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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, amylloid 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) (Hayashi 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 KYNA 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.
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 pathway 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 going on 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).

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Fig. 4. Potential drug candidates targeting the kynurenine pathway for ALS. 1-MT, methylthiohydantoin-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 $\beta$ (TGF-$\beta$) (Yang et al. 2004). Furthermore, laquinimod is able to act synergistically with IFN-$\beta$, though the mechanism of action is currently unknown but is independent of IFN-$\beta$ (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-$\kappa$B) activation (Manna and Aggarwal...
The Kynurenine Pathway

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

3HAA 3-hydroxyanthranilic acid
4-HNE 4-hydroxynonenal
Aβ Beta amyloid
AD Alzheimer’s disease
ALS Amyotrophic lateral sclerosis
BBB Blood-brain barrier

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The Kynurenine Pathway

CNS Central nervous system
CSF Cerebrospinal fluid
D-1-MTD-1-methyl-tryptophan
EAE Experimental autoimmune encephalomyelitis
GCN2 General control non-derepressible-2 kinase
GTP Guanosine triphosphate
HDH Huntington’s disease
HIV Human immunodeficiency virus
IDO Indoleamine 2,3-dioxygenase
IFN-γ Interferon gamma
IL Interleukin
KMO Kynurenine 3-monooxygenase
KYN Kynurenine
KYN A Kynurenic acid
MCP Monocyte chemotactic protein
MIP Macrophage inflammatory protein
MPTP Methyl-4-phenyl-1,2,3,6-tetra-pyridine
mRNA Messenger ribonucleic acid
NF-κB Nuclear factor kappa-light-chain-enhancer of activated B cells
NMDAN-methyl D-aspartate
NRN NMDA receptor
PIC Picolinic acid
QUIN Quinolinic acid
ROS Reactive oxygen species
SOD1 Superoxide dismutase 1
TDO Tryptophan 2,3-dioxygenase
TGFB Transforming growth factor β
TRP Tryptophan

7. References


The Kynurenine Pathway


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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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