are decreased in the CSF of patients with MS.⁵⁸ These results are supported by another study by Baran et al showing that the expression of KAT I and II (enzymes responsible for the production of KYNA) is decreased in post-mortem MS brain sections.⁵⁹ Kepplinger et al⁶⁰ however, found the opposite, that there is an increased in the KYNA levels in CSF samples of MS patients. This was supported by Hartai et al⁶¹ who found that KAT I and II activity



was increased in red blood cells and plasma from MS patients. These contradictory results probably relate to the differences in the time of collection of the samples during the course of the disease. Indeed, when Rejdak et al. quantified KYNA in active MS patients, their results are in agreement with the data from Hartai et al. The conflict between the earlier and later studies of Rejdak et al (2002) and the later study (2007) were likely resolved because the samples obtained from MS patients in the earlier study were in the chronic inactive phase of the disease while the later study used MS patients with an exacerbation.⁶² Thus the KP is induced during the active phase of MS leading to increased production of KYNA but as the disease progresses the KP profile changes resulting in decreased KYNA levels implicating the shift of the KP towards neurotoxicity.

Indirect Evidence for KP Involvement in MS using *in Vitro* Models

Microglia and macrophages

Previous studies have shown that only monocytic cells including activated microglia and macrophages are capable of producing QUIN in excitotoxic concentrations within the CNS.^{17,63} However, the amount of QUIN produced by microglia is significantly lower (20–40 times less) compared to macrophages.^{63,64} We previously showed that this is likely to be due to different levels of expression of three of the KP enzymes (See Table 1) between human microglia and macrophages.⁶⁵ It is very likely that KP activation in both perivascular macrophages and microglia may contribute to the neuropathology of MS.^{64,66} Indeed,

one of the hallmarks of MS lesions is the presence of activated microglia and perivascular macrophages along the boundary of the lesion site.⁶⁷ The presence of these activated cells is likely to be associated with the production of QUIN in concentrations sufficient to induce brain cell death at the site of lesion. These monocytic cells will also release some pro-inflammatory cytokines that can activate the KP resulting in an amplifying feedback mechanism leading to further production of QUIN and exacerbation of neuro- and gliotoxicity (discussed in section I-B.4). In addition, these same cytokines will also activate inducible nitric oxide synthase (iNOS) leading to an increased production of reactive oxygen species that would further exacerbate the neurodegenerative mechanisms involved in MS. Although speculative, we believe that both oxidative stress and the KP are playing a crucial role in MS pathology, which is further discussed in section V.

Astrocytes

Astrocytes represent the most abundant cell type in the CNS. Their representation in the CNS reflects their importance in critical roles such as glutamate recycling, cellular homeostasis, providing trophic and metabolic support, participating in the blood brain barrier cohesion and immune regulation within the CNS. We previously characterized the profile of the KP in human astrocytes (See Table 1) and showed that this cell type lacks the enzyme, kynurenine hydroxylase and hence, is unable to synthesize downstream KP metabolites, particularly QUIN.⁶⁸ Interestingly, primary monocultures of human astro-

Table I. Summary of KP enzymes expression in human neurons and glial cells.

KP enzymes	Macrophages + IFN- γ (Guillemin et al 2001a)	Microglia + IFN- γ (Espey et al 1997)	Astrocytes + IFN- γ (Guillemin et al 2001b)	Neurons + IFN- γ (Guillemin et al 2007)	Oligodendrocytes + IFN- γ (Lim et al 2007)
IDO	+	+	+	+	–
TDO	+	+	+	+	–
KAT-I	+	+	+	+	+
KAT-II	+	+	+	–	–
KMO	+	+	–	+	+
KYNU	+	+	+	+	+
3-HAO	+	+	+	+	+
QPRTase	+	+	+	+	+

+ , Enzyme expressed; – , Enzyme not expressed.

cytes, under cytokine stimulation generate large amounts of kynurenine (KYN) and subsequently lead to the production of the neuroprotective KYNA (see Fig. 1). Furthermore, Rejdak and colleagues showed an increased activation of astrocytes based on the astrocytic marker—S100 β —that correlates with increased production of KYNA in CSF of MS patients.⁶² This suggests that astrocytes probably play a neuroprotective role in MS. This fits well with the neuroprotective role of astrocytes under physiological condition or early pathologic stages of the disease to provide compensatory mechanisms against neurotoxicity. In pathological conditions especially where innate immunity is involved for example in MS, activated microglia and perivascular macrophages at the inflammatory site can take up and metabolise the large amounts of astrocyte-derived KYN as extra substrate to produce QUIN.⁶⁸ Furthermore, we have previously demonstrated that only small amounts of QUIN can be catabolised by human astrocytes due to the low saturable activity of quinolinate phospho-ribosyltransferase responsible

for QUIN degradation.^{68,69} Moreover, our previous studies demonstrated QUIN at pathophysiological concentrations of 500 to 1200 nM can induce apoptosis in up to 14% of human astrocytes.⁴³ Finally, QUIN can impair the function of glutamine synthetase thereby augmenting glutamate related toxicity.^{46,70}

Neuron

Apart from oligodendrocyte death and demyelination, neuronal loss is another pathological feature of MS.^{71,72} Although the exact mechanism for axonal injury in MS is not well understood, there have been studies supporting the idea of monocytic cells and/or glial cells playing a role in producing inflammatory mediators leading to axonal loss at the site of active lesions.^{73–75} Glutamate excitotoxicity is a likely candidate because glutamate antagonists reduce axonal damage, the effect is not significant: neither lesion size nor course of inflammation is affected.⁷⁶ Thus an alternative toxin appears more significant. As monocytic cells produce QUIN, it is biologically plausible that it might exert independently, or synergistically act with

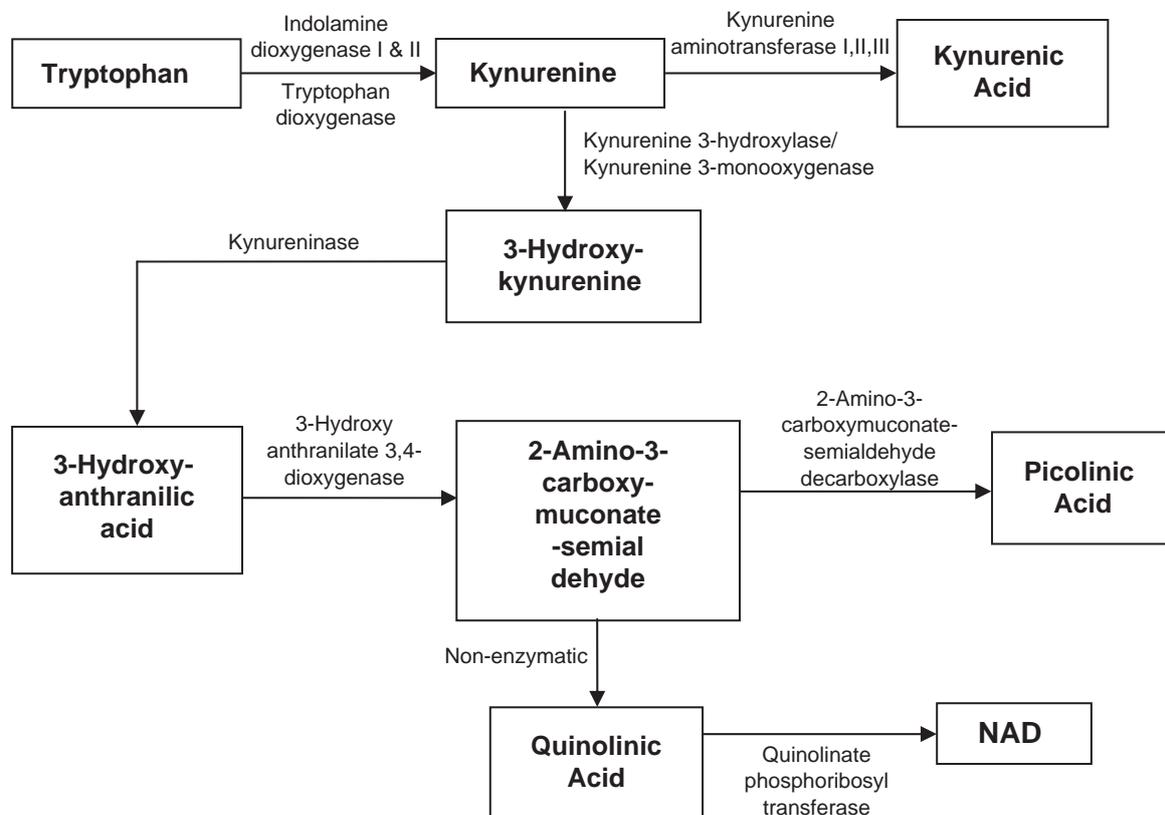


Figure 1. Simplified diagram of the kynurenine pathway.



glutamate, to alter neuronal cytoskeleton⁵² ultimately leading to axonal loss.

We have recently characterized the KP in human neurons (See Table 1), showing that cytokine stimulation can lead to the production of two neuroprotective KP metabolites, KYNA and picolinic acid (PIC).⁷⁷ It is likely that neurons will produce neuroprotective and anti-inflammatory (for PIC) compounds in the inflammatory areas in MS brains. Similar to astrocytes, neurons can also produce KYNA at the low micromolar range, which is unlikely to be sufficient (see B2, page 5) to completely antagonize the excitotoxic effects of QUIN produced by surrounding microglia and macrophages. Schwartz and co-workers have previously shown that acute administration of QUIN can induce axon sparing lesions at pathophysiological concentrations in a rat brain slice.⁷⁸ Similarly, chronic exposure to QUIN in the rat striatum leads to cognitive deficit.⁷⁹ We have previously shown that chronic exposure of human primary neurons to QUIN at nanomolar concentrations is sufficient to induce neuronal cell death.^{80,81} This suggests that minute amounts of QUIN present in the human CNS may be involved in the chronic progression of axonal loss in MS.

Oligodendrocytes

We have recently characterized the KP in purified primary cultures of human oligodendrocytes isolated from foetal brain tissue.⁸² Our data indicate that human foetal oligodendrocytes are among the rare cell types lacking IDO expression. This finding is potentially important for MS because the lack of IDO expression in human oligodendrocytes suggests that these cells have a lesser ability to protect themselves from activated T cell attack in the early stages of MS where adaptive immunity is important. However, this remains speculative, as IDO expression in *adult* oligodendrocytes is still unknown. Until recently, it was believed that oligodendrocytes only expressed AMPA/kainate receptors but not NMDA receptors.⁸³⁻⁸⁵ However, in 2005 Salter and Fern demonstrated that NMDA receptors are present on oligodendrocyte processes whereas AMPA/kainate receptors were localized on the cell somata.⁸⁶ This further defined a new role for QUIN toxicity in MS, as QUIN, which is also an agonist of the NMDA receptor is likely to activate the oligodendrocyte NMDA receptors

leading to excitotoxicity, cell death and demyelination. Furthermore, inhibition of the AMPA/kainate receptor with NBQX (2,3-dioxo-6-nitro-1, 2, 3, 4-tetrahydrobenzo [f] quinoxaline-7-sulphonamide) had no effect on the lesion size and no reduction of inflammatory response in EAE mouse brain.⁷⁶ This implies that glutamate excitotoxicity may actually play only a limited role in the loss of oligodendrocytes. QUIN produced during the primary inflammation response, might lead to an even more significant excitotoxic effect on oligodendrocytes (see Fig. 2). This is further supported by data showing that complete rescue of oligodendrocyte injury requires the blocking of both AMPA/kainate and NMDA receptors.⁸⁶ Furthermore, Cammer showed that *in vitro*, QUIN induces up to 30 and 50% apoptotic cell death of oligodendrocytes upon 48 h of 0.1 and 1mM QUIN exposure, respectively.⁸⁷ This study strongly supports the potential involvement of QUIN toxicity in oligodendrocyte injury and death via apoptosis during MS. However, the concentration of QUIN used in this study was above the pathophysiological concentrations found during neuroinflammatory conditions.^{16,28}

Indirect Evidence of KP Involvement in MS Using Experimental Autoimmune Encephalomyelitis (EAE) Animal Model

EAE is a commonly used animal model to study MS.⁸⁸ Several studies with the EAE model have provided relevant information concerning the involvement of the KP in MS. Kwidzinski and co-workers demonstrated the importance of IDO-1 in the modulation of the immune response in EAE.⁸⁹ The study showed that inhibition of IDO-1 activity using 1-methyl-tryptophan (1-MT) resulted in a significant exacerbation of the disease status, implying that IDO-1 can down-regulate neuroinflammation. Sakurai and co-workers showed that the proliferative response of the T cells was increased when IDO-1 was inhibited by 1-MT.⁹⁰ More recently, Matysiak and co-workers demonstrated that IDO-1 induction in the presence of dendritic cells led to T cell inhibition while 1-MT abolished this effect.⁹¹ Flanagan et al showed that the levels of the excitotoxin QUIN are elevated in the spinal cord of EAE rats.⁹² Another

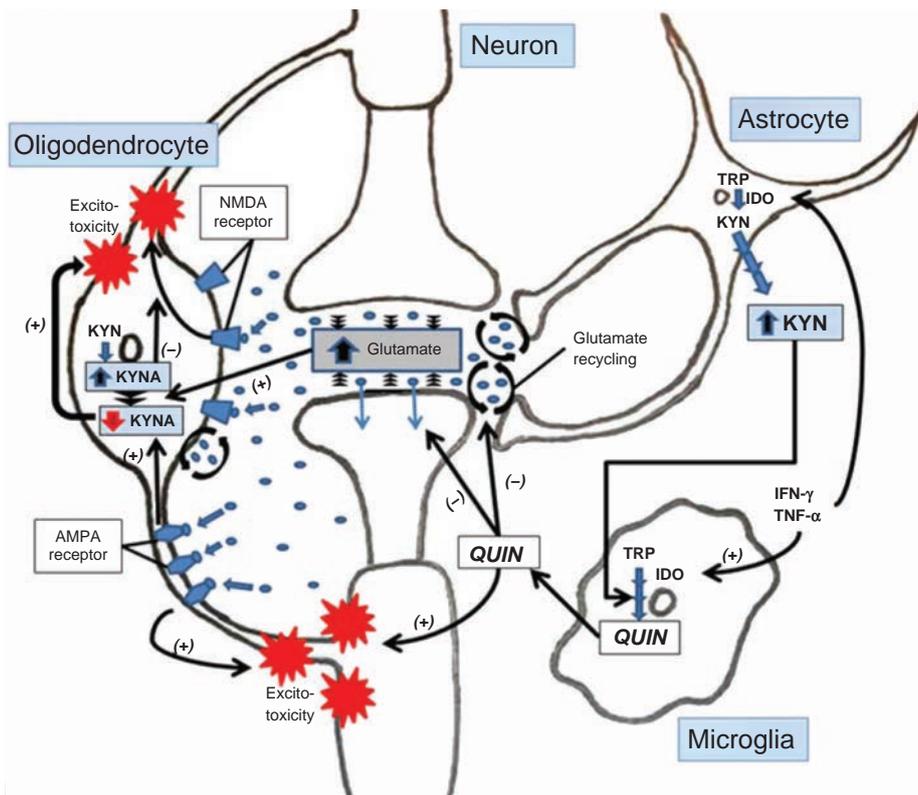


Figure 2. Expression of the KP enzymes in human primary neurons, astrocytes, macrophages, microglia, and oligodendrocytes.

neurotoxic KP metabolite, 3-HK has also been found increased in EAE rat.⁹³

Current Speculations and Hypothetical Model of KP Involvement in MS

Activation of KP in MS — Good or Bad?

It is unclear whether KP activation is detrimental or beneficial in the context of MS as both neuroprotectant and neurotoxin compounds can be produced through this pathway. Interferon-β1, a current treatment for MS, can activate the KP and possibly limit the benefit of the treatment.⁹⁴ Hence, the following hypothetical model can be raised: The KP may be beneficial in the early stage of the disease because adaptive immunity is thought to be important and as previously mentioned activation of the KP via IDO-1 can down regulate T cell proliferation. However, prolonged activation of the KP may lead to chronically elevated levels of QUIN and other neurotoxins produced by perivascular macrophages. This would lead to further neurological deficits and as such

would be expected to be a feature of the later stages of MS.

As mentioned above (I-B.4), QUIN facilitates glutamate release by neurons and inhibits glutamate uptake by astrocytes leading to an accumulation of glutamate in the microenvironment and excitotoxicity.⁴⁷ Oligodendrocytes are constitutively involved in glutamate clearance from the white matter.⁹⁵ Although speculative, it is likely that QUIN also inhibits glutamate uptake and recycling by oligodendrocytes. It is important to mention that glutamate is a potent inhibitor of KYNA synthesis in oligodendrocytes and that AMPA but not NMDA can potentiate such an inhibitory effect by decreasing KYNA production.⁹⁶ Hence, during neuroinflammatory conditions such as MS, over production of QUIN by activated monocytic cells will lead to 1) an increase in glutamate levels; and 2) a decrease of neuroprotective KYNA, both phenomena in combination leading to an exacerbation of excitotoxicity (see Fig. 2). Apart from its involvement in the disturbance of the glutamine-glutamate cycle, QUIN is also likely to induce directly neurotoxicity and gliotoxicity.^{43,97}



Based on our data,⁸² it is likely that the KP in oligodendrocytes will lead to production of neuroprotective molecules during MS. We have shown that human foetal oligodendrocytes can express one of the KYNA producing enzymes, KAT I, but not KAT II. This is supported by a previous study showing that the rat oligodendrocyte cell line OLN-93 expressed both KAT I and II that results in KYNA production when KYN was added to the cell culture.⁹⁶ We obtained similar results showing that the human oligodendroglial cell line MO3.13 express both KAT I and II. Nonetheless, we still need to show that human primary adult oligodendrocytes also express KAT I and/or KAT II in before unequivocally concluding their neuroprotective functions.^{16,77,98} It is tempting to speculate that, as for neurons,⁷⁷ human oligodendrocytes are more likely to synthesize KYNA as a compensatory mechanism against the excitotoxicity of QUIN production by activated monocytic cells and again similar to neurons they are able to take up and metabolise at least some of this QUIN. Braidy et al recently showed that human primary neurons and astrocytes can catabolise QUIN as substrate to produce NAD⁺ providing more energy to the cell and promotion of the enzymes involved in DNA repair.⁸¹ This is likely to happen in human oligodendrocytes as they also express the QUIN-catabolising enzyme quinolinate phosphoribosyltransferase (QPRT) (see Fig. 1 and Table 1). However additional experiments are needed to demonstrate that QPRT in human oligodendrocytes is fully functional.

KP and oxidative stress in MS pathology

Emerging data suggests that oxidative stress plays a major role in the pathogenesis of MS.^{99,100} Inflammatory cytokines inducing IDO-1 also activate iNOS, especially in monocytic lineage. INOS activation leads to production of nitric oxide (NO), which plays an important role in both oxidative stress and regulation of IDO-1 activity.¹⁰¹ NO has a bidirectional effect on the activity of IDO-1 with an inverse relation between NO concentration and IDO-1 activity.¹⁰² Studies had indicated that iNOS is up regulated in EAE and MS.¹⁰³⁻¹⁰⁵ Patients with active MS have significantly higher NOS activity and NO concentration in the CSF.¹⁰⁶

As we mentioned previously, at the early stages of the disease, KP/IDO-1 activation is crucial for the immunosuppression of T cells and the presence of high levels of NO might suppress IDO-1 activity and thus promote MS progression. Furthermore, production of QUIN from activated macrophages, also producing ROS and NO, further potentiates oxidative stress and irreversible cell death. Then a question could be: if NO suppresses IDO-1, where is the source of QUIN? As mentioned, even if IDO-1 is down regulated, activated astrocytes are capable of producing large amounts of KYN that are taken up by macrophages as substrate for QUIN production.¹⁰⁷ In the chronic progressive form of MS with a moderate and constant activation of the KP, production of neurotoxic KP metabolites, such as QUIN, 3HK together with ROS might further amplify the neurodegenerative processes.⁵⁰ The possibility of those neurotoxic KP metabolites fuelling oxidative stress further highlights the importance of regulating the KP in MS.

Conclusion

In this review we have tried to combine and discuss known and potential links between the KP metabolites and the neuropathogenesis of MS. While it is still unclear whether KP activation is beneficial or detrimental, it seems likely that the KP would be more beneficial in the short term and become detrimental in the long term. Further studies are necessary to characterise KP components at different stages of MS to determine whether the hypotheses raised in this manuscript are valid.

Acknowledgements

This work was supported by the Multiple Sclerosis Research Association (MSRA) and the University of New South Wales.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.



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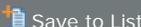
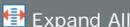
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Abstracted / Indexed	Yes
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