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The Kynurenine Pathway

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1. Introduction

The kynurenine pathway represents a major route for the catabolism of tryptophan (TRP). In the body, TRP is transported around the periphery either bound to albumin (90%) or in free form (10%), the two states existing in equilibrium (McMenamy 1965). However, only free form TRP can be transported across the blood-brain barrier (BBB) by the competitive and non-specific L-type amino acid transporter (Hargreaves and Pardridge 1988). Once in the central nervous system (CNS), TRP acts as a precursor to several metabolic pathways, such as for the synthesis of kynurenine (KYN), serotonin, melatonin and protein (Fig. 1) (Ruddick *et al.* 2006).

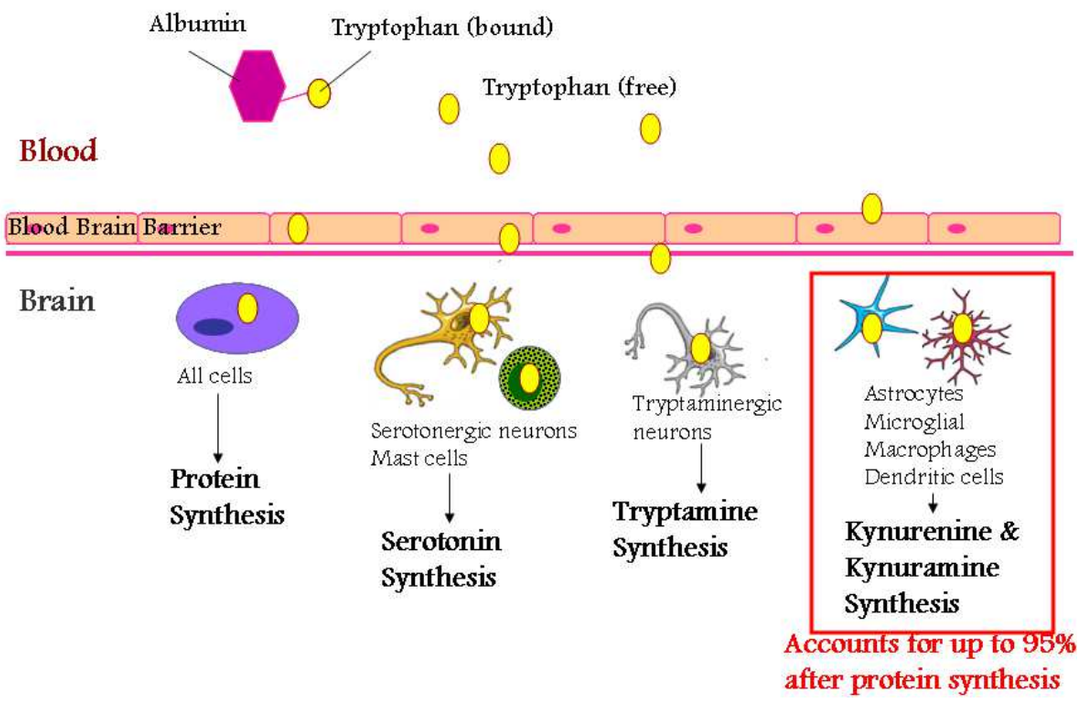

Fig. 1. TRP in the CNS. Only free TRP can cross the BBB and act as precursor for protein, serotonin, tryptamine, and kynurenine and kynuramine synthesis. The kynurenine pathway is a major pathway for TRP catabolism. Adapted from (Ruddick *et al.* 2006).

In the CNS, the kynurenine pathway is present to varying extents in most cell types, including astrocytes (Guillemin *et al.* 2000), neurons (Guillemin *et al.* 2007), infiltrating macrophages and microglia (Guillemin *et al.* 2003), oligodendrocytes (Lim *et al.* 2007), and endothelial cells (Owe-Young *et al.* 2008). Infiltrating macrophages, activated microglia and neurons have the complete repertoire of kynurenine pathway enzymes. On the other hand, neuroprotective astrocytes and oligodendrocytes lack the enzyme, kynurenine 3-monooxygenase (KMO) and indoleamine 2,3-dioxygenase 1 (IDO-1) respectively, and are incapable of synthesizing the excitotoxin, quinolinic acid (QUIN) (Guillemin *et al.* 2000; Lim *et al.* 2007).

The oxidation of TRP, initiating the kynurenine pathway (Fig. 2), may be catalyzed by one of three enzymes - TRP 2,3-dioxygenase (TDO), IDO-1 or IDO-2, a newly discovered IDO related enzyme (Salter and Pogson 1985; Takikawa *et al.* 1986; Ball *et al.* 2007; Metz *et al.* 2007). TDO resides primarily in the liver, although it is also expressed in low quantities in the brain, and is induced by TRP or corticosteroids (Salter and Pogson 1985; Miller *et al.* 2004). In contrast, IDO-1 is the predominant enzyme extra-hepatically and is found in numerous cells, including macrophages, microglia, neurons and astrocytes (Guillemin *et al.* 2001; Guillemin *et al.* 2003; Guillemin *et al.* 2005; Guillemin *et al.* 2007). IDO-1 is up regulated by certain cytokines and inflammatory molecules, such as lipopolysaccharides, amyloid peptides and human immunodeficiency virus (HIV) proteins (Fujigaki *et al.* 1998; Guillemin *et al.* 2003; Takikawa 2005), and its most potent stimulant is interferon gamma (IFN-γ) (Hayaishi and Yoshida 1978; Werner-Felmayer *et al.* 1989). IFN-γ induces both the gene expression and enzymatic activity of IDO-1 (Yasui *et al.* 1986; Dai and Gupta 1990). IDO-2 possesses similar structural and enzymatic activities as IDO-1. However, the two enzymes differ in their expression pattern and signalling pathway, and IDO-2 is preferentially inhibited by D-1-methyl-tryptophan (D-1-MT) (Ball *et al.* 2007; Metz *et al.* 2007).

The first stable intermediate from the kynurenine pathway is KYN. Subsequently, several neuroactive intermediates are generated. They include the free-radical generator, 3-hydroxyanthranilic acid (3HAA) (Goldstein *et al.* 2000), the excitotoxin and *N*-methyl *D*-aspartate (NMDA) receptor agonist, QUIN (Stone and Perkins 1981), the NMDA antagonist, kynurenic acid (KYNA) (Perkins and Stone 1982), and the neuroprotectant, picolinic acid (PIC) (Jhamandas *et al.* 1990).

The kynurenine pathway first aroused great interest when it was observed that an accelerated and sustained degradation of TRP occurred when activated T cells released IFN-γ during an immune response (Pfefferkorn 1984). The significance was speculated to be a defence mechanism that starved tumour cells, pathogens and parasites of TRP (Pfefferkorn 1984; Brown *et al.* 1991). Further research soon discovered that IDO-1 activity was necessary for the preservation of allogeneic foetuses in mice, and that TRP depletion had an anti-proliferative and apoptotic effect on T cells (Munn *et al.* 1998; Munn *et al.* 1999; Lee *et al.* 2002). Hence, the kynurenine pathway appeared to exert an immuno-regulatory effect. In particular, the general control non-derepressible-2 kinase (GCN2) was identified as a key mediator in IDO-1 induced TRP depletion immunosuppression (Munn *et al.* 2005). The activation of GCN2 triggered a stress-response program that resulted in cell-cycle arrest, differentiation, adaptation or apoptosis (de Haro *et al.* 1996; Rao *et al.* 2004; Bi *et al.* 2005). Furthermore, some of the kynurenines, such as QUIN and 3HAA, can selectively target immune cells undergoing activation, thus suppressing T cell proliferation (Frumento *et al.* 2002; Fallarino *et al.* 2003). They can also act in concert to produce an additive effect (Terness *et al.* 2002). Lastly, the production of the excitotoxic QUIN was often significantly increased following inflammation and resulting immune activation (Moffett *et al.* 1997).

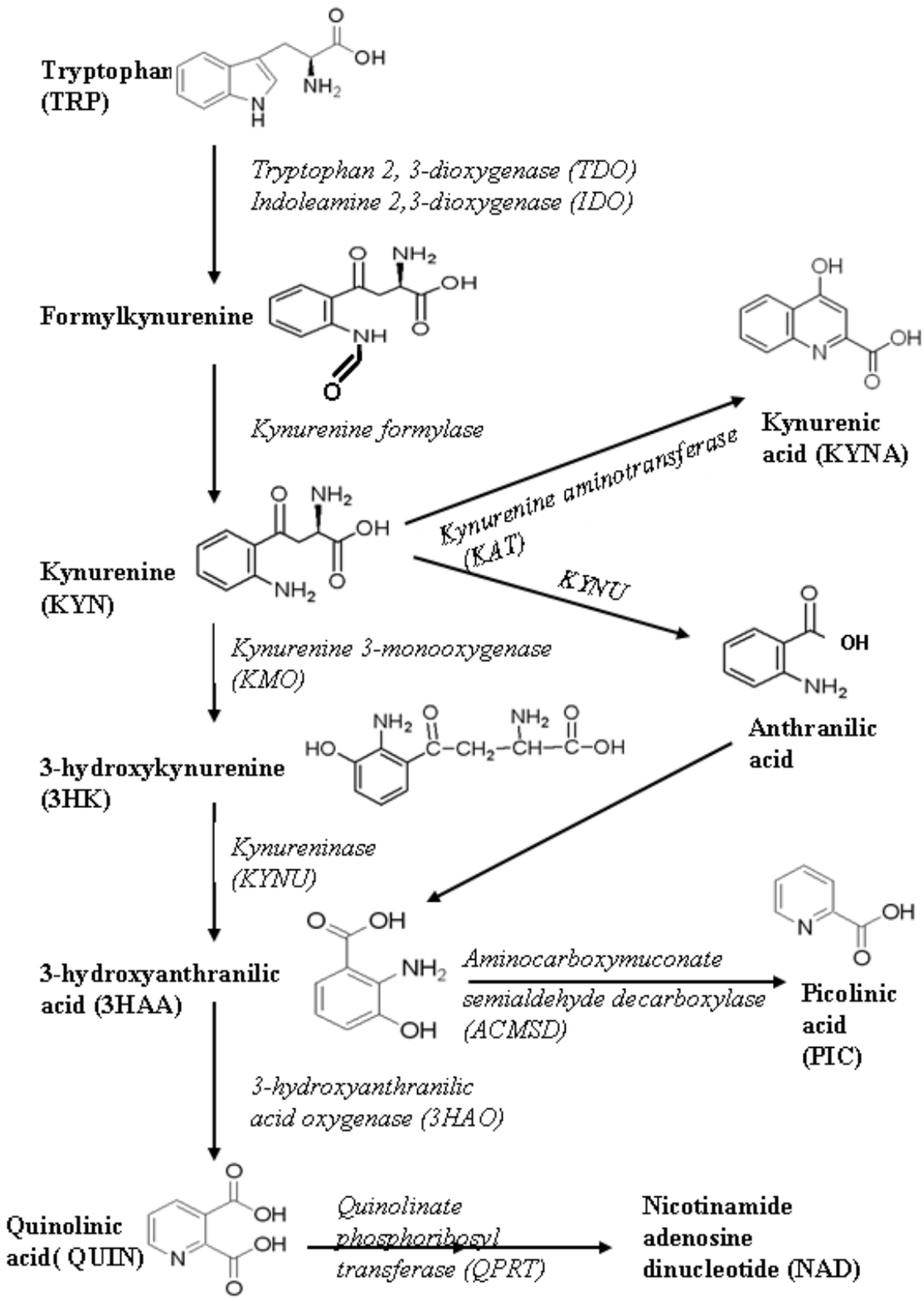

Fig. 2. The kynurenine pathway. Via the kynurenine pathway, TRP is converted to nicotinamide adenine dinucleotide (NAD) in a series of biochemical steps. In the process, neuroactive intermediates are produced. The neuroprotectants include kynurenic acid and picolinic, and the neurotoxin, QUIN.

To date, the kynurenine pathway has been implicated in a wide range of diseases and disorders, including infectious diseases (e.g. HIV), neurological disorders (e.g. Alzheimer's disease (AD), Huntington's disease (HD) and ALS), affective disorders (e.g. schizophrenia, depression and anxiety), autoimmune diseases (e.g. multiple sclerosis and rheumatoid arthritis), peripheral conditions (e.g. cardiovascular disease) and malignancy, and a key indicator is often the up-regulation in IDO-1 resulting in an accelerated and sustained degradation in TRP.

2. The kynurenine pathway and QUIN in ALS

The interest in the kynurenine pathway in the pathogenesis of ALS is relatively new. However, a number of studies have provided relevant results demonstrating the involvement of the kynurenine pathway in ALS.

For the kynurenine pathway to be involved in the pathogenesis and progression of ALS, a key prerequisite has to be met – the activation of the immune response, particularly the presence of: (1) IFN-γ, which is the most potent stimulator of IDO-1 (Takikawa *et al.* 1999); and (2) activated microglia and/or infiltrating macrophages, which are the main producers of QUIN in the CNS (Brew *et al.* 1995; Heyes *et al.* 1996). Figure 3 summarizes the main adverse events exerted by QUIN leading to motor neuron injury and death.

A few studies have provided direct evidence between TRP metabolism and ALS. Patients with severe clinical status had significantly higher cerebrospinal fluid (CSF) KYNA levels compared to controls; however, serum KYNA levels were significantly lower in patients with severe clinical status compared to either controls or patients with mild clinical status (Ilzecka *et al.* 2003). This increase in CSF KYNA in patients was conjectured to be associated with the neuroprotective effect of KYNA, produced mainly by activated astrocytes (Guillemin *et al.* 2001). ALS samples have also been found to have significantly higher levels of CSF and serum KYN and QUIN and decreased levels of serum PIC (Chen *et al.* 2010).

Another study looked at Trp-32 in superoxide dismutase 1 (SOD1) protein. The aggregation of SOD1 is one of the hallmarks of familial ALS. Trp-32 is the only aromatic residue in SOD1 protein and is found on the SOD1 protein surface (Zhang *et al.* 2003). The oxidation of Trp-32 to KYN is responsible for bicarbonate mediated peroxidase activity induced SOD1 aggregation (Zhang *et al.* 2003). By substituting Trp-32 with phenylalanine, which oxidizes more slowly, mutant SOD-1 motor neurons survived longer and were less likely to form cytoplasmic inclusions (Taylor *et al.* 2007).

3. Indirect evidence for the role of QUIN in ALS

In addition to the direct evidence demonstrating the link between the kynurenine pathway and ALS, numerous other studies have provided indirect evidence supporting the role of QUIN, in particular, in ALS.

3.1 QUIN and SOD1 expression

Mutations in SOD1 constitute about 20% of familial ALS cases. In rat brain, intracerebral injection of QUIN resulted in significant neuronal loss and a markedly increased level of SOD1 expression in a time-dependent manner (Noack *et al.* 1998). This increase in SOD1 expression was thought to be a neuroprotective response to limit the oxidative damage caused by QUIN. Presumably, QUIN could have a similar effect on mutant SOD1, which would amplify the deleterious effects associated with mutant SOD1 pathology in ALS.

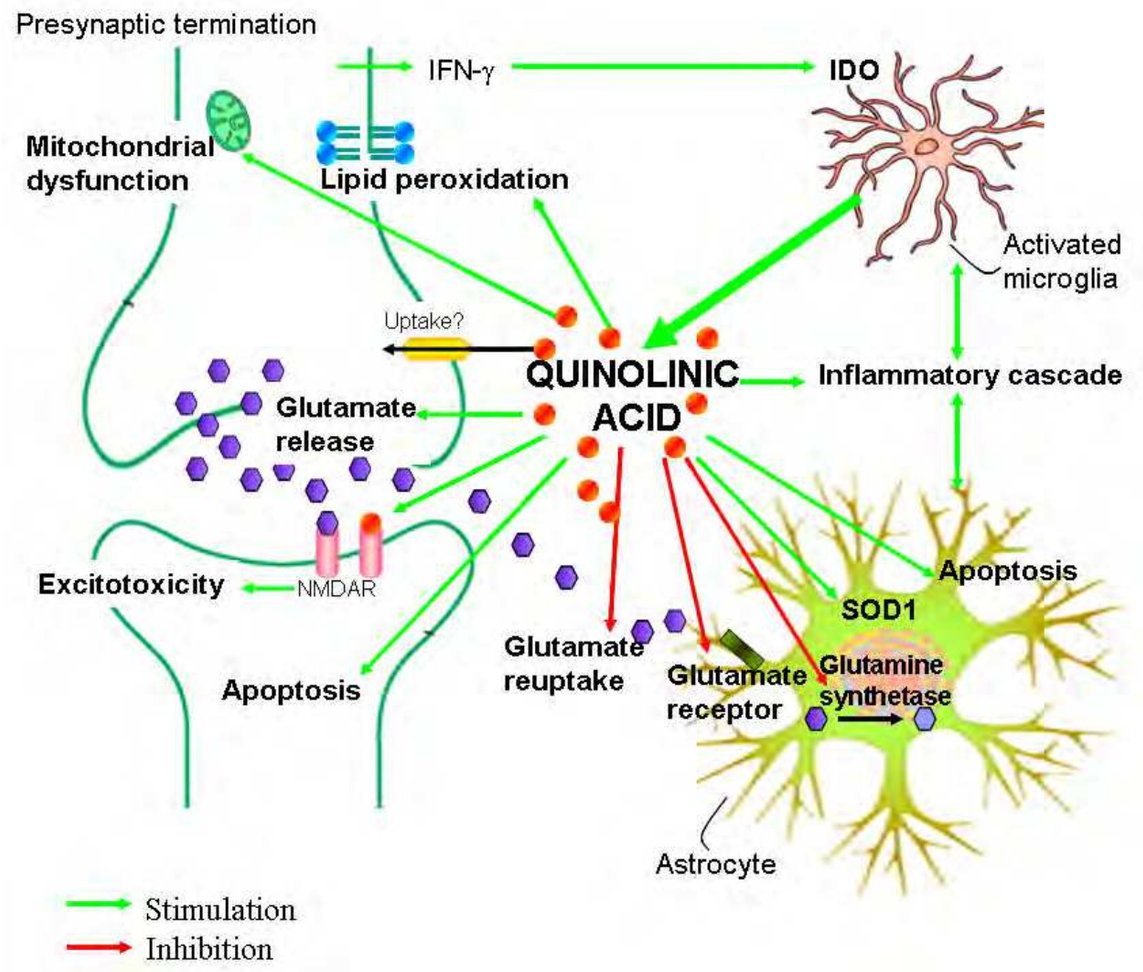

Fig. 3. Hypothetical model of the involvement of QUIN in the pathogenesis of ALS. QUIN, released from activated microglia, can induce various effects in astrocytes and motor neurons, including excitotoxicity, oxidative stress, apoptosis, mitochondrial dysfunction and the inflammatory cascade, all putatively thought to contribute to ALS disease pathogenesis and progression. Adapted from (Guillemin *et al.* 2005).

3.2 QUIN and excitotoxicity

QUIN is an excitotoxin and can be linked to excitotoxicity in ALS in two ways: (1) through the activation of the NMDA receptor; and (2) its effect on glutamate levels. The heteromeric NMDA receptor (NR) has three families of subunits: NR1 (A and B), NR2 (A to D) and NR3 (A and B). In the ventral and dorsal horns of ALS spinal cord, up to 78% loss of NR2A has been detected (Samarasinghe *et al.* 1996). Interestingly, QUIN acts on the NR subtypes, NR1+NR2A and NR1+NR2B (Priestley *et al.* 1995), and the loss of NR2A in ALS patients may possibly reflect an excitotoxic mechanism involving QUIN.

Glutamate induced toxicity has been implicated in the selective neuronal damage seen in ALS and counteracting glutamatergic toxicity, thus far, is the only treatment available for ALS. QUIN can potentiate its own toxicity and that of other excitatory amino acids, such as glutamate, under energy deprived conditions (Schurr and Rigor 1993). Moreover, QUIN

contributes to excessive microenvironment glutamate concentrations and neurotoxicity via at least three mechanisms: (1) stimulation of synaptosomal glutamate release by neurons (Tavares *et al.* 2002); (2) inhibition of glutamate uptake into synaptic vesicle by astrocytes (Tavares *et al.* 2000); and (3) limiting glutamate to glutamine recycling in astrocytes by decreasing glutamine synthetase activity (Baverel *et al.* 1990).

3.3 QUIN and oxidative stress

One of the putative causes of ALS is the increased production and accumulation of reactive oxygen species (ROS) leading to oxidative stress and lipid peroxidation. Toxicity induced by QUIN has been related to increase ROS and oxidative stress. Intracerebral injection of QUIN shows neuronal damage and increase in ROS content occurring as early as 4 hrs after administration (Ganzella *et al.* 2006).

The lipid peroxidative effect of QUIN has also been demonstrated *in vivo* in adult rat brain (Rios and Santamaria 1991), and in rat brain synaptosomes *in vitro* (Santamaria *et al.* 2001). Similarly, in sheep foetal brain infused with QUIN, 4-hydroxynonenal (4-HNE), a toxic product of lipid peroxidation, immunoreactivity was observed in Purkinje cells and in the cytoplasm of cell bodies and dendrites, reaching into the molecular layer of the cerebellum (Yan *et al.* 2005). A sub-lethal dose of 4-HNE will also lead to the loss of spinal motor neurons in mice (Vigh *et al.* 2005). This may be a consequence of microglia activation, as 4-HNE is a potent activator of microglia, which will further contribute to neuroinflammation and oxidative stress in ALS (Hall *et al.* 1998).

In sporadic ALS patients, 4-HNE was enhanced in motor neurons and glia cells in the spinal cord (Shibata *et al.* 2001), and significantly elevated in the serum and CSF, correlating positively with the stage of disease (Simpson *et al.* 2004). CSF 4-HNE levels from sporadic ALS patients were also sufficient to cause the demise of motor neurons *in vitro* (Smith *et al.* 1998).

3.4 QUIN and mitochondrial dysfunction

Mitochondrial dysfunction is a prominent feature of ALS and predisposes motor neurons to ionotropic glutamate receptor-mediated excitotoxicity (Kanki *et al.* 2004). Excitotoxicity may lead to the activation of mitochondrial permeability transition pore, resulting in mitochondrial swelling and progressive motor neuron death (Bendotti *et al.* 2001). Intracerebral injection of QUIN, in addition to being excitotoxic, also produces progressive mitochondrial dysfunction leading to time-dependent energetic dysfunction, which may be a common and critical event in the cell death cascade seen in ALS (Bordelon *et al.* 1997).

3.5 QUIN and the inflammatory cascade

The presence of neuroinflammation is a pathological hallmark of ALS. Activated astrocytes and microglia are often seen in the degenerating areas surrounding injured motor neurons (McGeer and McGeer 2002). Elevated levels of chemokines and cytokines, such as monocyte chemoattractant protein 1 (MCP-1), macrophage inflammatory protein (MIP)1-α, chemokine ligand 5, interleukin (IL)-1 to IL-12, TNF-α and IFN-γ, have been detected in both G93A SOD1 mice and ALS patients (Hensley *et al.* 2003; Wilms *et al.* 2003; Henkel *et al.* 2004). It has been demonstrated that QUIN can induce astrocyte proliferation and the production of chemokines, particularly MCP-1 (Croitoru-Lamoury *et al.* 2003; Guillemin *et al.* 2003; Ting 2008), and IL-1β messenger ribonucleic acid (mRNA) expression (Guillemin *et al.* 2003) in human astrocytes and macrophages.

3.6 QUIN and apoptosis

In ALS, apoptosis is evident from the increased expression of pro-apoptotic proto-oncogenes, BCl-2 and c-jun, and caspases 1 and 3 in tissue, and from the morphological features of apoptosis displayed by dying motor neurons. QUIN has been demonstrated to induce neuronal and astrocytic apoptosis involving the activation of caspase 3 (Macaya *et al.* 1994; Jeon *et al.* 1999; Guillemin *et al.* 2005). Astrocytes are essential for the homeostasis of the CNS and so, the well-being of neurons. Hence, the loss of normal astrocytes in ALS would be detrimental to motor neurons and could exacerbate disease progression in ALS (Yamanaka *et al.* 2008).

4. Potential therapeutics targeted at the kynurenine pawthay for ALS

In 1995, riluzole became the first drug, and remains the only drug, approved by the FDA (USA) for treatment of ALS. The approval was based on two large placebo controlled clinical studies where riluzole decreased the rate of muscle deterioration and modestly improved the survival rate of ALS patients (Bensimon *et al.* 1994; Lacomblez *et al.* 1996). Though the precise mechanism of riluzole remains unclear, it appears to interfere with excitatory amino acid signalling, perhaps through the inhibition of glutamate release (Mizoule *et al.* 1985; Cheramy *et al.* 1992; Martin *et al.* 1993), blockade of inactivated sodium channels (Benoit and Escande 1991) and interaction with guanosine triphosphate (GTP)-binding proteins (Doble *et al.* 1992). 16 years on, there is still a lack of effective treatment available and an intense search is on going to discover better treatments for ALS.

In developing therapeutic agents aimed at modulating the kynurenine pathway, two approaches may be taken: (1) to develop analogues of the neuroprotective kynurenines; (2) to inhibit the synthesis of the neurotoxic QUIN. Figure 4 summarizes the drugs targeting the kynurenine pathway that could be potential candidates for ALS.

4.1 IDO inhibitors

As the first enzyme in the kynurenine pathway, suppression of IDO would lead to decrease QUIN production. Although it has not been specifically tested in neurodegenerative disorders, it is a novel therapeutic target in cancer research and the results have been positive. Using transgenic mouse model of breast cancer, IDO-1 inhibitors, 1-MT and methyl-thiohydantoin-tryptophan, were able to potentiate the efficacy of chemotherapy drugs, promoting tumour regression without increasing the side effects (Muller *et al.* 2005).

4.2 4-chlorokynurenine

QUIN neurotoxicity can be prevented by blocking the glycine modulatory site of the NMDA receptor (Foster *et al.* 1990; Hartley *et al.* 1990). 7-chlorokynurenate, a synthetic derivative of KYNA, is such an NMDA receptor antagonist (Kemp *et al.* 1988) but has difficulty crossing the BBB (Rao *et al.* 1993). On the other hand, its precursor, 4-chlorokynurenine, is rapidly transported across the BBB (Hokari *et al.* 1996). Intracerebral and intraperitoneal administration of 4-chlorokynurenine with QUIN showed successful enzymatic transamination of 4-chlorokynurenine into the neuroprotective 7-chlorokynurenate (Wu *et al.* 1997; Wu *et al.* 2000).

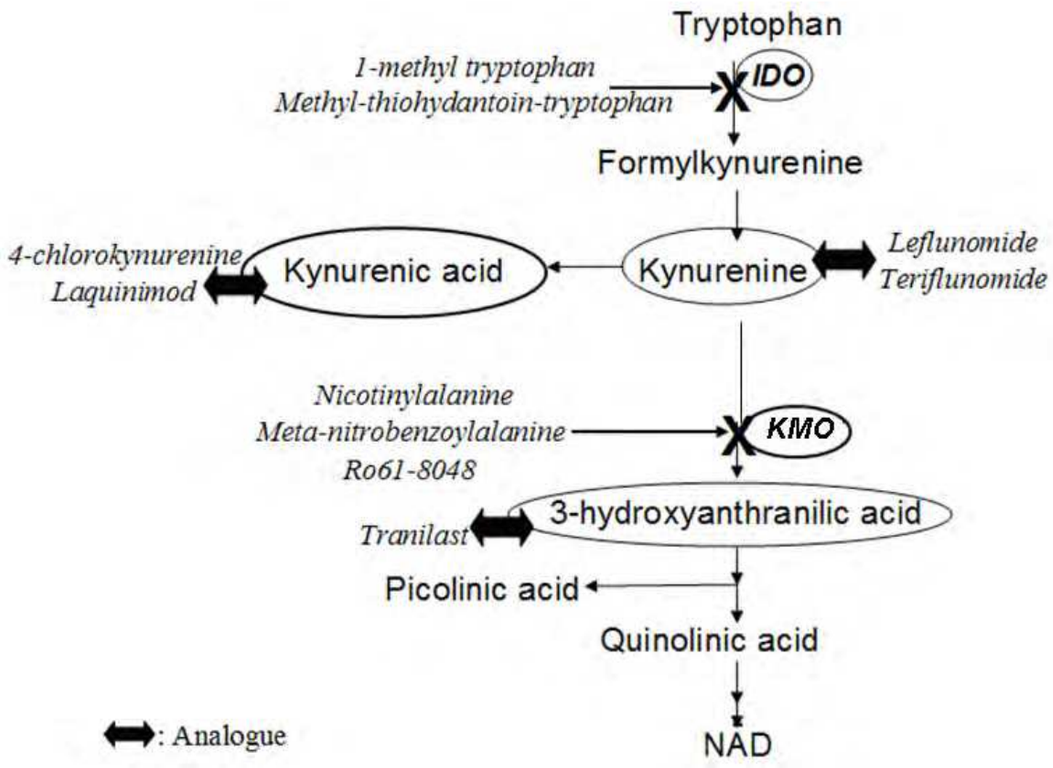

Fig. 4. Potential drug candidates targeting the kynurenine pathway for ALS. 1-MT, methyl-thiohydantoin-tryptophan, nicotinylalanine, meta-nitrobenzoylalanine and Ro61-8048 are kynurenine pathway inhibitors, while 4-chlorokynurenine, laquinimod, leflunomide, teriflunomide and tranilast are analogues of kynurenines.

4.3 Laquinimod

Laquinimod (ABR-215062) is a novel synthetic quinoline with high oral bioavailability. In preclinical trials, the compound exhibited immunomodulatory properties without immunosuppression (Brunmark *et al.* 2002; Zou *et al.* 2002; Yang *et al.* 2004). In rats with experimental autoimmune encephalomyelitis (EAE), a widely used animal model for MS, laquinimod inhibited disease progression and infiltration of CD4+ T cells and macrophages into the CNS (Yang *et al.* 2004). It also shifted the cytokine profile towards Th2/Th3 cytokines IL-4, IL-10 and transforming growth factor β (TGF-β) (Yang *et al.* 2004). Furthermore, laquinimod is able to act synergistically with IFN-β, though the mechanism of action is currently unknown but is independent of IFN-β (Runstrom *et al.* 2006). In addition, laquinimod has also successfully reduced the development of active lesions in patients with relapsing MS (Polman *et al.* 2005).

4.4 Leflunomide

Leflunomide (Avara®) is an immunosuppressive and anti-inflammatory pro-drug, which is converted *in vivo* to its active open-ring metabolite, teriflunomide (A771726), an inhibitor of mitochondrial dihydroorotate dehydrogenase, an essential enzyme for *de novo* pyrimidine synthesis (Williamson *et al.* 1995). Leflunomide is a potent inhibitor of the nuclear factor *kappa*-light-chain-enhancer of activated B cells (NF-κB) activation (Manna and Aggarwal

1999) and prevents Th1 cell activation while promoting Th2 cell differentiation (Dimitrova *et al.* 2002). The exact mechanism of action is still unclear though it has been shown to attenuate EAE independent of pyrimidine depletion (Korn *et al.* 2004).
In 1998, leflunomide was approved by the FDA (USA) for the treatment of rheumatoid arthritis. Leflunomide has also been successful in inhibiting disease progression in animal models of autoimmune diseases, such as experimental autoimmune neuritis (Ogawa *et al.* 1990), EAE (Bartlett *et al.* 1993) and experimental myasthenia gravis (Vidic-Dankovic *et al.* 1995). In a phase II trial recently, teriflunomide proved to be well tolerated and effective in reducing active lesions in patients with relapsing MS (O'Connor *et al.* 2006).

4.5 Tranilast

Tranilast (Rizaben®) is a synthetic anthranilic acid derivative drug with several inhibitory actions. It has the ability to inhibit the release of chemical mediators, such as histamine, during hypersensitivity reactions and from mast cells and also suppresses the release of TGF-β and inhibits angiogenesis (Suzawa *et al.* 1992; Isaji *et al.* 1997). Thus, it is effective against many diseases, including allergic rhinitis, atopic dermatitis, bronchial asthma, hypertrophic scar formation and keloid. Recently, tranilast showed promising results against EAE, shifting the cytokine profile towards favouring Th2 cells, inhibiting the actions of Th1 cells and promoting the generation of IL-10 producing Th2 cells, an effect similar to that of natural TRP catabolites (Platten *et al.* 2005).

4.6 Alanine derivatives

The synthesis of QUIN can also be blocked by inhibiting either KYNU or KMO activity, thus diverting the kynurenine pathway towards the synthesis of KYNA. Nicotinylalanine is one such agent (Decker *et al.* 1963). When administered together with probenecid (to allow for the accumulation of KYNA by inhibiting the organic acid transport system), nicotinylalanine increased the amount of KYNA produced in the brain and protected the brain from induced seizures (Connick *et al.* 1992; Russi *et al.* 1992) and QUIN induced striatal damage (Harris *et al.* 1998).
Another alanine derivative capable of inhibiting KMO is meta-nitrobenzoylalanine (Pellicciari *et al.* 1994). The inhibition of KMO results in an increase in brain KYN and KYNA, which is associated with sedation and anticonvulsant effects (Chiarugi and Moroni 1999) and reduction in neuronal loss from brain ischemia (Cozzi *et al.* 1999). In immune activated mice, meta-nitrobenzoylalanine also significantly reduced the formation of QUIN in the periphery and CNS (Chiarugi and Moroni 1999).

4.7 Ro61-8048

Ro61-8048 (3,4-dimethoxy-N-[4-(3-nitrophenyl)thiazol-2-yl] benzenesulfon-amide) is another potent KMO inhibitor (Rover *et al.* 1997). In addition to raising brain KYNA level, Ro61-8048 also reduces glutamate concentration in the extracellular spaces of the basal ganglia in rats without impairing the learning or memory process typically associated with glutamate receptor antagonists (Moroni *et al.* 2005). In rats with EAE, administration of Ro61-8048 significantly reduces the neurotoxic levels of 3-hydroxykynurenine and QUIN in the CNS (Chiarugi *et al.* 2001). Like meta-nitrobenzoylalanine, Ro61-8048 also decreases neuronal loss due to brain ischemia (Cozzi *et al.* 1999).

4.8 Clioquinol

Clioquinol (5-chloro-7-iodo-8-hydroxyquinoline) is a quinoline metal chelator that binds selectively to zinc and copper ions (Cherny *et al.* 2001). Having a hydrophobic nature, it crosses the BBB easily. Recent research with clioquinol in neurological disorders contributed by an imbalance in metal ions has led to promising results, presenting the possibility of a new therapeutic strategy. In AD transgenic mice, treatment with clioquinol resulted in the dissolution of aberrant neocortex beta amyloid (Aβ) aggregates, which are enriched with copper and zinc ions (Cherny *et al.* 2001). In a pilot phase II clinical trial, the drug was well tolerated and led to a significant decrease in Aβ plasma levels in AD patients, providing support for future trials (Ritchie *et al.* 2003). In PD, elevated levels of iron in the substantia nigra, the brain region affected in PD, has been reported. In mice, oral administration of clioquinol antagonized the action of the Parkinson's inducing agent 1-methyl-4-phenyl-1,2,3,6-tetra-pyridine (MPTP) (Kaur *et al.* 2003). In HD, where iron, copper and zinc have been implicated, clioquinol improved the symptoms and lifespan of transgenic HD mice (Nguyen *et al.* 2005).

A second generation 8-hydroxyquinoline, PBT2, has been developed to improve the safety and efficacy of clioquinol and also its pharmaceutical properties, such as solubility and bioavailability. In preclinical *in vivo* and *in vitro* trials on transgenic AD mice, PBT2 was more effective in lowering plaque formation and reducing plaque toxicity. More importantly, it may also improve cognition.

5. Conclusion

The current consensus is that ALS is a multifactorial disease. However, an explanation for the initiation of the putative causative mechanism of ALS remains elusive, and there lacks a hypothesis that can link all the mechanisms together. In recent years, the implication of the kynurenine pathway in multiple diseases, particularly neurodegenerative diseases, has led to an increase in assessing the efficacy of drugs targeting the kynurenine pathway in ameliorating disease symptoms and/or retarding disease progression.

The kynurenine pathway has been demonstrated to be involved in ALS and this provides an important link that ties together some of the major hypotheses underlying the pathogenesis of ALS, namely glutamate excitotoxicity, oxidative stress, non-cell-autonomous mechanism and apoptosis, which are also the major mechanisms via which QUIN exerts its neurotoxicity effects. Due to the multiple pathways involved in the pathogenesis and progression of ALS, it may be speculated that a combination therapy could be more efficacious. Hence, by targeting the kynurenine pathway, it is hoped that more effective therapeutic agents, acting in synergy with other agents, may uncover a better treatment for ALS.

6. Appendix

3HAA3-hydroxyanthranilic acid
4-HNE4-hydroxynonenal
Aβ Beta amyloid
ADAlzheimer's disease
ALSAmyotrophic lateral sclerosis
BBBBlood-brain barrier

CNSCentral nervous system
CSFCerebrospinal fluid
D-1-MTD-1-methyl-tryptophan
EAEExperimental autoimmune encephalomyelitis
GCN2General control non-derepressible-2 kinase
GTPGuanosine triphosphate
HDHuntington's disease
HIVHuman immunodeficiency virus
IDOIndoleamine 2,3-dioxygenase
IFN-γInterferon gamma
ILInterleukin
KMOKynurenine 3-monooxygenase
KYNKynurenine
KYNAKynurenic acid
MCPMonocyte chemoattractant protein
MIPMacrophage inflammatory protein
MPTPMethyl-4-phenyl-1,2,3,6-tetra-pyridine
mRNAMessenger ribonucleic acid
NF-κBNuclear factor *kappa*-light-chain-enhancer of activated *B* cells
NMDA*N*-methyl *D*-aspartate
NRNMDA receptor
PICPicolinic acid
QUINQuinolinic acid
ROSReactive oxygen species
SOD1Superoxide dismutase 1
TDOTryptophan 2,3-dioxygenase
TGF-βtransforming growth factor β
TRPTryptophan

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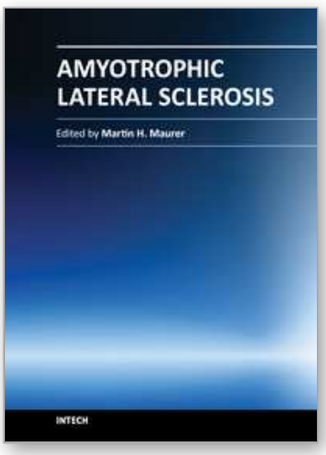

Amyotrophic Lateral Sclerosis

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Though considerable amount of research, both pre-clinical and clinical, has been conducted during recent years, Amyotrophic Lateral Sclerosis (ALS) remains one of the mysterious diseases of the 21st century. Great efforts have been made to develop pathophysiological models and to clarify the underlying pathology, and with novel instruments in genetics and transgenic techniques, the aim for finding a durable cure comes into scope. On the other hand, most pharmacological trials failed to show a benefit for ALS patients. In this book, the reader will find a compilation of state-of-the-art reviews about the etiology, epidemiology, and pathophysiology of ALS, the molecular basis of disease progression and clinical manifestations, the genetics familial ALS, as well as novel diagnostic criteria in the field of electrophysiology. An overview over all relevant pharmacological trials in ALS patients is also included, while the book concludes with a discussion on current advances and future trends in ALS research.

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