

The role of kynurenines in the pathomechanism of amyotrophic lateral sclerosis and multiple sclerosis: therapeutic implications

Judit Füvesi · Cecilia Rajda · Krisztina Bencsik ·
József Toldi · László Vécsei

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Abstract Tryptophan is one of the essential amino acids, 80% of which is catabolised in the extrahepatic tissues by indoleamine-2,3-dioxygenase (IDO), the rate-limiting enzyme of the kynurenine pathway. Metabolites along the kynurenine pathway have been implicated to play a role in the pathomechanism of neuroinflammatory and neurodegenerative disorders. Changes in the concentration levels of kynurenines can shift the balance to pathological conditions. The ability to influence the metabolism towards the neuroprotective branch of the kynurenine pathway, i.e. towards kynurenic acid (KYNA) synthesis, may be one option in preventing neurodegenerative diseases. Three potential therapeutic strategies could be feasible to develop drugs to live up to expectations: (1) chemically related drugs with better bioavailability and higher affinity to the binding sites of excitatory receptors; (2) prodrugs of KYNA, which easily cross the blood–brain barrier combined with an inhibitor of organic acid transport for enhancement of the brain KYNA concentration; (3) inhibitors of enzymes of the kynurenine pathway. In this review, we focus on aspects of the pathomechanism and therapeutic possibilities of

amyotrophic lateral sclerosis and multiple sclerosis that may be influenced by kynurenines.

Keywords Neurodegeneration · Inflammation · Kynurenic acid · Multiple sclerosis · Amyotrophic lateral sclerosis

Introduction

It has been proven that several molecules of amino-acid metabolism have an important role as neurotransmitters in the signaling in the nervous system. Tryptophan is an essential amino acid, which is metabolized into L-kynurenine, then kynurenic acid (KYNA) and quinolinic acid (QUIN). The latter is transformed into nicotinylnucleotide (NAD) in several successive steps (Stone 1993, 2001a) (Fig. 1). KYNA is an endogenous antagonist at several subtypes of glutamate receptor with a particularly high affinity to the strychnine-resistant glycine-coagonist site of the NMDA receptor (Johnson and Ascher 1987; Kiss and Vécsei 2009). It also has an antagonist activity on the alpha7-nicotinic acetylcholine receptor (Carpenedo et al. 2001). KYNA has neuroprotective effects, while QUIN on the other hand, is neurotoxic (Stone 1993). Several experimental models have been developed to study neurodegenerative disorders based on excitotoxicity and this knowledge hopefully will soon lead to novel therapies applicable in the clinical practice as well (Malpass 2011). In this review, we focus on the role of the kynurenine pathway (KP) in the pathomechanism and therapeutic possibilities of amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS). Although the two diseases differ in their pathomechanism—both involve inflammation as well as neurodegeneration. Moreover,

J. Füvesi · C. Rajda · K. Bencsik · L. Vécsei (✉)
Department of Neurology, Faculty of Medicine,
Albert Szent-Györgyi Clinical Centre, University of Szeged,
Semmelweis u. 6, Szeged 6725, Hungary
e-mail: vecsei.laszlo@med.u-szeged.hu

J. Toldi
Department of Physiology, Anatomy and Neuroscience,
Faculty of Natural Sciences, University of Szeged,
Szeged, Hungary

J. Toldi · L. Vécsei
Neuroscience Research Group of the Hungarian Academy
of Sciences, University of Szeged, Szeged, Hungary

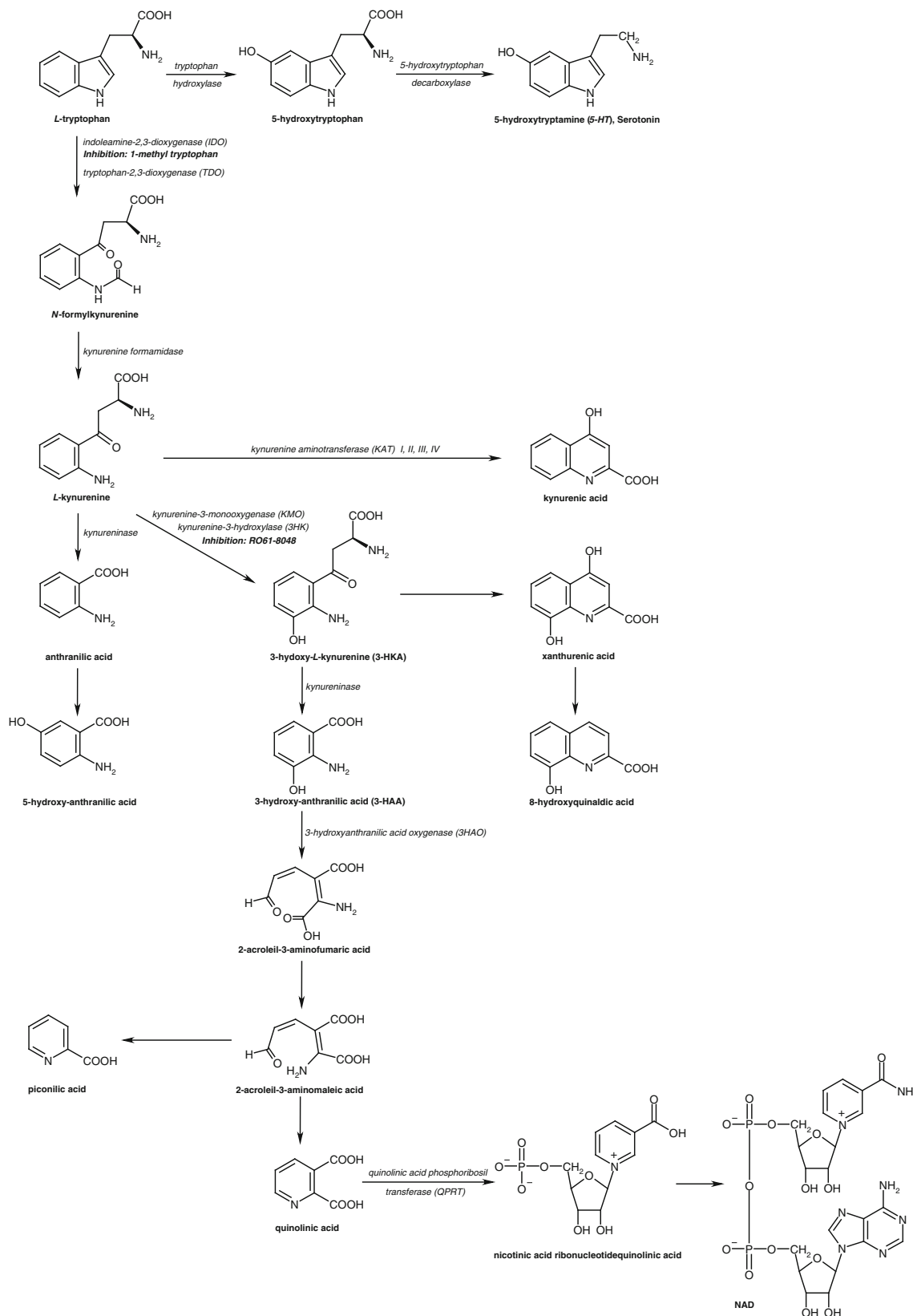


Fig. 1 Tryptophan metabolism and the kynurenine pathway

implications that the kynurenine system is affected in both diseases, and consequently KYNA-based therapies may be relevant have been extensively studied.

ALS is the most common motor system disease, a general term designating a group of progressive degenerative disorders of motor neurons (MN) in the spinal cord, brainstem, and motor cortex, manifest clinically by muscular weakness, atrophy, and corticospinal tract signs, all in the absence of sensory change (Ropper and Samuels 2009). It is a disease of middle life in most cases and progresses to death in 2–5 years. In approximately 10% of cases the disease is familial, inherited as an autosomal dominant trait. The principal pathological finding in ALS is a loss of nerve cells in the anterior horns of the spinal cord and motor nuclei of the lower brain stem. Currently, the single drug approved for the treatment of ALS is riluzole, an antiglutamate agent. In a prospective double-blind placebo-controlled trial it was able to slow the progression of the disease and it may improve survival in patients with disease of bulbar onset (Bensimon et al. 1994). After 12 months 58% in the placebo group and 74% in the riluzole group were still alive. The deterioration of muscle strength was significantly slower in the riluzole group than in the placebo group.

MS, a demyelinating disorder of the central nervous system (CNS), affects mainly young adults in their most productive parts of their life. There are twice as many female as male patients. The clinical course is relapsing-remitting in the majority of cases and after a varying disease duration it is transformed into a secondary progressive phase (Lublin and Reingold 1996). In 10–15% of cases the disease is progressive from the very beginning. Patients present with different symptoms: sensory, fatigue, nystagmus, internuclear ophthalmoplegia, optic neuritis, hyperreflexia, weakness of the upper or lower limbs, cerebellar signs. In later stages spasticity, cognitive impairment and vegetative disturbances also become apparent.

There is still no curative therapy for MS. Until the middle of the 1990s, treatment of patients with the relapsing-remitting clinical form of the disease was restricted to treating the relapses with megadose parenteral corticosteroids. The first pharmacological agent with proved efficacy for the treatment of patients with the relapsing-remitting (RR) or relapsing-progressive (RP) forms of MS was interferon beta-1b (IFN β -1b) (Lublin and Reingold 1996; Lublin et al. 1996). Early results of a multi-center, double-blind, placebo-controlled clinical trial proved that treatment with IFN β -1b was well tolerated and significantly reduced the activity of the disease and the number of active and new lesions detected by MRI in the RR form of MS (The IFNB Multiple Sclerosis Study Group 1993; Paty and Li 1993).

Currently available first-line immunomodulatory drugs (IMDs) are interferon beta-1a, interferon beta-1b and

glatiramer acetate. All of them are administered parenterally by self-injection. In pivotal randomized placebo-controlled trials of IMDs reductions in relapse rates ranged from 18 to 34% and the treatment has been shown to slow the accumulation of lesion burden as determined by MRI (Jacobs et al. 1996; Johnson et al. 1995; PRISMS Study Group 1998; Rudick et al. 1999; Simon et al. 1998; The IFNB Multiple Sclerosis Study Group 1993). The latest drugs are natalizumab, a monoclonal antibody administered in monthly i.v. infusions and fingolimod, a sphingosine 1-phosphate receptor modulator, which is the first approved pharmacological agent with an oral route of administration (Miller et al. 2003; Polman et al. 2006; Kappos et al. 2010; Chun and Hartung 2010). Both are second-line treatments at present for RR MS patients with very active disease course. They are able to decrease the relapse rate by 68 and 56%, respectively. However, this greater efficacy comes with more severe potential side-effects and we do not have long-term safety data as opposed to the interferons and glatiramer acetate, which are used for decades (Reider et al. 2010a, b).

Tryptophan catabolism and pharmacology

Tryptophan (Trp) is one of the essential amino acids, 80% of which is catabolized in the extrahepatic tissues by *indoleamine-2,3-dioxygenase* (IDO), the first and rate-limiting enzyme of the KP (Fig. 1). IDO converts tryptophan to formyl-kynurenine. The activation of IDO may lead to the production of KYNA and/or QUIN along the KP.

The expression of IDO is induced by the proinflammatory cytokines interferon gamma (IFN- γ) and to a lesser degree by interferon beta (IFN- β) in dendritic cells, fibroblasts and macrophages. The induction of this enzyme could be the common pathway of neuroinflammation and degeneration, because after the initiation of the process, neuroprotective as well as toxic metabolites are produced (Kwidzinski et al. 2005). In the extrahepatic tissues, IDO not only limits the growth of infectious agents, but affects the strength of the immune response as well (see review by Mándi and Vécsei 2011). The down-modulatory effect of IDO activation on T cells might be due to its ability to create a tryptophan-depleted microenvironment that limits their proliferation (Munn et al. 1998) or the susceptibility of T cells to apoptosis is enhanced by the degradation products of tryptophan (Fallarino et al. 2002).

KYNA is synthesized by *kynurenine aminotransferases* (KATs). There are four subtypes of KATs (see review by Guidetti et al. 2007; Han et al. 2010; Okuno et al. 1991; Yu et al. 2006). The enzymes differ in substrate specificity and pH optimum of action (see review by Kiss and Vécsei 2009). In the human brain KAT II is the main

KYNA-producing enzyme. Astrocytes seem to be the primary source of KYNA in the brain (Guillemin et al. 2001b; Kiss et al. 2003).

The neuroprotective KYNA is a noncompetitive NMDA receptor antagonist. Recent data indicate that KYNA displays opposite effects in micromolar and nanomolar concentrations. KYNA affected the field excitatory postsynaptic potentials in the rat hippocampus in a dose-dependent manner, thus at low dosage (at nanomolar levels) it acted as a neuroexcitatory agent (Prescott et al. 2006; Rozsa et al. 2008), but in the higher micromolar concentrations exerted the contrary effect. It not only acts as an antagonist on the strychnine-insensitive glycine-binding site of the NMDA receptor, but also blocks non-competitively the alpha7-nicotinic acetylcholine receptors (Carpenedo et al. 2001). These findings indicate that KYNA could be able to modify the glutamatergic as well as the nicotinic neurotransmission (Carpenedo et al. 2001), which in turn affects the excitability of the microenvironment and neuronal function.

QUIN is synthesized from kynurenine in successive steps involving the enzymes kynurenine-3-hydroxylase (KH), kynureninase and 3-hydroxyanthranilic acid dioxygenase (Fig. 1). Microglial cells produce the majority of QUIN (Espey et al. 1997; Lehrmann et al. 2001). The neurotoxic QUIN exerts its effect through the *N*-methyl-D-aspartate (NMDA) receptor.

Depending on its concentration QUIN causes acute neuronal death or chronic progressive neuronal dysfunction by four mechanisms: (1) NMDA receptor activation in pathological concentration leads to increased intracellular calcium level (Kerr et al. 1995); (2) increases glutamate release by neurons and inhibits its uptake into the synaptic vesicle by astrocytes increasing the glutamate concentration in the microenvironment and causing neurotoxicity (Tavares et al. 2000); (3) lipid peroxidation (Rios and Santamaria 1991) and (4) energy depletion (Bordelon et al. 1997; Guillemin et al. 2005a). In pathophysiological concentrations QUIN induces apoptosis in neurons and astrocytes (Macaya et al. 1994; Kelly and Burke 1996; Guillemin et al. 2005b).

Astrocytes—synthesizing KYNA—might counteract the production of neurotoxins by microglia in case of local damage (Kwidzinski and Bechmann 2007).

The role of kynurenines in ALS

The level of the excitotoxic QUIN is significantly elevated in serum and CSF of ALS patients (Guillemin et al. 2005a). In ALS brain and spinal cord large numbers of activated microglia, reactive astrocytes, T cells and infiltrating macrophages have been described (Graves et al. 2004; Henkel et al. 2004) that release inflammatory and neurotoxic mediators, among others IFN- γ , the most potent inducer of IDO (McGeer and McGeer 2002). The neuronal and microglial expression of IDO and QUIN was found to be increased in ALS motor cortex and spinal cord (Chen et al. 2010). Serum levels of picolinic acid (PIC) were decreased and CSF and serum levels of Trp, KYN and QUIN were significantly increased.

Microglia play a major role in MN death in ALS (see review by Sargsyan et al. 2005). The number of activated microglia in postmortem spinal cord tissue of ALS patients is significantly higher than in controls. Besides microglia, peripheral macrophages entering the CNS contribute to QUIN production. In fact, macrophages are able to produce 20- to 30-fold more QUIN compared to microglia (Espey et al. 1997).

The concentration of KYNA in CSF of ALS patient with bulbar onset is higher compared to controls and patients with limb onset (Ilzecka et al. 2003). KYNA concentration in CSF of ALS patients with severe clinical status is also elevated compared to controls, indicating a neuroprotective role of KYNA against excitotoxicity. In the CNS KYNA is mainly produced by activated astrocytes, being part of their neuroprotective function.

ALS has been linked to generation of reactive oxygen species, oxidative stress and lipid peroxidation. A major aspect of QUIN toxicity is lipid peroxidation (Sas et al. 2007). Another component of the KP also has an

Table 1 Compounds related to the KP with therapeutic possibilities

Compound	References
<i>Kynurenine analogue</i>	
Laquinimod	Comi et al. (2010, 2008); Polman et al. (2005)
<i>N</i> -(3,4)-Dimethoxycinnamoyl anthranilic acid (3,4-DAA)	Platten et al. (2005)
<i>KYNA-analogues</i>	
Glucosamide-kynurenic acid	Füvesi et al. (2004); Robotka et al. (2005)
2-(2- <i>N,N</i> -dimethylaminoethylamine-1-carbonyl)-1H-quinolin-4-one hydrochloride	Marosi et al. (2010); Zádori et al. (2011a)
<i>Prodrugs of KYNA</i>	
L-4-Chloro-kynurenine	Hokari et al. (1996)

antioxidant role: 3-hydroxyanthranilic acid (3-HAA) is a potent free radical scavenger and inhibits peroxidation of LDL (Thomas et al. 1996). However, its concentration in the CNS might not be enough to exert these beneficial effects, because normally it is metabolized further in the KP.

Excitotoxicity may also play an important role in the pathogenesis of ALS (Beal and Vécsei 1992). Glutamate toxicity contributes to the selective MN injury in ALS. The single therapeutic agent able to slow ALS progression in patients (riluzole) is targeting glutamate-mediated toxicity. Glutamate level has been shown to be high in the CSF of ALS patients (Spreux-Varoquaux et al. 2002). Higher glutamate concentration was correlated with spinal onset, more impaired limb function and higher rate of muscle deterioration. QUIN increases extracellular glutamate concentrations by: (1) stimulating synaptosomal glutamate release by neurons; (2) inhibiting glutamate uptake into the synaptic vesicle by astrocytes (Tavares et al. 2000) and (3) limiting glutamate recycling to glutamine in the astrocytes by decreasing glutamine synthetase activity.

Mitochondrial dysfunction is an important feature of ALS that makes MNs more vulnerable to ionotropic glutamate receptor-mediated excitotoxicity (Kanki et al. 2004). QUIN produces mitochondrial dysfunction disrupting energy metabolism, which may be critical in the cell death cascade (Sas et al. 2007).

Therapeutic implications in ALS

In a study designed to identify candidate drugs for the treatment of ALS, a list of currently used pharmacological agents were tried in a model examining embryonic rat MNs from spinal cords exposed to increased extracellular glutamate (Vincent et al. 2005). Six major types of cellular activity could be identified from the list of MN protective drugs: (1) protein synthesis inhibition; (2) Cox inhibition; (3) regulation of anion flux; (4) modulation of GABA receptors; (5) antioxidants; and (6) cell cycle inhibition. Excitotoxic insults produce a calcium influx in neurons that cause programmed cell death. In the case of NMDA, full activation of the receptor is normally toxic to the cells, but modest activation using the 1 μ M dose in these studies may precondition the MN against glutamate-mediated toxicity.

In the study of Chen et al. (2011), 1-methyl tryptophan (Fig. 1) was able to decrease QUIN release by the rodent microglial cell line BV2 and as a result protected NSC-34 cells (a rodent motor neuron cell line) from cell death. A combination drug therapy involving agents targeting KP may provide a novel treatment strategy (Chen et al. 2009).

The role of kynurenines in multiple sclerosis

Increasing evidence indicates that the accumulation of neurotoxic kynurenine metabolites is an effect closely associated with the activation of the immune system. In a study of Alberati-Giani et al. (1996), the regulation of the kynurenine pathway enzymes by interferon- γ (IFN- γ) was studied in immortalized murine macrophages and microglia. Their findings suggest that during inflammation the activated invading macrophages may be one of the major sources of quinolinic acid in the CNS. Macrophages may contribute to QUIN production to a larger extent than microglia by virtue of higher IDO activity upon activation. Kynureninase activity was stimulated by IFN- γ in macrophages but not in microglia. The ability of IFN- γ to increase kynureninase activity supports the view that the opening of the pyrrole ring of L-tryptophan by IDO may not be the only enzymatic step controlling this pathway in activated macrophages. To a lesser extent, the activity of kynurenine 3-hydroxylase (KH), a NADPH-dependent enzyme, was also shown to be stimulated by IFN- γ . On the other hand, KAT and 3-hydroxyanthranilic acid dioxygenase (3-HAO), the enzymes directly responsible for the biosynthesis of KYNA and QUIN were not modulated by IFN- γ in these murine cell lines (Alberati-Giani et al. 1996).

QUIN in experimental allergic encephalomyelitis (EAE), a model of MS

EAE is a T-cell mediated, autoimmune animal model of MS that has behavioral and histopathological similarities to the human disorder (Paterson 1980). QUIN was found to be selectively elevated in the spinal cords of rats with EAE (Flanagan et al. 1995). A significant increase in the activity of the enzyme kynurenine-3-mono-oxygenase (KMO) was also reported, and as a consequence, the spinal cord content of 3-hydroxykynurenine and QUIN reached neurotoxic level (Chiarugi et al. 2001). The origin of the increased QUIN in EAE was suggested to be the macrophages. Cultures of human macrophages have been reported to synthesize and release QUIN (Heyes et al. 1992b) in concentrations determined to be neurotoxic (Whetsell and Schwarcz 1989). CSF levels of QUIN are \sim 20 nM in humans (Heyes et al. 1992a) and concentrations as low as 100 nM have been reported to cause damage to cultured neurons (Whetsell and Schwarcz 1989). Therefore, a five-fold elevation in QUIN could be toxic to neurons. QUIN is an initiator of lipid peroxidation and high local levels of QUIN near myelin may contribute to the demyelination in EAE and possibly MS.

Trp metabolites in patients with MS

It was already described in 1979 that tryptophan level is decreased in the plasma of patients with MS and degenerative diseases and CSF tryptophan was decreased in MS and MN disease (Monaco et al. 1979). CSF levels of KYNA were found to be significantly lower in relapsing-onset MS patients during remission or not progressing for at least 2 months, compared to subjects with other neurological diseases (non-inflammatory and inflammatory included) (Rejdak et al. 2002). During relapse, CSF KYNA and S100B protein, a biomarker of astrocyte activation were significantly higher in RRMS patients compared to controls (Rejdak et al. 2007; Rajda et al. 2007). These results suggest the activation of the KP leading to the increase of neuroprotective KYNA in the CSF of MS patients during acute relapse. KAT I and KAT II activities were significantly higher in the red blood cells of MS patients compared to controls (Hartai et al. 2005) and the concentration of KYNA was found to be elevated in the plasma of MS patients.

Interferon beta 1b (IFN- β 1b)—in pharmacologically relevant concentrations (comparable to those found in the sera of IFN- β treated patients)—induces KP metabolism in human macrophages, which may be a limiting factor in its efficacy in the treatment of MS (Guillemin et al. 2001a). IFN- β 1b induces mRNA expression of IDO, but not 3HAO and QPRTase. Twenty-four hours after IFN- β administration, increased kynurenine levels and kynurenine/tryptophan ratio were found in the plasma of MS patients receiving IFN- β injection for the first time compared to healthy subjects (Amirkhani et al. 2005). The increase of kynurenine/tryptophan ratio in the first IFN MS group indicates an induction of IDO by IFN- β . Kynurenine, synthesized peripherally after IDO induction, crosses the BBB and is also synthesized at high level by astrocytes within the brain. Exposure of human neurons to QUIN concentrations of 350 nM may disturb the ability of neuronal dendrites to integrate incoming signals. QUIN can kill oligodendrocytes (Cammer 2001). IFN- β 1b induces QUIN concentration in a similar range. In IFN- β 1b-treated patients concomitant blockade of the KP with one of the KP inhibitors that are under development may improve its efficacy.

Therapeutic implications in MS

The currently available treatments for MS are all anti-inflammatory in their mechanism of action, but there is still no approved drug with a neuroprotective effect or one that would facilitate remyelination. A new molecule, BG-12, is an oral formulation of dimethylfumarate for the treatment of RR MS and is now in a Phase 3 clinical trial. It has dual

anti-inflammatory and neuroprotective effects: it activates the nuclear factor (erythroid-derived 2)-like 2 Nrf2 transcriptional pathway and defends against oxidative stress (Linker et al. 2011; Gold et al. 2011). It may offer a novel cytoprotective modality that further augments the natural antioxidant responses in multiple sclerosis.

Similarly, KYNA, its pharmacologically altered derivatives and inhibitors of enzymes in the KP may be promising new agents to fill this gap in the “therapeutic palette”. Kynurenines are important in the dialogue between the immune system and the CNS, and consequently are a target for drug development (Stone 2000, 2001b). There is accumulating evidence that inhibition of the KP may be able to defend against excitotoxicity (Braidy et al. 2009; Jhamandas et al. 2000; Vamos et al. 2009; Zádori et al. 2011b) and induce remyelination (Matysiak et al. 2008), therefore it is neuroprotective.

It is suggested that IDO, the rate-limiting enzyme in Trp catabolism has a direct role in the tolerogenic effects of altered peptide ligands (APLs) (Platten et al. 2005). APLs are peptides modified at important receptor-binding residues to modulate proliferation and the cytokine profile of antigen-specific T cells by altering the strength of TCR signaling. APLs inducing a T_{H2} immune response have therapeutic potential to induce self-tolerance to autoantigens and to treat autoimmune diseases such as MS (Platten et al. 2005). One of the mechanisms of action of glatiramer acetate, an example of APL and an approved treatment for MS is shifting the cytokine responses toward T_{H2}.

Kynurenine 3-mono-oxygenase (KMO) (or kynurenine-3-hydroxylase, K3H) is the enzyme responsible for 3-hydroxykynurenine formation. It is a flavin-containing protein localized in the outer mitochondrial membrane that may be a rate-limiting step enzyme for QUIN synthesis. KMO immunoreactivity has been detected both in neurons and astrocytes. KMO inhibitors have been proposed as neuroprotective agents. Systemic administration of Ro 61-8048, a selective KMO inhibitor (Fig. 1), caused accumulation of KYNA and reduced the increase of both 3-hydroxykynurenine and QUIN (Chiarugi et al. 2001).

The effects of the orally active synthetic Trp metabolite *N*-(3,4,-dimethoxycinnamoyl) anthranilic acid (3,4-DAA) (Table 1) were examined in both in vitro and in vivo experiments (in microglial cells and in the RR version of EAE) (Platten et al. 2005). It interfered with IFN- γ -induced antigen presentation by microglia and suppressed the activation of autoreactive T_{H1} cells. Animals treated with 3,4-DAA had fewer and milder relapses and less severe disease. There was a reduction in the number of inflammatory foci in the brains and spinal cords of 3,4-DAA-treated mice compared to vehicle-treated animals indicating an immunosuppressive effect of the molecule. 3,4-DAA as well as natural Trp metabolites induced antigen-specific

IL-10-producing T cells with regulatory potential in vitro and in vivo. Interestingly, immunomodulator laquinimod, a molecule in Phase 3 trial for the treatment of RRMS is a quinoline carboxamid with structural homology to the Trp metabolites 3-HAA and 3-HKA (Comi et al. 2010, 2008; Fernandez 2011; Polman et al. 2005).

There is no therapy at present that can replace or repair damaged myelin or oligodendrocytes. Remyelination in experimental lesions occurs in two major phases: in the recruitment phase neural stem cells (NSCs) and oligodendrocyte precursor cells (OPCs) proliferate to populate demyelinated areas followed by differentiation into mature, myelinating oligodendrocytes (Chari 2007). If Trp metabolism through the KP is induced by inflammation it will result in the cellular depletion of Trp, an amino acid that is essential for protein synthesis (Trp depletion hypothesis) (Lee et al. 2002). It may be a major problem in rapidly dividing cells such as oligodendrocyte precursor cells. Additionally, several KP metabolites, such as 3-HK and QUIN may impair cell division (Trp utilization hypothesis) (Fallarino et al. 2002; Frumento et al. 2002). This process might be responsible for the failure to remyelinate especially in patients with a very active disease, where relapses occur frequently. Consequently, demyelination leads to axonal degeneration and accumulation of disability, as seen clinically and in the spinal cord of secondary progressive MS patients (Lovas et al. 2000). Modulation of the KP in NSCs and OPCs may play a role in such MS-related tissue repair (Matysiak et al. 2008). Optimizing stem cell proliferation and differentiation would facilitate their use in MS (Croitoru-Lamoury et al. 2011).

General therapeutic considerations

Kynurenic acid is not able to cross the blood–brain barrier (BBB). To overcome this problem in drug development several possible solutions have been applied (Table 1). Esters of KYNA and its analogues penetrate the CNS more readily and hydrolysed back to the analogues within the brain (Stone 2001b). A KYNA analogue, glucosamide-kynurenic acid showed similar behavioral and electrophysiological effects to KYNA in case of both intracerebroventricular and systemic (intraperitoneal) administration, indicating that it was able to cross the BBB (Füvesi et al. 2004; Robotka et al. 2005). Another novel KYNA analogue, 2-(2-*N,N*-dimethylaminoethylamine-1-carbonyl)-1*H*-quinolin-4-one hydrochloride, also behaved quite similarly to KYNA in an in vitro electrophysiological study (Marosi et al. 2010). Moreover, it exhibited neuroprotective effects in a transgenic mouse model of Huntington's disease (Zádori et al. 2011a).

Another alternative is to use molecules which are metabolized to KYNA within the CNS. For example *L*-4-chloro-kynurenine is converted into 7-chloro-kynurenic acid and shows neuroprotective activity against quinolinic acid-induced damage. The combination of the BBB-penetrable *L*-KYN or analogues and probenecid, an inhibitor of organic acid transport enhances brain KYNA concentration (Vécsei et al. 1992). Modulating the KP enzymes is another strategy to regulate the generation of metabolites towards the neuroprotectant KYNA (Stone 2000, 2001b).

Summary

Trp metabolites are involved in the network of neural and immunological reactions, with a significant impact on the homeostasis of the normal functioning nervous system. Changes in the concentration levels of their metabolites can shift the balance to pathological conditions. The ability to influence the metabolism towards the neuroprotective branch of the KP, i.e. towards KYNA synthesis, might be one option to prevent neurodegenerative diseases.

Three potential therapeutic strategies could be feasible to develop drugs to live up expectations: (1) chemically related drugs with better bioavailability and higher affinity to the excitatory receptors; (2) prodrugs of kynurenic acid, which easily cross the BBB combined with an inhibitor of organic acid transport for enhancement of the brain kynurenic acid concentration; (3) inhibitors of enzymes of the KP. There is already one promising drug, 3,4-DAA, which reversed the paralysis in mice with EAE. It may present a novel class of drugs in the treatment of Th1-mediated autoimmune diseases. Hopefully, similar promising molecules will be developed to prevent MN death in patients with ALS.

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