REVIEW – SPECIAL ISSUE

Tryptophan, Neurodegeneration and HIV-Associated Neurocognitive Disorder

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Abstract: This review presents an up-to-date assessment of the role of the tryptophan metabolic and catabolic pathways in neurodegenerative disease and HIV-associated neurocognitive disorder. The kynurenine pathway and the effects of each of its enzymes and products are reviewed. The differential expression of the kynurenine pathway in cells within the brain, including inflammatory cells, is explored given the increasing recognition of the importance of inflammation in neurodegenerative disease. An overview of common mechanisms of neurodegeneration is presented before a review and discussion of the evidence for a pathogenetic role of the kynurenine pathway in Alzheimer's disease, HIV-associated neurocognitive disorder, Huntington's disease, motor neurone disease, and Parkinson's disease.

Keywords: neurodegeneration, HIV, kynurenine pathway, tryptophan, indoleamine 2,3-dioxygenase

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1. Introduction

This review will focus firstly on the tryptophan metabolic and catabolic pathways; with particular emphasis placed on the tryptophan catabolic pathway, the kynurenine pathway (KP), and the effects of each of its enzymes and products. The cells within the brain which have complete or partial expression of the KP are then discussed, including the KP in inflammatory cells, as there is increasing evidence that inflammation plays a role in at least some neurodegenerative diseases. The next section deals with the involvement of tryptophan and the KP in neurodegenerative disorders and HIV, first detailing the broad and specific pathways for neurodegeneration. Particular neurodegenerative diseases including Alzheimer's disease (AD), Huntington's disease (HD), motor neurone disease, Parkinson's disease (PD) as well as HIV-associated neurocognitive disorder (HAND) are discussed emphasizing the evidence for the involvement of the KP.

2. Tryptophan Metabolism and Catabolism

Tryptophan is one of the essential amino acids, critical for human metabolism. It plays a central role in protein synthesis, as well as in the production of melatonin, serotonin, and a variety of KP products including nicotinamide adenine dinucleotide (NAD+) and ultimately niacin (see Fig. 1).

2.1. Tryptophan transport into the brain

Tryptophan is the only amino acid that is bound to albumin with approximately 10% being found free in plasma.[1] Binding to albumin is influenced by several factors but especially by the presence of non-esterified fatty acids, as well as exogenous factors such as medications, that can displace bound tryptophan. There is some evidence for greater dissociation of tryptophan from albumin in the cerebral microvasculature, with highest dissociation rates occurring under conditions of low cerebral blood flow, perhaps regulated partly by the sympathetic nervous system.[2–4] It is at present unclear whether this translates into regional differences in tryptophan availability within the brain. Free tryptophan is transported from blood across the blood brain barrier by a competitive transport carrier (L-amino acid transporter 1; LAT-1), which is shared with several large neutral amino acids.[1] Factors that
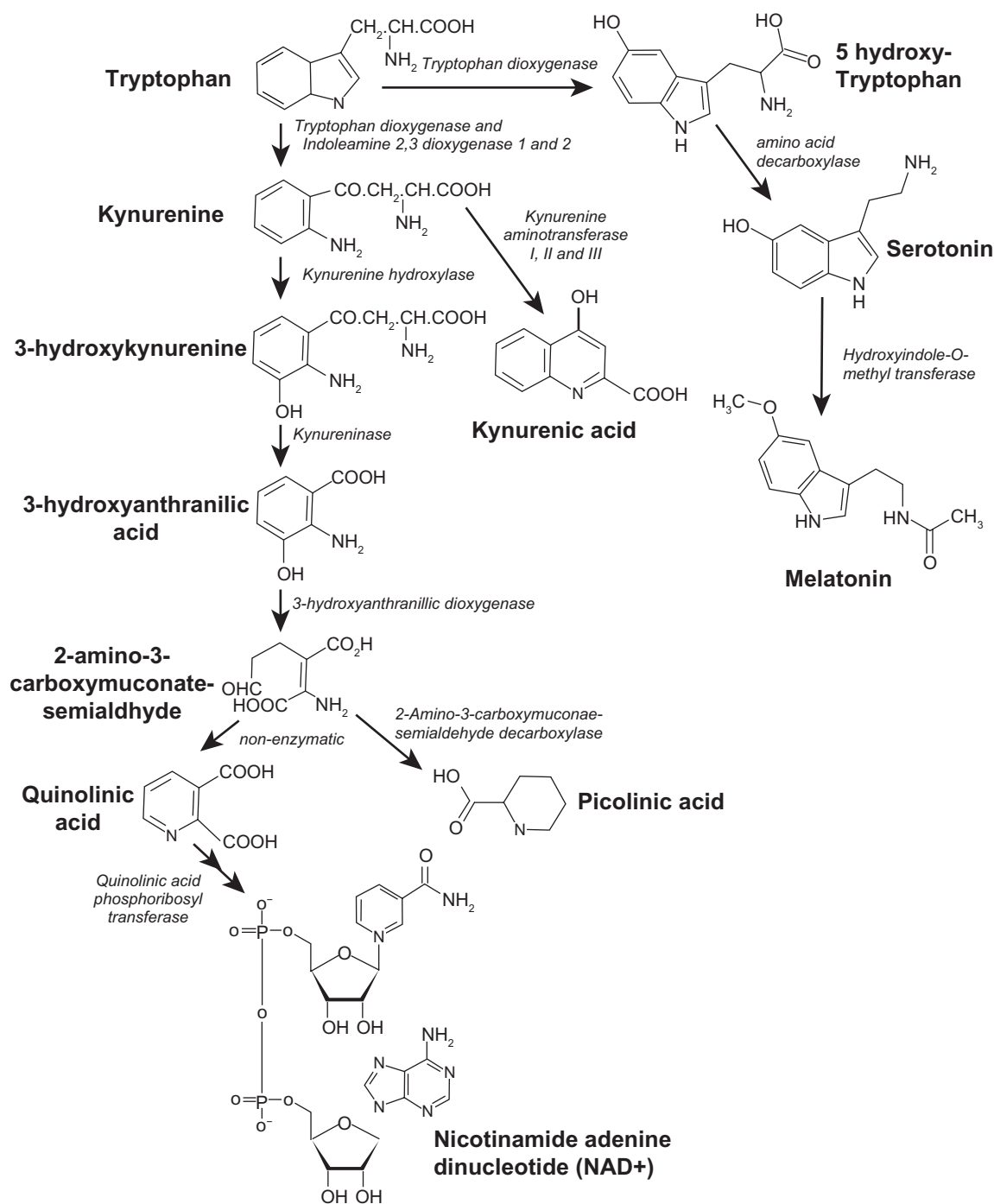
regulate this carrier and which might be disturbed in disease states are poorly understood, as are the factors determining the rate of tryptophan efflux from the brain.[5,6] The carrier found in the cerebral vasculature is known to have a higher affinity for tryptophan than that found outside the central nervous system (CNS). Nonetheless, other large neutral amino acids compete for the same transporter so that lower concentrations of such amino acids facilitate tryptophan transport. Once in the brain, tryptophan enters cells by mechanisms that are also unclear though there is some evidence for a transporter in serotonergic neurones[7,8] and pinealocytes.[9] It is unclear at present whether the LAT-1 and LAT-2 transporters, which are important in the bidirectional exchange of tryptophan and kynurenine in most systemic cells, are similarly important in brain cells.[10]

2.2. Tryptophan and protein synthesis

Mammalian cells cannot synthesize tryptophan and so rely on its uptake into the cell for protein synthesis. Indeed, tryptophan accounts for approximately 1.3% of the amino acids in human proteins. Because of its critical role in cell function it appears that some cells have a "storage mechanism" through which production of the cytoplasmic enzyme tryptophanyl-tRNAsynthetase (TTS) results in the formation of complexes of the enzyme with tryptophan.[11] Such complexes are then directly available for protein synthesis. Cytotoxic T-lymphocyte antigen-4 (CTLA-4) and interferon gamma (IFN-γ) are known to induce TTS but other modulatory factors remain possible.[12,13] Moreover, the cellular distribution, the relative expression of TTS in normal and pathological conditions as well as the duration of tryptophan supply in TTS complexes are areas that require exploration.

2.3. Melatonin

Melatonin is an indoleamine synthesized from tryptophan in the pineal gland by pinealocytes. It is also synthesised in the retina and outside the brain by enteroendocrine cells of the gastrointestinal mucosa, lymphoid organs and the bone marrow. Melatonin's chief physiological function appears to be regulation of the sleep-wake cycle but it is also an important antioxidant and free radical scavenger.[14] Additionally, melatonin has significant immune regulatory functions, both cellular and humoral. It stimulates the production

Figure 1. The Catabolic Pathway of Tryptophan
Note: Production of xanthurenic acid from 3-hydroxykynurenine is not shown on this figure.

of natural killer cells, monocytes and leukocytes; favours a Th-1 response and increases the production of cytokines such as interleukin IL-2, IL-6, IL-12 and IFN-γ.[15] It also plays a role in sexual maturation, reproductive behaviour and thermoregulation.[16,17]

The role of melatonin in neurodegeneration is largely speculative at present as it is unclear whether levels are significantly abnormal in these diseases. However, clinically melatonin supplementation appears to have some beneficial effects and is reported in AD to improve sleep, reduce "sundowning" and possibly slow cognitive impairment.[18] There is experimental evidence that melatonin has anti-amyloidogenic properties;[19] but conversely in a rotenone model

of PD, melatonin appeared to worsen the disease state.[20] Nonetheless, it is biologically plausible that the inflammation associated with neurodegeneration leads to melatonin deficiency through KP-mediated tryptophan depletion. Such deficiency would be expected to compromise melatonin-mediated antioxidant and free radical scavenger defences, both of which are important in the pathogenesis of neurodegeneration.

2.4. Serotonin

Serotonin is synthesized in the serotonergic neurones of the CNS and the enterochromaffin cells of the gastrointestinal tract.[21] Indeed, the latter is responsible for 95% of the total body's serotonin synthesis and storage.[22] Serotonin released into the circulation from enterochromaffin cells is rapidly taken up by platelets and stored in platelet dense granules, constituting almost all total body circulating serotonin.[23] Serotonin is implicated in the pathophysiology of many psychiatric disorders ranging from depression, anxiety, obsessive–compulsive disorder to eating disorders and dependence.[24–26] The association with such disorders is principally through serotonin deficiency.
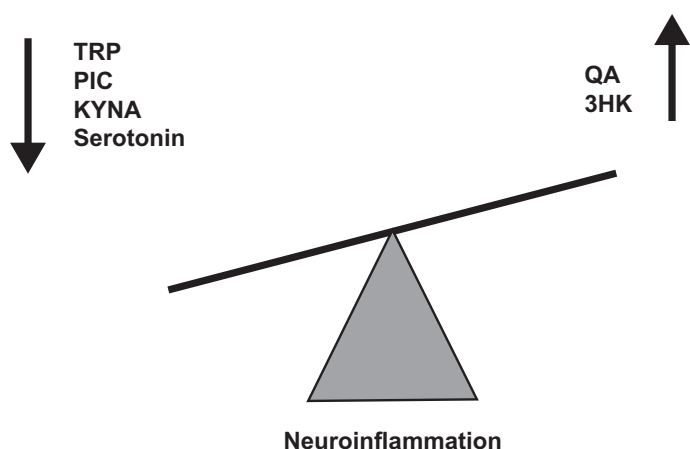
Currently, there is no evidence that serotonin has a direct role in neurodegeneration. Nonetheless, it is tempting to speculate that some of the psychiatric complications of neurodegeneration may have their genesis partly through serotonin deficiency in turn mediated by tryptophan depletion from KP activation (see below and Fig. 2). Certainly increased tryptophan degradation is linked to increased rates of depression and lower quality-of-life in HIV patients.[27]

2.5. The kynurenine pathway

The principal degradative route for tryptophan is the KP; about which much remains unknown despite the recent burgeoning interest. The KP is rich in complexity and subtlety. It differs between species, individuals, cells, and according to the agents that stimulate it. Species differences have hampered rapid progress with the use of knock out mice having limited relevance to humans. Differences between individuals whilst potentially contributing to vulnerability to, or protection from, neurological diseases means that research to elucidate mechanisms of the KP involvement in neurodegeneration have to be performed without pooling samples from different patients. The differential effect of stimuli on the cellular expression of the KP is an area that is only beginning to be appreciated. As will be discussed in more detail below, it is becoming apparent that whilst a particular cell may express all the components of the KP, the extent to which the component enzymes are modified by one stimulus may be different to another stimulus. For example, mesenchymal stem cells, which express all the KP enzymes, respond to IFN-γ stimulation with net quinolinic acid (QA) production but interferon ß results in upregulation of the distal enzymes of the pathway, favouring the degradation of QA.[28]

Induction of the KP is associated with significant immunomodulatory changes for which two non-mutually exclusive mechanisms have been proposed. Firstly, activation of the KP results in tryptophan depletion and impairment of the immune response through lack of this essential amino acid. Secondly, the actions of downstream metabolites of the KP suppress the immune system. For example, increased KP activity in dendritic cells is associated with complete blockage of clonal expansion of T-cells;[29] and tryptophan depletion and KP activation have been implicated in the development of immune tolerance associated with pregnancy and persistence of tumours.[30]

3. The Kynurenine Pathway Enzymes and their Products

Most of the work on the KP has focussed on indoleamine 2,3-dioxygenase (IDO)/tryptophan dioxygen-

TRP
PIC
KYNA
Serotonin

QA
3HK

Neuroinflammation

Figure 2. The Equilibrium of the Kynurenine Pathway in Neuroinflammation. **Abbreviations:** 3HK, 3-hydroxykynurenine; KYNA, kynurenic acid; PIC, picolinic acid; QA, quinolinic acid; TRP, tryptophan.

ase (TDO) particularly in relation to the factors that can modulate the activity of the latter enzymes. However, it is becoming clear that the other KP enzymes can also be significantly modulated. Furthermore, the following discussion is based on the KP enzymes acting "normally" in a variety of disease states. While this may be true for the most part there is reason to suspect that the KP may be altered in particular cells as a result of chronic activation or other processes. To illustrate this point, Guillemin et al showed that human neurones transformed into neuroblastoma cells changed their KP machinery from low net picolinic acid (PIC) production to high net QA production.[31] Similarly, SV-40 transformed human brain microvascular endothelial cells have essentially no functional KP in contrast to human brain microvascular endothelial cells (Owe-Young et al[32] and unpublished data).

The principal component enzymes and products of the KP will now be discussed in detail.

3.1. Indoleamine 2,3-dioxygenase

Indoleamine 2,3-dioxygenase is a haem containing glycoprotein, which has two isoforms, IDO-1 and IDO-2. It is expressed widely throughout the brain and its supporting vasculature but particularly within the choroid plexus and pineal gland.[33] IDO-1 is one of the chief cellular mechanisms to combat oxidative stress: superoxide dismutase being the only other enzyme that can use superoxide as a substrate. The substrates for IDO-1 are broad and in addition to tryptophan there are other indoleamines such as tryptamine, serotonin and melatonin. Relatively little is known about IDO-2 as it has only recently been described. It is thought that it uses similar substrates to IDO-1.[34] Nonetheless, the clinical significance of IDO-2 at this stage is under some doubt.[35]

Nitric oxide, interleukin-4, peroxynitrite and transforming growth factor beta inhibit IDO-1 but it is unclear whether these also inhibit IDO-2.[36,37] The interferons, especially IFN-γ, acting via STAT-1 and IRF-1, lipopolysaccharide, tumour necrosis factor alpha (TNFα), platelet activating factor, the HIV regulatory proteins *nef* and *tat*, CTLA-4 (via ligation of CD80/CD86) and the tumour suppressor Bin1 activate IDO-1—again their importance for IDO2 remains to be determined.[36,38] It seems likely that other factors

that can regulate the activity of this enzyme will be discovered.

3.2. Tryptophan 2,3-dioxygenase

Tryptophan 2,3-dioxygenase (TDO) is very similar to IDO-1 with the exception that it is induced by tryptophan, tryptophan analogues and glucocorticoids; these essentially have no effect on IDO-1 or IDO-2. TDO is inhibited by indoleamines and nicotinamide analogues[39,40] as well as antidepressants, especially tricyclic antidepressant medications and some selective serotonin reuptake inhibitors.[41–46] Systemically, the majority of TDO activity is in the liver.

3.3. Kynurenine

Kynurenine (KYN) is the next important KP product. Along with the other KP metabolites 3-hydroxykynurenine (3-OH-KYN) and anthranilic acid it can cross the blood brain barrier well; whereas kynurenic acid, 3-hydroxyanthranilic acid and QA cross poorly.[47,48] Transport across the blood brain barrier is by the neutral amino acid carrier.[47] KYN's physiological concentration in the brain is 2 μM.[49] It is metabolized in three distinct ways, serving as a substrate for kynureninase yielding anthranilic acid; for kynurenine aminotransferases (KATs) forming kynurenic acid (KYNA); and for kynurenine-3-hydroxylase giving rise to 3-OH-KYN.

The normal physiological roles for KYN are only poorly understood but there is evidence for its importance in mediating vasodilatation albeit at this stage in rabbits.[50,51] Nonetheless, given the finding that endothelial cells switch production from kynurenic acid to kynurenine under inflammatory signals, there is the real likelihood that activation of the KP in endothelial cells is important in vascular inflammation.[32]

3.4. Kynurenine-3-hydroxylase and 3-hydroxykynurenine

Kynurenine-3-hydroxylase, also known as kynurenine monoxygenase, produces 3-hydroxykynurenine (3-HK) from KYN. Its position in the KP gives it substantial significance: its activity principally determines whether KP activation in the cell will be neuroprotective through the generation of kynurenic acid or neurotoxic through production of the more distal KP metabolites. Kynurenine-3-hydroxylase activity is upregulated by the pro-inflammatory cytokine IFN-γ.[52]

3-HK is the substrate for kynureninase, which produces 3-hydroxyanthranilic acid. Less commonly and probably less significantly, 3-HK can be processed by KATs (see below) to give xanthurenic acid.

3-HK is neurotoxic by being pro-excitotoxic and generating free radicals,[53,54] though the latter is the dominant mechanism in killing cortical and striatal neurones.[55–58] Indeed, 3-HK can be converted to quinoneimines with the accompanying generation of reactive oxygen species;[59] however, it is a less potent toxin when compared to QA. Uptake of 3-HK into the cell is required for neurotoxicity as competition with large neutral amino acids can prevent damage by blocking uptake.[57,60] Furthermore, there is evidence that 3-HK inhibits complexes I, II and IV of the mitochondrial respiratory chain.[61]

3.5. Kynurenine aminotransferases

There are at least three isoforms of KAT: I, II, and III, which are involved in the transamination of L-kynurenine to kynurenic acid (KYNA). In addition, KAT I and II transaminate glutamine and α-aminoadipate respectively.[62] KAT II is the most important in the human brain. Under physiological conditions, it is localized mainly in astrocytes,[63] but it is also present in some neurones in the hippocampus and striatum as well most of the neurones in the medulla and spinal cord.[64,65] Little KAT activity is found in microglia.[51] KAT-II is more specific for KYN as a substrate. Thus, large amounts of newly produced KYNA in the brain can be attributed to KAT-II activity.[66] The novel KAT III has a pH optimum of 8.0 and a low capacity to transaminate glutamine or α-aminoadipate (respectively the classic substrates of KAT I and II). The enzyme is inhibited by aspartate, glutamate, and quisqualate but is insensitive to blockade by glutamine.[62]

3.6. Kynurenic acid

Dependent upon its concentration KYNA is an antagonist at four different receptors. It has a particularly high affinity for the glycine-binding site of the NMDA receptor, blocking its activity in low micromolar concentrations (IC50 ~7.9–15 µM).[67,68] Blockade of the glutamate-binding site of the NMDA receptor complex requires concentrations 10–20-times higher than those for the glycine site (EC50 ~200–500 µM)[67], whereas KYNA exhibits a weak

antagonistic effect on the α-amino-3-hydroxy-5-methyl-isoxazolepropionate (AMPA) and kainate receptors.[69,70] A recently identified site of action for KYNA is the α-7 nicotinic acetylcholine receptor, where it acts in a non-competitive manner (IC50 ~7 µM).[71] NMDA receptors have been found to be substantially less sensitive than α-7 nicotinic receptors to KYNA.[51] Curiously, KYNA is ineffective as an antagonist at the glycine site in cerebellar granule cells.[72]

KYNA thus can potentially antagonize some of the effects of QA and other excitotoxins but it is noteworthy that in disease states where excess QA is produced there is insufficient KYNA to block its neurotoxic effects.[73] *In vitro* KYNA inhibits the dopaminergic neuronal death on exposure to 1-methyl-4-phenylpyridinium[74] but KYNA penetrates the blood brain barrier poorly therefore administration peripherally offers little hope of therapeutic neuroprotection.[47] However, some KYNA derivatives do cross the blood brain barrier and have been assessed for their neuroprotective effect in a rat model.[75] The mechanism(s) for KYNA catabolism or re-uptake has yet to be established and it could yet provide other targets for therapeutic intervention.[51] Recently KYNA has been shown to trigger firm arrest of leukocytes to vascular endothelium under conditions of flow.[76] Therefore KYNA may also act as an early mediator for inflammatory cell entry into the CNS.

3.7. 3-Hydroxyanthranilic acid

Three-hydroxyanthranilic acid (3-HAA) is the product of the catabolism of 3-HK by kynureninase or to a lesser extent metabolism of anthranilic acid. 3-HAA is metabolised by 3-hydroxyanthralinic acid oxygenase to an intermediate (α-amino-ω-carboxymuconoic acid semialdehyde); before a non-enzymatically-induced rearrangement occurs to form QA. A minority of 3-HAA is enzymatically metabolised to PIC by 2-amino-3-carboxymuconate-semialdehyde decarboxylase (ACMSD). Elevated levels of 3HAA have been documented in several neurodegenerative diseases.[61] Noted direct effects of 3-HAA include *in vitro* apoptotic cell death of neurones,[57] macrophages and monocytes.[77] The cellular apoptosis is thought to stem from mitochondrial dysfunction as 3-HAA inhibits mitochondrial complexes I and II.[61] Non-toxic levels of 3-HAA may have a role in inhibition of

homeostatic proliferation of CD8+ T-cells but 3-HAA does not affect antigen stimulus-driven proliferation of these cells.[78] 3-HAA also inhibits nitric oxide synthetase (although not in microglial cells) and nuclear factor κB expression;[79,80] of which the former could result in positive feedback and upregulation of IDO activity, which is inhibited by nitric oxide, as well as neuronal dysfunction through impairment of nitric oxide's neurotransmitter function.[36]

3.8. Xanthurenic acid

A minority of 3-HK is metabolised to xanthurenic acid by KAT and subsequently to 8-hydroxyquinaldic acid. The function of xanthurenic acid is not clear. It may act as both an antioxidant and pro-oxidant.[81] It is pro-apoptotic accelerating caspase activation[82] and recently has been implicated as a novel neurotransmitter in the rat brain, possibly through the action of a specific synaptic receptor.[83]

3.9. Quinolinic acid

QA is found in nanomolar concentrations in healthy brain tissue. Its neurotoxicity is mediated through several pathways. It is only a weak competitive agonist of NMDA receptors acting on the subgroup containing the NR2A and NR2B subunits;[84,85] where it has a low receptor affinity (ED50 > 100 μM). Therefore levels of QA must be raised by several orders of magnitude to exert excitotoxic effects via NMDA receptors.[51] However, QA can cause stimulation of NMDA receptors independently of its agonist action through inhibiting astrocytic glutamate uptake, increasing synaptosomal release and reducing its catabolism by astrocytes through inhibiting glutamine synthase activity.[86,87] Alternative routes for neurotoxicity include production of reactive oxygen species, mitochondrial dysfunction and lipid peroxidation.[88–90] This is supported by the observation that free radical scavengers and anti-oxidants reduce QA-induced neurotoxicity.[91–93] Nitric oxide potentiates QA-induced lipid peroxidation[90] and 3-HK and 6-hydroxydopamine act synergistically with QA causing increased neurotoxicity.[36] Levels of QA only slightly greater than that found in healthy brain tissue can cause neurotoxicity when cells are exposed for several hours[94–96] or weeks;[97] with some neurones being damaged after exposure to only 100 nM QA.[98,99] Concentrations of 350 nM for 5 weeks were shown by Kerr et al[100,101] to induce changes in the neuronal cytoskeleton, which in turn result in dendritic

varicosities and damaged microtubules.[60,102] As the only mechanisms for removal of QA appear to be through the blood stream or further metabolism in the KP pathway, acute rises in QA concentration may be particularly toxic for neurones whereas more subacute rises better tolerated.[60] Spinal neurones are particularly sensitive to QA with approximately half dying when exposed to concentrations of 100 nM.[36] Cortical neurones have varying susceptibility, with the expression of low levels of Bcl-2-i being reported to correlate with their vulnerability to QA neurotoxicity.[103] Differences in neuronal vulnerability to QA-induced NMDA receptor-mediated neuronal apoptosis may be of developmental importance in shaping maturation of the CNS.[60] An indirect mechanism through which QA might exert neurotoxicity involves S100ß. Activated astrocytes release the calcium-binding protein S100ß, which in fact can upregulate macrophage QA production; and conversely QA can induce astrocytic S100ß production.[104] Whilst a low concentration S100ß is neuroprotective at micromolar concentrations it can induce astrocytic and neuronal apoptosis.[105,106] Lastly, QA is toxic to oligodendrocytes *in vitro*, where after exposure to mM concentrations of QA the cells undergo apoptosis.[107]

3.10. 2-amino-3-carboxymuconate semialdehyde decarboxylase

ACMSD, also known as picolinic acid decarboxylase, is a critical enzyme in the KP as it directly affects the equilibrium between QA and PIC. Cloning and sequencing of the enzyme reveals it to have little homology with any other mammalian enzyme and it is expressed at low levels in mouse brain tissue.[108] Two alternatively spliced transcripts are recognised in humans (ACMSD-1 and 2), of which only ACMSD-1 has enzymatic activity.[109] It can be inhibited by QA, PIC and KYN.[109] A low protein or low polyunsaturated fatty acid diet will down regulate ACMSD expression, whereas adrenaline, glucocorticoids, female hormones and diabetes lead to up regulation.[108] Recent research has ascertained differences in expression of ACMSD by human neurones in health and diseased states, which is discussed further in section 4.[31]

3.11. Picolinic acid

PIC within the brain is an endogenous neuroprotective compound that human primary neurones are able to produce in μM concentrations.[110] Levels rise with

age and secretion into CSF follows a diurnal pattern being found in highest concentration between 11 pm and 4 am.[111] PIC protects both cholinergic and dopaminergic neurones against QA neurotoxicity;[112,113] and in nM concentrations it protects against QA and kainic acid-induced neurotoxicity after injection in rat brains.[114,115] PIC is also considered the major endogenous metal chelator within the brain; being the most efficient chelator for minerals such as chromium, zinc, manganese, copper, and iron. This may have relevance for several neurodegenerative diseases, including AD and PD, where such metals are thought to be cofactors for protein aggregation; and for which strategies for their chelation are proposed as therapy.[116,117] PIC has immunomodulatory effects upon macrophages potentiating their effects against *Mycobacterium tuberculosis*, stimulating a Th-1 response;[118] one mechanism for this action implicates the role iron chelation.[119] PIC has also been reported to have anti-viral properties inhibiting replication of both HIV and herpes simplex virus in cell culture.[120]

3.12. Quinolinic acid phosphoribosyl transferase

Quinolinic acid phosphoribosyl transferase (QPRT) metabolises QA to nicotinic ribonucleotide. Within the CNS the enzyme is found predominantly in glial cells and is located intracellularly within cytoplasmic bodies, which may prevent intracellular degradation of QA or allow secretion of the enzyme to counteract elevated extracellular concentrations of its substrate.[36] QPRT activity does not appear to be inducible, rather it is constitutively expressed and therefore *in vivo* it may be saturated resulting in accumulation of QA and consequent toxicity.[121]

3.13. Nicotinamide adenine dinucleotide

NAD+, a pyridine nucleotide, is one of the end products of the KP and is essential for cell survival.[60,122] In particular it is a cofactor for the DNA repair enzyme poly(ADP-ribose) polymerase (PARP)—an essential intracellular enzyme for repair of DNA damage caused by reactive oxygen species. Excessive activity of PARP causes intracellular NAD+ depletion and contributes to cell death. Therefore some investigators have proposed that the KP is a cellular protective pathway as NAD+ is a metabolic product. However, data from Braidy et al[123] demonstrate that at least in human astrocytes and neurones this is only partly correct. The KP product QA at concentrations greater than 150 nM leads to a progressive dose dependent decrease in intracellular NAD+ whilst concentrations below 50 nM were associated with an increase in NAD+.
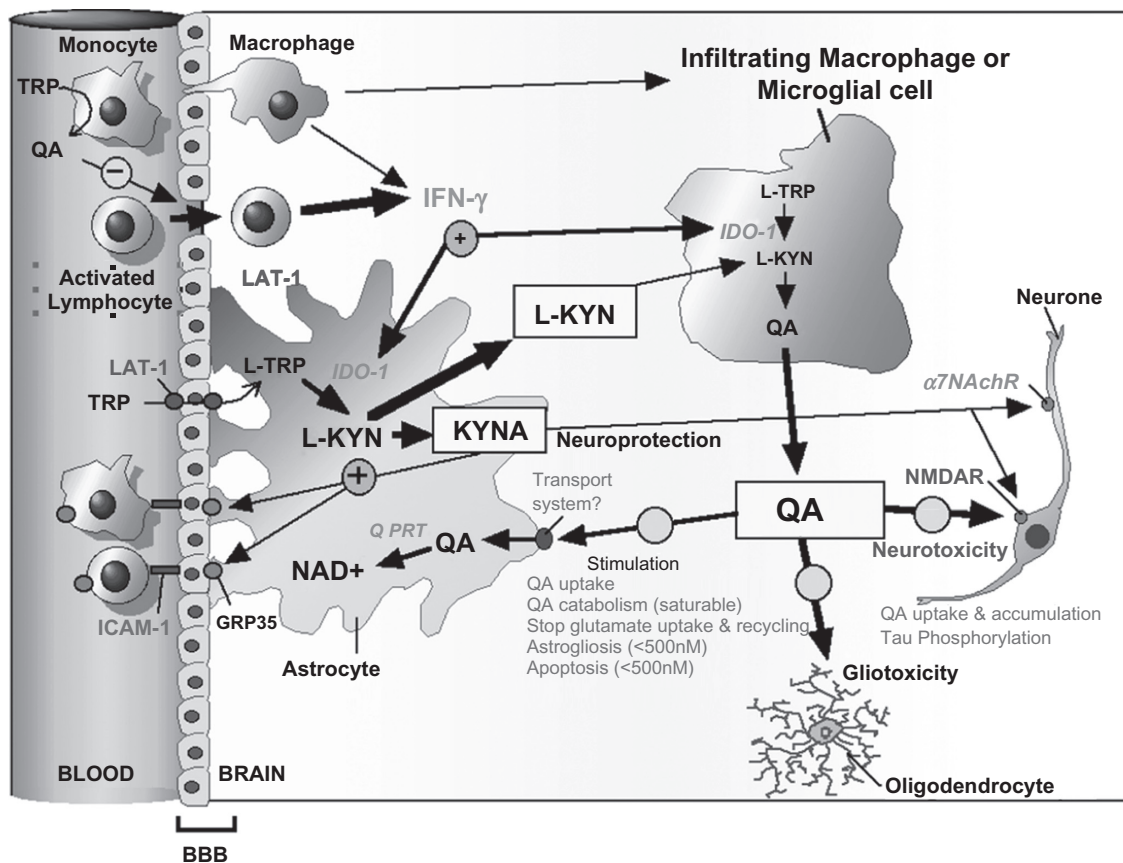
4. Cellular Representation of the Kynurenine Pathway in the Brain

The cellular location of the KP in the brain is only partly understood (see Fig. 3). It is complete in cells of monocytic lineage including macrophages and microglia.[29,124] Macrophages have greater capacity to produce QA than microglia and express higher levels of IDO, kynureninase and kynurenine-3-hydroxylase.[110] The pathway is partly present in human astrocytes,[125] neurones[110] and endothelial cells[126] as key enzymes are not expressed. Preliminary data indicates in that the KP is complete and active in both mesenchymal and neural stem cells.

Astrocytes lack kynurenine-3-hydroxylase and therefore produce only early metabolites KYN, in μM concentration and KYNA in nM concentration. Astrocytes do not produce QA but instead can up take it and catabolise it.[126] Similarly brain microvascular endothelial cells do not express kynurenine-3-hydroxylase, 3-hydroxyanthranilic acid oxygenase and ACMSD, which result in net production basally by the KP of KYN or with induction by IFN-γ, KYNA.[32] In contrast, blood brain barrier pericytes do not produce KYNA and only KYN after IFN-γ induction but do secrete low levels of the distal KP metabolite PIC; although kynurenine-3-hydroxylase has not been shown in these cells.[32] Both astrocytes and blood brain barrier endothelial cells express low levels of QPRT and thus have limited ability to metabolise and mitigate against the toxic effects of exogenously produced QA.[32,126] Importantly, cells of the blood brain barrier are capable of transducing systemic inflammation, without breakdown of blood brain barrier integrity, as basolaterally excreted KYN can be metabolised by brain microglia to produce QA.[32]

Neurones can express both the enzymes IDO-1, IDO-2 and TDO as demonstrated in the cytoplasm immunohistochemically in contrast to microglia, which do not express TDO.[31] There appears to be a reciprocal relationship between TDO and IDO-1 in primary neurones whereby IFN-γ-induced IDO-1 expression is associated with a decrease in TDO

Figure 3. Current Understanding of the Kynurenine Pathway in Brain Inflammation.
Abbreviations: α-7NAchR, α-7 nicotinic acetylcholine receptor; 3HK, 3-hydroxykynurenine; LAT-1, L-amino acid transporter 1; L-KYN, L-kynurenine; KYNA, kynurenic acid; IDO-1, Indoleamine 2,3-dioxygenase 1; NAD+, nicotinamide adenine dinucleotide; NMDAR, NMDA receptor; PIC, picolinic acid; QA, quinolinic acid; QPRT, quinolinic acid phosphoribosyl transferase; L-TRP, tryptophan.

production. Human neurones do not produce QA, instead expressing ACMSD that catalyses conversion of α-amino-ω-carboxymuconoic acid semialdehyde to PIC.[31] However, malignant cells of neuronal origin (SK-N-SH neuroblastoma cell line) can produce QA. Human and rat neurones express KAT-I, -II, and -III and thus can produce neuroprotective KYNA.[31,127] Rat permanently immature oligodendrocytes express KAT-I and -II and produce KYNA but this has yet to be reported in human oligodendroglia.[128] Whilst it is clear that malignant transformation can change neuronal expression of the KP it is less clear whether this can occur with different anatomical localisation within the brain or with changes associated with other disease states.

5. General Pathogenetic Framework for Neurodegenerative Diseases

While there are many aspects of neurodegenerative diseases that are specific to the disease in question,

there are mechanisms that are common to most, if not all, of them. A frequently articulated model is that there is a breakdown of cellular defence mechanisms that then leads to a cascade of damage. In broad terms, a pathogenic insult, which in the case of most neurodegenerative diseases often appears to be a misfolded protein, leads to activation of cellular defence pathways. These include heat shock proteins, endoplasmic reticulum chaperones, the ubiquitin-proteasome complex, autophagy, possibly the KP through production of PIC, and the P-glycoprotein system. Most of these defences are well known and documented but the importance of PIC is only emerging. PIC is up regulated in a variety of disease states,[129] and as mentioned previously, it is the most potent endogenous metal chelator and therefore may be important in cellular defence against the effects of protein misfolding.[130] In addition it is increasingly recognised that neurodegeneration is accompanied by an inflammatory immune response.

Pathologically there is evidence in many neurodegenerative diseases for disturbance in these cellular defence pathways. In AD, PD and motor neurone disease inhibition of the ubiquitin-proteasome complex occurs;[131,132] and evidence from several investigators points to HIV inhibiting this system as well.[133–135] Autophagy is inhibited by HIV and in neurodegenerative diseases.[136–138] Furthermore, dysfunction of the P-glycoprotein system is thought to have a role in the pathogenesis of some neurodegenerative diseases, most particularly PD through its role in the removal of potential toxins,[139,140] and there is some evidence that it is important in the normal clearance of amyloid from the brain.[141] Interestingly, P-glycoprotein expression is deliberately inhibited in HIV therapy to enhance the efficacy of particular antiretroviral agents, the protease inhibitors, and it is possible, but remains to be established, that such inhibition could lead to the accumulation of amyloid within the brain with consequent tissue damage.

Oxidative stress is increasingly thought to be a final common pathway for several neurodegenerative diseases such as AD in addition to HAND.[142,143] Furthermore, nitrosative stress with peroxynitrite formation leading to modification of tyrosines in proteins is considered to enhance the aggregation of α-synuclein, which in turn is pathogenically significant in PD as well as HAND.[144,145]

Evidence of increased inflammation is common to many neurodegenerative diseases and will be reviewed by syndrome in section 6; however, common themes exist. For instance, immune activation can be interpreted from two standpoints: whether inflammation is "beneficial" and a protective response to damage, or a detrimental pathological process. Following acute or chronic exposure there is evidence to indicate differences in immune response to cytokines. For instance, chronic exposure of microglia to monocyte chemoattractant protein-1 (MCP-1), or lipopolysaccharide, is associated with a more neurotoxic microglial phenotype while acute exposure is linked to a more phagocytic phenotype.[146] The increase in immune activation products, especially MCP-1, as found in chronic neurodegenerative diseases is therefore likely to render a more neurotoxic microglial environment. Activation of microglia and monocytes can be modulated by mutations affecting the innate immune system; for example loss of function of Toll-like receptor-4

reduces microglia activation to amyloid plaques in a cell culture model AD.[147] Conversely, decreased immune surveillance, for which there is evidence in AD, perhaps representing a "premature immunosenescence", might hasten accumulation of neurotoxicity through failure to remove toxic products.[148] Lastly, the blood brain barrier is frequently impaired in both HAND and neurodegenerative diseases, which might allow access to the CNS to neurotoxic compounds.[149,150]

The pathogenic insult and the defence mechanisms are in a dynamic equilibrium until the burden of the insult exceeds the defence capacity or the defence pathways become exhausted. The consequences then are the activation of further inflammation, excitotoxicity, oxidative and nitrosative stress, mitochondrial dysfunction, and transcription dysregulation. The inter-relationships among these are complex and often bi-directional. Nonetheless, the end result is cell dysfunction and death, and consequently, neurodegeneration.

6. The Role of the Kynurenine Pathway in Specific Diseases
6.1. Alzheimer's disease

AD, an age-related neurodegenerative disorder with progressive loss of memory and deterioration in cognition, is characterized by extracellular plaques of aggregated beta-amyloid (Aβ), and intracellular neurofibrillary tangles that contain hyperphosphorylated tau protein. Inflammation is a hallmark of the neuropathology of AD; activated astrocytes and microglia surround plaques and elevated levels of microglial-derived inflammatory cytokines are found within AD brains.[151] The evidence for involvement of the KP in AD may be categorized into direct and indirect or circumstantial.[73] Direct evidence may be found systemically as well as in the AD brain. AD patients show decreased serum levels of tryptophan, which correlates with the level of cognitive impairment, increased serum KYN, and increase in the KYN/tryptophan ratio.[152,153] Acute tryptophan depletion is associated with worsening of cognitive function in AD, illustrating the importance of serotonergic function in this disease.[154] In AD CSF levels of KYNA are lower than controls but there are no significant differences in CSF QA concentration between these groups.[155]

However, KYNA is elevated throughout the brain but to greatest extent in the caudate and putamen, where in addition, an increase in KAT-1 is found.[156] Furthermore, using an immunohistochemistry triple staining method, there is evidence for IDO over-expression and QA over-production in microglia, astrocytes and neurones within sections of the medial temporal lobe, frontal and cingulate cortex of AD brains.[157] Microglial and astrocytic expression of IDO and QA are highest at the perimeter of senile plaques; but in addition, QA staining was observed within the neuronal cell body and granular deposits as well as uniformly labelling neurofibrillary tangles. Laser capture microdissection applied to AD brain hippocampal sections has allowed demonstration that newly formed senile plaques, which are characterised by marked immune activity with high density of microglia/macrophages, contain very high amounts of QA, in contrast to those found at the end stage of AD.[158] Immunohistochemistry also reveals co-localisation of QA with hyperphosphorylated tau—the intracellular pathological hallmark of AD. *In vitro* the amyoidogenic fragment of Aβ (Aβ1-42), but not another Aβ fragment or prion peptides, stimulates increased QA production by human primary microglia and macrophages through induction of IDO.[159] Within primary cultures of neurones, pathophysiological levels of QA increase tau phosphorylation and upregulate 10 neuronal genes associated with AD.[102] As tau phosphorylation is a prerequisite for neurofibrillary tangle formation, upregulation *in vivo* of phosphorylase activity might be pathophysiologically significant in AD. Interestingly, the AD drug and NMDA receptor antagonist memantine inhibits the QA-mediated increased tau phosphorylation *in vitro*. Therefore the effect of QA on major tau phosphorylases is likely to be glutamatergic-mediated.

Indirect evidence for the role of the KP in AD relate to observations of QA metabolism associated with advancing age and the known attributes of the KP in cells whose activation is associated with AD. It can be subdivided into processes potentially associated with the neurodegeneration, or those exerting a potentially functional effect. For example, elevated levels KYNA, an ionotropic glutamate receptor antagonist, might impair memory formation as the physiological basis of memory requires activation of these receptors.[51] Ageing is associated with increasing

brain levels of QA and AD with blood brain barrier dysfunction.[150,160] Microglia and astrocytes, when activated as occurs in AD, show upregulation of the KP. QA is known to inhibit glutamate uptake by astrocytes that might enhance excitotoxic damage to neurones in AD.[86] Interestingly the NR1/2A or 2B subunits of the NMDA receptor, on which QA acts, show altered expression in the hippocampus and entorhinal cortex of AD.[161] Furthermore, QA can induce IL-1b production by astrocytes and macrophages, which can promote neuronal synthesis and processing of Aß.[162] As discussed above, QA can promote production of reactive oxygen species and lipid peroxidation as well as promoting mitochondrial dysfunction in the brain. AD is associated with increased markers of oxidative stress and products of lipid peroxidation in CSF,[163,164] as well as reduced levels of complex IV in the electron transport chain indicating mitochondrial dysfunction.[165] Therefore circumstantial evidence exists implicating QA indirectly in AD through contributing to excitotoxic neuronal damage, promotion of oxidative stress and increased Aß production and processing.

6.2. HIV-associated neurocognitive disorder

Cognitive changes in patients infected with the human immunodeficiency virus type-1 (HIV) are common, forming a spectrum from asymptomatic impairment to dementia, and collectively are described as HAND.[166] Prior to the advent of combined anti-retroviral therapy approximately one-third of patients with advanced HIV disease were demented.[167] In resource-rich countries with the widespread availability of combined anti-retroviral therapy the incidence of HIV dementia has fallen but milder forms of HAND continue to occur. Clinically HAND is a syndrome characterised by impairments of motor functioning, behaviour and cognition. Pathologically, the highest burden of disease is found within the frontal lobes and basal ganglia, where marked atrophy can be found as well as subcortical white matter changes. Microscopically, mononuclear inflammatory cell infiltrates, multinucleated giant cells, astrocytosis, activated microglia, loss of dendritic arbour and neuronal loss are seen.[168–170] However, the burden of HIV brain infection does not reflect the degree of inflammation or cognitive impairment;[171] and within the brain, productive HIV infection

only occurs in cells of monocyte lineage.[172] Instead, a stronger correlation is found between markers of inflammation, such as microglial activation or markers of immune activation in CSF, and impairment.[173,174] Therefore, indirect viral-initiated and driven mechanisms are key to the pathogenesis of HAND; putatively mediated through the toxic products of HIV or activated inflammatory cells.

The evidence for involvement of the KP in HAND is both direct and indirect. Significantly elevated CSF levels of QA are found in adults (>150-fold increase) and children with HAND, which correlate with cognitive deficit, but CSF KYNA levels are not altered by such magnitude compared to controls.[175–178] Both serum and CSF tryptophan levels are reduced and KYN to tryptophan ratio increase with disease progression.[179,180] Treatment with one or more antiretrovirals is associated with a fall in CSF QA and increase in serum and CSF tryptophan; and this fall correlates with decrease in CSF HIV viral load, indicating a strong relationship between QA and active infection.[175,181,182] Studies of *post mortem* brain tissue from patients with HIV dementia show highest QA levels in patients with more severe infection, and regionally, the deep grey matter had the highest QA concentrations.[183] Others have reported elevated brain levels of neuroprotective KYNA in the frontal cortex and cerebellum accompanied by elevation of KAT-I and II in frontal cortex and just KAT-I in cerebellum.[184] Regional variations in NMDA receptor subtype and their susceptibility to QA's agonist effect may be important in accounting for the regional pattern of disease seen in HIV dementia.[121] The NMDA receptor is a tetramer consisting of variable combinations of subunits. QA shows greatest agonist activity at the NMDA receptors containing the NR1 plus NR2A or NR2B subunits. These combinations of subunits within NMDA receptors are found to predominate in the basal ganglia but are expressed at low levels in areas of the brain seldom affected in HIV dementia, such as the brain-stem or cerebellum.[185] Within the basal ganglia NMDA receptor function is integral to neuronal circuitry controlling motor function. Therefore, these observations might link QA with the pathological and clinical phenotypic observations of HAND.

Indirect evidence of a pathogenetic role for QA in HAND relate to the observations of the effect of QA on neurones and astrocytes in cell culture, the effect on the KP by the inflammatory milieu described in HAND, and the relationship of macrophage-tropic HIV to the KP. As described above QA can induce neuronal necrosis and apoptosis both of which are well described in the neuropathology of HIV dementia. Furthermore, proinflammatory cytokines, such as IL-1b and IFN-γ, which induce IDO causing QA production, are elevated in the brains and serum of HIV patients.[186,187] In fact, QA may amplify the inflammatory process by inducing astrocytes to produce large amounts of MCP-1, resulting in increasing ingress of HIV-infected monocytes.[121] Although this may be "double-edged" as MCP-1 is neuroprotective for neurones and astrocytes.[188] Macrophage-tropic HIV is necessary, but not sufficient alone, for HAND. Subsets of macrophage-tropic HIV are both neurotropic and lead to QA production further support the importance of the KP in HAND.[121,189] In addition to the potential neurotoxicity of KP activation, QA production amplifies infection through upregulating CCR5 receptor expression on macrophages and microglia and CXCR4 expression on astrocytes thereby facilitating HIV infection.[121]

Not only are HIV proteins (such as *gp*120, *tat*, *vpr* and *nef*) directly neurotoxic,[190–192] but *tat*, *vpr* and *nef* induce QA production by macrophages.[193] Furthermore, the effect of *tat* on astrocyte IDO-1 expression varies according to the clade of HIV from which the protein originates, with greater activity being associated with the more neurotoxic strain. However, the HIV envelope glycoprotein *gp*120 can stimulate macrophages to produce neurotoxic factors without induction of the KP.[194] Therefore other macrophage neurotoxicity pathways remain to be elucidated in addition to the KP.

6.3. Huntington's disease

HD is an autosomal dominant neurodegenerative disease characterised by a movement disorder and cognitive decline. The genetic locus for the disease is on chromosome 4 where an expansion of a trinucleotide repeat is found in the gene encoding huntingtin. Neuropathologically the disease demonstrates disproportional loss of striatal medium-sized spiny GABAergic neurones as well as evidence of microglia and astrocytic activation. The microglial activation can be assessed non-invasively through

positron emission tomography, using a specific ligand ([11]C-[R]-PK11195), which correlates with disease severity but also the finding that abnormalities precede the onset of symptomatic neurological disease.[195,196] Interest in the role of KP in the pathogenesis of HD stems from the observation that injection of QA into rat striatum shows histological and neurochemical similarities to the disease.[197,198] However, elevated levels of QA are not found in post mortem brain tissue[199] or CSF[200] from HD patients late in the disease in contrast to 3-HK;[201] although elevated brain levels of QA, KYNA and 3-HK are reported early in the disease,[202] paralleling findings in a mouse HD model.[203] Elevated levels of 3-hydroxyanthranilic acid oxygenase but not of KAT or kynurenine-3-hydroxylase have been found in HD, where elevation in the former enzyme correlates with elevated QA levels[204] and it has been suggested that this might relate to 3-HK induction.[60] Furthermore, there is evidence of systemic differences in the KP amongst HD patients. Elevation in the KYN/tryptophan ratio is reported indicating greater IDO activity; but there is no evidence to suggest increased KYNA production from this is a compensatory neuroprotective measure.[205] In fact, within the brain in HD low levels of KYNA and its synthetic enzymes KAT-I and -II have been found, which through loss of the neuroprotective benefit of their product may also contribute to HD pathogenesis.[206,207] Furthermore, deletion of KAT-II in mice results in potentiation of the neurotoxic effect of striatal QA injection.[208]

Recent work has begun to link the perturbations in the KP noted in HD to the known genetic basis for the illness. Polyglutamine repeat diseases are often associated with pathogenetic changes caused by toxic gain of function of the mutant protein. To this end mutant huntingtin is known to cause transcriptional abnormalities in neurones.[209] Furthermore, it has been demonstrated in a yeast model that mutant huntingtin can activate the KP, which can be abrogated by an inhibitor of histone deacetlyase Rpd3.[210] However, yeast with kynurenine-3-hydroxylase and 3-hydroxyanthranilic acid oxygenase gene knockouts are resistant to the KP stimulating effect and toxicity of the protein; whereas those lacking KAT or a gene that encodes an enzyme key to synthesising NAD+ from nicotinic acid result in increased toxicity.[210] Thus enzyme knockouts resulting in reduced QA or 3-HK

production prevent huntingtin toxicity. In contrast, KAT knockouts inhibit production of neuroprotective KYNA, hence worsening mutant huntingtin toxicity. Inhibition of NAD+ production from nicotinic acid is thought likely to upregulate the KP, consequently causing increased huntingtin toxicity.

6.4. Motor neurone disease/amyotrophic lateral sclerosis

The commonest cause of adult-onset motor neurone disease is amyotrophic lateral sclerosis (ALS), which is a progressive disease resulting in degeneration both of upper and lower motor neurones. Clinically the disease is characterised by the onset of progressive weakness that may affect limb, bulbar and diaphragm musculature; however, cognitive deficits can occur in some patients. The aetiology is unknown in the majority with only a minority (~10%) having a genetic cause. The majority of patients with genetic forms of ALS have mutations affecting the superoxide dismutase gene indicating the importance of oxidative stress to the disease pathogenesis. To that end only one medication has benefit, albeit very modest, in sporadic ALS—riluzole—that targets glutamatergic excitotoxicity. In sporadic disease and disease models dysfunction of protein aggregation, mitochondria and axonal transport can be found.[211] Furthermore, there is evidence for immune activation in ALS as levels of TNFα, IL-1β, IL-6, IFN-γ, and prostaglandin E2 are elevated, some of which can upregulate the KP.[211] Previously published data reported increased CSF KYNA in patients with bulbar onset ALS with severe impairment, but in other clinical phenotypes of ALS lower serum KYNA was associated with increased disease severity.[212] Recently published data demonstrates definite activation of the KP in ALS showing elevation in CSF and serum concentrations of tryptophan, KYN and QA, and reduction in serum PIC.[213] Immunohistochemical studies show activation of microglia with increased neuronal and microglial production of IDO and QA. Therefore evidence exists to indicate a role for the KP in this degenerative disease, suggesting imbalance favouring net production of neurotoxic compounds. The explanation for the raised tryptophan levels, with KP activation, and whether microglial-derived QA plays a role in excitotoxic neuronal death in ALS remains to be established.

6.5. Multiple sclerosis

The role of the KP in multiple sclerosis is reviewed elsewhere in this edition of the journal (see Lim et al) and therefore is not discussed further in this review.

6.6. Parkinson's disease

PD is an idiopathic neurodegenerative disease clinically characterised primarily by a movement disorder, although increasingly non-motor symptoms are recognised, such as cognitive impairment and autonomic nervous system dysfunction. PD pathologically is associated with loss of dopaminergic neurones projecting from the substantia nigra pars compacta in the brain-stem to the basal ganglia; as well as loss of ascending cholinergic, noradrenergic and serotonergic neurones from other brain-stem nuclei. Intracellular proteinaceous inclusions named Lewy bodies are found in dopaminergic neurones within and outside the CNS in PD. Lewy bodies consist of aggregates of α synuclein, ubiquitin, neurofilaments and α B crystalline, which are thought to occur as a result of dysfunction of the intracellular proteasomal system. Dopaminergic neurones of the substantia nigra possess NMDA receptors and receive glutamatergic input from multiple cortical and subcortical structures. The exact pathogenic mechanisms resulting in PD have yet fully to be ascertained. However, there is evidence to indicate roles for mitochondrial dysfunction, increased oxidative stress, and production of endogenous excitotoxins.[51] Rarely is the disease purely hereditary in nature and environmental factors are thought likely to play key roles in pathogenesis. Increasingly, inflammation is recognised pathogenetically in PD both histopathologically as well as through measurement of inflammatory markers in blood, CSF and brain.[214] Therefore the potential for involvement of the KP in PD is wide. However, in contrast to animal models of HD, QA injection into brain produces relative sparing of damage to the substantia nigra compared to striatal, pallidal and hippocampal structures.[215]

Evidence for mitochondrial dysfunction in PD is found systemically in platelets where complex 1 activity is reduced[216] and similarly *post mortem* in tissue from the substantia nigra.[217] Such mitochondrial dysfunction is thought to predispose dopaminergic neurones to excitotoxic dysfunction, particularly through glutamatergic stimulation, which can be modulated by the KP.[218] Inflammation is recognised in PD to affect the substantia nigra where activated microglia and astrocytes are found;[219,220] and throughout the brain increased CD8+ and CD4+ T-cells are reported compared to controls.[221] Of particular interest is the reported low density of astrocytes in healthy individuals in areas associated with greatest pathological change in PD, although astrocytes numbers are increased in diseased substantia nigra in PD.[220] Hypothetically, constitutively low astrocyte density in the substantia nigra might predispose to reduced potential for free radical detoxification. Despite an increased number of reactive astrocytes in the substantia nigra at death in PD patients and the role of these cells in KYNA production, *post mortem* studies have revealed reduced levels of KYNA in the substantia nigra and frontal cortex with increased levels of 3-OH-KYN.[222] This deficit might arise from loss or blocking of astrocytic KP activity (as these cells lack kynurenine-3-hydroxylase) with elevated levels of 3-OH-KYN arising from direction of the KP in cells expressing the full pathway, such as microglia, away from KYNA production. Decreased KAT-I levels in mouse substantia nigra and KAT-II in rat cortical slices have been described in animal models of PD;[223,224] with the reduced levels of KAT-I found in neurones of the substantia nigra but conversely increased KAT-I–expressing astrocytes reported.[225] Pathogenetically, increased levels of 3-OH-KYN can lead to greater neurotoxicity through heightened oxidative stress. Whereas low levels of KYNA could reduce antagonism of NMDA receptors and consequently increase excitotoxicity with pathological consequences, as *in vitro*, NMDA receptor activation is associated with substantia nigra dopaminergic neurone death.[226] Furthermore, reduced KYNA antagonism of NMDA receptors might also be of pathogenic importance as the neurotoxicity of putative environmental causes of PD, as modelled by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), are thought to be mediated by glutamatergic excitotoxicity. However, in rats MPTP can itself reduce KYNA levels through inhibition of KAT-1 and II.[224] A further twist in explanation of the *post mortem* reduction in KYNA levels in PD substantia nigra is that exogenous levodopa administration to rats lowers KYNA levels through inhibition of KAT.[227] Therefore treatment itself might affect KYNA levels, albeit that this could still enhance neurotoxicity. However, loss of KYNA antagonism at α-7 nicotinic receptors may be of benefit in PD.[71] Stimulation of microglial

α-7 nicotinic receptors inhibits their activation,[228] and nicotinic stimulation reduces dopaminergic neuronal death when co-cultured with microglia.[229] It has even been hypothesised that the apparent protective effect of smoking against PD results from nicotinic inhibition of microglial activation and that selective α-7 nicotinic receptor agonists might be candidate PD treatments.[214]

7. Conclusion

Neurodegenerative diseases and HAND share many common potential pathogenetic mechanisms. We have summarised the increasing evidence not only that the KP pathway is activated in a wide variety of neurodegenerative diseases but also that changes in the dynamic equilibrium between its neurotoxic and neuroprotective products results in neural tissue damage. The study of the KP is complicated by its multiple layers and changes in its dynamics between health and disease. However, ultimately it is hoped that the KP will offer avenues for successful therapeutic intervention. To that end, several drugs that block the KP are under investigation. For example, KYNA analogues are in or about to enter clinical trials (L695902, L701324, GV150526A, RPR104632, ZD150526A) for treatment of epilepsy, stroke and possibly PD;[36] and two KP inhibitors are currently in phase III clinical trial for multiple sclerosis (Teriflunomide [Sanofi-Aventis] and Laquinimod [Teva Neuroscience]). Recently, one KP analogue has reached the market (in Japan) as a potent immunomodulative drug for the treatment of multiple sclerosis, asthma, and dermatitis, Tranilast/Rizaben® (Angiogen Ltd), which is an anthranilic acid derivative. However, it remains to be established what role these compounds have in the management of neurodegenerative and neuroinflammatory disease long term.

Acknowledgements

Conflicts of Interest

The authors have no conflicts of interest.

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