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Brain Aging and Disorders of the Central Nervous System: Kynurenines and Drug Metabolism

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Abstract: ***Introduction:*** The kynurenine pathway includes several neuroactive compounds, including kynurenic acid, picolinic acid, 3-hydroxykynurenine and quinolinic acid. The enzymatic cascade of the kynurenine pathway is tightly connected with the immune system, and may provide a link between the immune system and neurotransmission.

Main Areas Covered: Alterations in this cascade are associated with neurodegenerative, neurocognitive, autoimmune and psychiatric disorders, such as Parkinson's disease, Huntington's disease, Alzheimer's disease, multiple sclerosis, amyotrophic lateral sclerosis, migraine or schizophrenia.

Highlights: This review highlights the alterations in this metabolic pathway in the physiological aging process and in different disorders. A survey is also presented of therapeutic possibilities of influencing this metabolic route, which can be achieved through the use of synthetic kynurenic acid analogues, enzyme inhibitors or even nanotechnology.

Keywords: Kynurenine pathway, neurodegeneration, neuroprotection, glutamate excitotoxicity, Parkinson's disease, Alzheimer's disease, multiple sclerosis, migraine, Huntington's disease, schizophrenia, amyotrophic lateral sclerosis, picolinic acid, aging, *Toxoplasma gondii*.

1. RECENT DATA RELATING TO THE MECHANISMS OF DISORDERS OF THE CNS

Chronic progressive neurodegenerative diseases such as Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS) are becoming increasingly more prevalent, which may be related to the aging of the population. The significance of neurological diseases is highlighted by the fact that brain disorders have been stated to be responsible for around 35% of the total burden of all diseases in Europe [1]. Migraine, a common primary headache disorder with an overall prevalence of 16% in the adult population, is listed among the 20 most important causes of disability worldwide [2-3]. The increasing prevalence, the high socioeconomic impact and the limited therapeutic possibilities have generated considerable research interest in recent decades. Although the various neurodegenerative disorders present distinct clinical symptoms, their pathomechanisms share several features. A long line of evidence indicates that neuroinflammation, mitochondrial disturbances, glutamate (Glu) excitotoxicity and oxidative stress are involved to various extents in the neurodegenerative process [4-6]. Neuroinflammation is an important mechanism that has been implicated in the pathomechanism of many neurodegenerative diseases [7-9] and the normal aging process [10]. Activation of the microglia and astrocytes has been detected in neurodegenerative disorders such as PD and HD, and this process may even influence the release of Glu [11-14]. Mitochondrial disturbances result in an energy deficit and the production of free radicals, which results in disruption of the membrane potential and in oxidative stress. Free radicals may lead to protein misfolding or lipid peroxidation, thereby damaging neuronal cells. As the brain has high oxygen and energy demands, it is especially sensitive to energy impairment and oxidative damage. A mitochondrial dysfunction and oxidative damage have been described in AD, PD and ALS [15-18]. Another key mechanism in the neurodegenerative process is Glu-mediated excitotoxicity. Glu, the main excitatory neurotransmitter in the brain, has a crucial role in a number of physiological functions, such as memory formation. However, the overactivation of excitatory amino acid receptors may induce vicious downstream signalling pathways, finally leading to neuronal damage. The N-methyl-D-aspartate (NMDA) receptors (NMDARs) are of oustanding importance in this process. Under physiological conditions, activation of the NMDARs is under strong control, mainly by a voltage-dependent block by magnesium (Mg^{2+}). Accordingly, any disruption of the membrane potential as a consequence of a mitochondrial impairment makes the neurons more vulnerable to excitotoxicity, for it releases Mg^{2+} and allows excessive NMDA activation.

Recent findings strengthen the linkage between the endocannabinoid system (ECS) and the kynurenine pathway (KP) [19-20]. There has been growing interest in the potential of the therapeutic palette of cannabis and cannabinoid-based chemicals in neurological conditions in recent decades. A role of the ECS has been implicated in motor control, cognition, mood, feeding behaviour and pain [21-24]. Alterations in the ECS and/or the benefits of therapy have been considered in PD [26-28], HD [29-31], migraine [20], pain [32, 33] and multiple sclerosis (MS) [34, 35]. The preclinical and clinical research into the value of cannabinoids in movement disorders has been reviewed by Kluger *et al.* [36]. There is an important risk of abuse in the case of cannabis-based drugs [37], but the enhanced endogenous brain kynurenic acid (KYNA) levels could probably mitigate this [19].

The emerging evidence links chronic *Toxoplasma gondii* infections to disorders of the CNS. This obligate intracellular protozoan parasite affects 30-50% of the total human population, the frequency increasing with age [38-39]. Many publications have linked this infection with AD [40], PD [41-42], schizophrenia [43], migraine [44-45], headache [46-48], autism [48-49], autoimmune diseases [50], MS [51] and other diseases. There is evidence that toxoplasmosis has an impact on the KP. The infection causes induction of the expression of indoleamine 2,3-dioxygenase (IDO), the increased formation of L-kynurenine (L-KYN), a decreased level of tryptophan (Trp), and an increased level of dopamine, thereby

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stimulating tachyzoites proliferation [52-53]. Moreover, *T. gondii* infection is associated with persistent (life-long) neuroinflammation, and this abnormality is associated with an increased production of Glu, mitochondrial damage, and oxidative stress [54]. Investigations of the role of such infections in modulation of the KP in different neurological disorders began with schizophrenia [55]. This field promises interesting findings in the future.

The role of the KP has been extensively investigated in immunoregulation, in which the enzyme IDO is of outstanding importance. IDO causes Trp depletion and is responsible for the production of kynurenines, which occurs at the beginning of the enzymatic pathway. IDO is expressed in various immune cells: monocytes, macrophages and microglia [56-57]. The activity of IDO can be enhanced by interferons and lipopolysaccharides. Interferon-γ is considered to be the main activator of IDO. The IDO activation leads to elevations in the levels of the various kynurenines, among them KYNA. IDO counteracts the proliferation of reactive lymphocytes, and can therefore be an important regulator of immune activation. This give rise to a depletion of Trp, whereas quinolinic acid (QUIN) and 3-hydroxyanthranilic acid (3HAA) result in the selective apoptosis of Th1 cells [58-59]. This function is considered to play a significant role as a negative feedback loop in the regulation of the immune response and may contribute to the development of immune tolerance [60-63]. IDO-mediated T cell inhibition affects primarily the Th1 cells however, through the activation of regulatory T cells [57] this process may influence Th2 cell activation as well.

2. THE KYNURENINE PATHWAY (KP)

2.1. The Kynurenine Metabolism

The scientific world has recently been demonstrating increasing interest in the therapeutic potential of the metabolites and enzymes of the main degradation pathway of the essential amino acid Trp. Trp is transported across the blood-brain barrier (BBB) with the assistance of the large neutral amino acid transporter [64]. In the human brain, 95% of the Trp is involved in the KP [65] (the remaining 5% participates in the serotonin pathway and the formation of proteins) (Fig. **1**). This metabolic route is responsible for the synthesis of nicotinamide adenine dinucleotide (NAD) and NAD phosphate, KYNA, xanthurenic acid (XA) and picolinic acid (PIC). The central compound of the KP is L-KYN, formed from Trp, the rate-limiting steps of its synthesis involving the enzymes IDO and tryptophan 2,3-dioxygenase (TDO). Most of the L-KYN (approximately 60%) is taken up from the blood [66] with the aid of the neutral amino acid carrier [67], the remainder being generated locally in the CNS. After the synthesis of L-KYN, the cascade branches into three routes. The first possibility is the synthesis of KYNA from L-KYN through irreversible transamination by kynurenine aminotransferases (KATs). The other main branch of the cascade begins with the formation of the neurotoxic 3-hydroxykynurenine (3HK) through the action of kynurenine-3-monooxygenase (KMO), the third important enzyme in the KP. KMO is responsible for the neurotoxic branch of the cascade, the concentration of KYNA depending indirectly on its activity. Kynureninase converts 3HK to 3HAA. In the third route, kynureninase converts L-KYN to anthranilic acid, which further metabolize to 3HAA. Another neurotoxic metabolite in the route is QUIN, which is synthesized from 3HAA by 3HAA oxygenase (3HAO). QUIN is the precursor of NAD and NADP synthesis (Fig. **1**).

The infiltrating macrophages, activated microglia and neurons are capable of the complete enzymatic cascade within the CNS, whereas the astrocytes and oligodendrocytes lack IDO and KMO and are unable to produce the neurotoxic QUIN [68]. Most of the locally synthesized neuroprotective KYNA and PIC [69] is therefore generated in the astrocytes and neurons, while QUIN is synthesized by the infiltrating macrophages and microglia [70].

The term kynurenines is the overall name for the metabolites of this pathway; most of them display neuroactive properties and three of them (KYNA, 3HK and QUIN) have key roles in certain CNS disorders.

2.2. Neuroactive Kynurenine Metabolites and their Impact on Receptors in the CNS

KYNA: The most characteristic feature of this metabolite is the broad-spectrum, competitive antagonism of all three ionotropic excitatory Glu receptors (the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), the kainate receptor and the NMDAR) at high micromolar concentrations (to approximately the same degree) [70]. It is most active at the NMDARs, after binding at the strychnine-insensitive glycine co-agonist site of the NMDAR complex [71]. NMDAR-mediated excitotoxicity and free radical production are involved in the pathology of many neurodegenerative disorders and the number of endogenous Glu receptor antagonists (similarly to the level of KYNA) is very low. Besides its main impact on the NMDAR complex, KYNA exerts weak antagonistic impacts on the AMPARs and kainate receptors too. However, its effect on the AMPARs depends on its concentration: at low concentrations (nanomolar to micromolar) it behaves as a facilitator, whereas at high concentrations (micromolar to millimolar) it behaves as an inhibitor [72-73].

The α7 nicotinic acetylcholine receptors (nAChRs) are also important targets for KYNA, and under physiological conditions this has proved to be extremely determinative [74]. Its non-competitive antagonistic impact results in reduced acetylcholine, dopamine and Glu signaling [74].

The G protein-coupled receptor 35 (GPR35) and the aryl hydrocarbon receptor have recently been identified as sites of action of KYNA, but their roles in connection with the brain function remain to be clarified. The action of KYNA on GPR35 may trigger the production of inositol trisphosphate and cause Ca^{2+} mobilization. Nevertheless, its function is questionable, because of the expression of GPR35 in the brain is low [75].

Independently of its impact on the receptors, the *in vitro* and *in vivo* evidence confirms that KYNA has antioxidant and free radical scavenger properties [76]; this broadens its neuroprotective features and focuses attention on the importance of KYNA-mediated neuroprotection.

A recent study with the model organism *Caenorhabditis elegans* suggested a new feature of KYNA: it is a nutritional cue that enables behavioural plasticity [77].

QUIN: The neurotoxic properties of QUIN have led to its being widely used in animal models of HD [78-80]. Its neurotoxic features [81] are a consequence of its weak, but specific competitive agonist action on the NMDAR subgroup including NR2A and NR2B [56, 82]. The NMDARs have brain region-specific locations. NMDARs which contain NR2C subunits are hindbrain-specific, while NMDARs with NR2B subunits are found predominantly in the forebrain. This results in regional selectivity, because QUIN binds with 10-fold lower activity to the hindbrain-specific NR2C subunits of the NMDARs as compared with the NR2B subunits [83]. Apart from its activation on the NMDARs, it has a complex neurotoxic potential, including the enhancement of presynaptic Glu release [84-85], the inhibition of astrocytic Glu uptake [85], depletion of the local antioxidant supply [86], the generation of reactive oxygen intermediates [87] and the peroxidation of lipid molecules [82, 88], which depends strictly on the amount of Fe^{2+} [89]. Moreover, by influencing lipid peroxidation, Fe^{2+} directly regulates the binding of QUIN to the NMDARs [70, 90].

3HK: The toxic features of this metabolite are independent of the NMDARs and are connected only to the production of free radicals [91]. Cultured striatal and cortical neurons treated with 3HK exhibited a reduced viability, irregular somata, and shrunken and

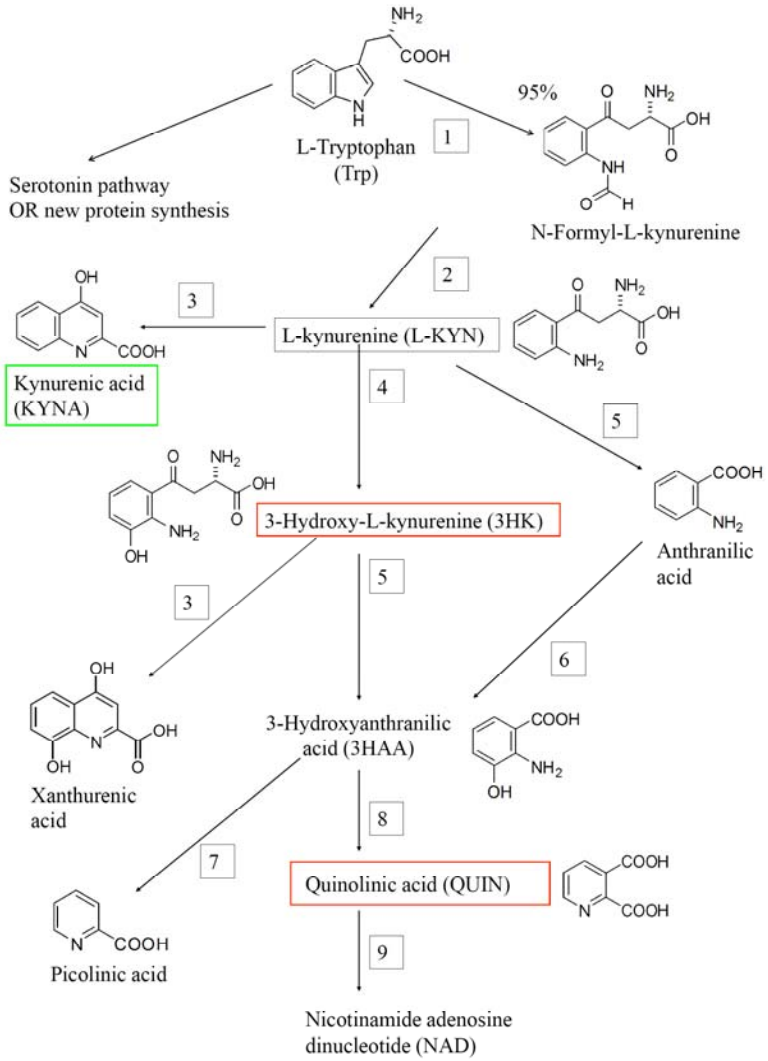

Fig. (1). Kynurenine pathway

Figure footnotes: 1: Tryptophan 2,3-dioxygenase (TDO) and indoleamine 2,3-dioxygenase (IDO). These enzymes represent the rate-limiting step of the synthesis of the central metabolite, L-kynurenine (KYN). The expressions of the two enzymes differ: IDO is mainly expressed in the CNS, and TDO primarily in the liver. 2: Formamidase. 3: Kynurenine aminotransferases (KATs). Four types of KATs (KAT I-IV) have so far been identified. In humans the most important are KAT I and KAT II. 4: Kynurenine-3-monooxygenase (KMO). Inhibition of this enzyme results in a metabolic shift towards the neuroprotective kynurenic acid (KYNA). 5: Kynureninase. 6: Non-specific hydroxylation. 7: Aminocarboxymuconate semialdehyde decarboxylase. 8: 3-Hydroxyanthranilic acid oxygenase. 9: Quinolinic acid phosphoribosyltransferase.

reduced neuritic outgrowths [92-93]; this was prevented by the antioxidant catalase [94]. In contrast with neuronal cells [93-94], cultured glioma cells did not display susceptibility to 3HK [95-96]. These data indicate that glial cells may tolerate the presence and toxic effect of 3HK much more easily than do neurons, in which 3HK is endogenously not present [97]. 3HK potentiates quinolinate, but not NMDA toxicity in the rat striatum [98]. Intrastriatal co-administration of 3HK and QUIN in subtoxic doses results in neuronal death in the striatum, which indicates that 3HK has neurodegenerative properties in the presence of QUIN [98].

3HAA: Kynureninase converts 3HK to 3HAA. This metabolite undergoes auto-oxidation, during which highly reactive hydrogen peroxide and hydroxyl radicals are formed [99-100]. Superoxide dismutase 1 enhances, whereas catalase abolishes these reactions [94, 100]. These findings are evidence that the detrimental effect of 3HAA is mediated by reactive oxygen species.

PIC: PIC is one of the metabolic products of the KP [101]. Besides KYNA, PIC displays antagonism towards the toxic action of QUIN, though the exact mechanism is unknown [102-104]. *In vitro* studies suggest that it has an immunomodulatory character besides its antiviral, antimicrobial and antitumour effects, but the experimentally used concentrations in these studies were much higher than the reported endogenous concentration of PIC [105]. The large discrepancy between the endogenous and experimental PIC levels means that these observations may not be related to the natural physiological function of PIC.

XA: XA is formed from 3HK through the action of KATs. XA is closely related to KYNA structurally (the difference is merely a hydroxy group) (Fig. **1**). It has been verified as a ligand of the endogenous Group II (mGlu2 and mGlu3) metabotropic Glu receptors [106]. These receptors and the metabolites of the KP have been implicated in the pathophysiology of schizophrenia. A recent study postulated that XA is probably the first potential endogenous allosteric agonist for the mGlu receptors [106]. It has also been demonstrated to exert an anti-inflammatory effect through a reduction of interferon-γ [107].

3. THE KYNURENINE PATHWAY AND THE IMMUNE SYSTEM IN AGING

Alterations in the levels of the KP enzymes and compounds have been observed not only in neurological disorders [108-110],

but also in the aging process [110-113]. If the KP metabolism is compared in older individuals and in young adults, upregulation of the Trp-KYN metabolism may be noted in the elderly [114]. Moreover, the activity of IDO in nonagenarians is markedly increased and predicts mortality [115]. Exploration of the relationship between the KP and aging through the use of animal models is a unique and useful technique, because the KP is conserved evolutionarily in insects, rodents and humans.

Drosophila melanogaster is an ideal animal model of the aging process [116], because it is a cheap, fast-growing species in which many mutants have been described. In Drosophila, the genes of the KP are responsible for the colour of the eyes. The end-product of the KP pathway is the brown eye pigment [117]. The life spans of the mutant insects with vermilion (TDO-deficient) or white eyes (ABC transport impaired) were longer than that of the wild-type flies [118]. Moreover, a prolongation of the life span was exhibited in wild-stock flies treated with inhibitors of TDO and the ABC transporter, treatments which presumably limit the conversion of Trp into L-KYN. Inhibition of the conversion of Trp into L-KYN might therefore be a target for anti-aging intervention [118].

Additionally, the alterations in the levels of the metabolites of the KP could underlie the cognitive decline observed in aging. Investigations of cardinal Drosophila mutants (a 3HK excess) demonstrated a decline in learning and memory [119]. Vermilion Drosophila mutants (no kynurenines) displayed a gradual decline of memory performance until complete memory failure [113].

An investigation of the KP metabolism in the brain, liver and kidney of aged female rats revealed that the Trp levels and TDO activity declined in all tissues with advancing age, whereas the IDO activity in the brain increased, while that in the liver and the kidney decreased [111]. Trp depletion as a consequence of IDO activation may contribute to the development of the immunodeficiency observed in the elderly [114]. Braidy *et al*. measured not only the enzyme activity, but also the metabolite levels. They found that the levels of KYN, KYNA, QUIN and PIC in the brain tended to rise with advancing age, while those of KYN in the liver and kidney exhibited a tendency to decrease [111]. The content of KYNA in the kidney increased, but in the liver it did not change [111]. The concentrations of PIC and QUIN increased significantly in the liver, but showed a tendency to decrease in the kidney [111]. The enhanced brain IDO activity may be responsible for the observed age-dependent increase in brain KYN, which is the central metabolite of the pathway. The elevated concentration of KYN therefore adequately explains the observed age-dependent increases in the KYNA, QUIN and PIC concentrations. The elevated levels of KYNA were strengthened by the results of two experiments. An age-related increase was found in the level of KYNA in the human CSF [120], and elevated levels of KYNA and QUIN in the rat brain [121-122].

Nevertheless, age-dependent alterations in the KP have been described not only in healthy animal models, but also in specific disease models, e.g. in the YAC128 mouse model of HD [110] and a *C. elegans* AD model [112].

In summary, investigations of the KP are of considerable importance not only in diseases and in disease models, but also in aging models. Exploration of the differences between normal aging and neurodegenerative diseases may facilitate a better understanding of both processes.

The decline of the immune system with age can be detected in the increased susceptibility to infections, in the modest immune response after vaccination, in the growing number of cancer cases, and in the increased number of autoimmune and other chronic diseases characterized by a pro-inflammatory state among the elderly [123-126]. Both the innate [127] and the adaptive immune responses showed changes because of the aging process, but the adaptive response seems to be more affected [10]. This topic is summarized in Table **1** and has been well reviewed by Castelo-Branco and Soveral [10]. Inflamm-aging [128], the characteristic chronic low-grade inflammatory state observed in aged individuals has been implicated in the pathogenesis of many age-related diseases, such as AD [129-130]. This process is characterized by increased levels of proinflammatory markers and cytokines and it should be taken into account when we speak about CNS disorders, which appear mostly in elderly populations.

4. ALTERATIONS IN THE KYNURENINE PATHWAY IN SOME DISORDERS OF THE CNS

The social significance of these disorders is enormous, even if only the worktime lost because of migraine or the costs of drugs and hospitalization are considered. Unfortunately, the therapeutic options in a number of these diseases are limited. The pathomechanisms of neurological disorders exhibit common features. The char-

Table 1. Changes in the adaptive and innate immune system with age.

Type of changes	Innate immune system	Adaptive immune system
Increase	Impairment of anatomical barriers: Numbers of less functional NK cells	Apoptosis resistance of memory B cells Delayed antibody response to new antigens: Antigen-independent activation and proliferation of naive T cells Apoptosis resistance of memory T cells
Decrease	Impairment of anatomical barriers: Number of Langerhans cells Pathogen recognition by dendritic cells Neutrophil survival in response to stimuli Neutrophil phagocytic function and respiratory burst generation Cytokine production by macrophages T cell activation by macrophages	Lymphoid progenitor production Number of B cells, especially naive cells Antibody production, with lower affinities and decreased opsonizing abilities Delayed antibody response to new antigens: Number of T cells, especially naive and $CD8^+$ cells $CD28^+$ T cells as a result of accumulation of mature cells Acquisition of NK cell markers by T cells: Cytotoxic capability of $CD8^+$ cells

Source of the data: Castelo-Branco, C.; Soveral, I., The immune system and aging: a review. *Gynecol Endocrinol* **2014,** *30* (1), 16-22.

acteristic changes are a mitochondrial dysfunction, the accumulation of free radicals, the starting of neuroinflammatory processes and excitotoxic and oxidative damage of the cells, ultimately leading to neuronal cell death. Since the destruction of nerve cells can result in a permanent loss of function, there is a need for the prevention of cellular damage, i.e. neuroprotection [56].

4.1. Parkinson's Disease

PD is a chronic progressive neurodegenerative disease with characteristic pathological hallmarks, including selective degeneration of the dopaminergic neurons in the substantia nigra pars compacta (SNPC) and the appearance of intracytoplasmic alpha synuclein protein inclusions, Lewy bodies [131]. The accumulation of free radicals, malfunctioning of the mitochondria, abnormal protein aggregations, neuroinflammatory processes and overproduction of the excitatory neurotransmitter Glu have critical roles in the pathogenesis of the disease. The most widely utilized treatment is with L-Dopa and a dopaminergic agonist, but these only relieve the symptoms at most; moreover, their long-term usage may give rise to serious side-effects (dyskinesia or motor fluctuations) [132].

Increasing evidence has emerged of an association between PD and alterations in the KP (Table **3**). Lower concentrations of KYN and KYNA were measured in the frontal cortex, putamen and SNPC of PD patients as compared with controls [133]. Additionally, the concentration of 3HK was elevated in the putamen and SNPC in the PD group [133].

There are alterations in the KP in the two widely used animal models of PD [134-136]. The expression of KAT I in the substantia nigra of mice was decreased after 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine treatment [134]. Moreover, 1-methyl-4-phenylpyridinium and 3-nitropropionic acid diminished the cortical synthesis of KYNA in rats via interference with the KATs [136]. Alterations in the KP in the periphery have also been demonstrated in PD. The increased activity of KAT II in correlation with the elevated KYNA level in the red blood cells may relate to a possible protective process [137]. The importance of the KP was supported by experiments in which the inhibition of KMO increased the KYNA level, thereby not only preventing neurotoxic damage of the striatal dopaminergic neurons, but also alleviating the dyskinesia caused by dopamine replacement [138-139]. However, despite increasing evidence of the linkage of KP and PD, genetic evidence is not yet available [131]. Both *in vitro* [140] and *in vivo* [138, 141-142] experiments indicate therapeutic possibilities through elevated levels of KYNA.

4.2. Huntington's Disease

HD is an autosomal dominantly inherited neurodegenerative disease caused by trinucleotide expansion (CAG-glutamine) within exon 1 of the huntingtin protein (htt-located 4p16.3). This leads to neuronal cell death in the brain, and especially in the striatum and cortex, which causes motor, cognitive and psychiatric symptoms. The age at disease onset correlates inversely with the length of the CAG expansion. Genetic modifiers and the environment play critical roles in patients who have 36-39 repeats [143]. Especially in these individuals, but certainly in those who exhibit symptoms (>40 repeats), manipulation of the KP may be a beneficial tool.

In the early phase of the disease, increased QUIN and 3HK and moderately increased KYNA concentrations have been measured in the striatum, associated with decreased KYNA/QUIN and KYNA/3HK ratios [56, 144] (Table **3**). These results were strengthened by a full-length mutant huntingtin mouse model [145]. In the late stages, the KYNA levels are decreased in the cortex, striatum and CSF [146-147], while that of 3HK is increased in the brain [148]. Decreased KAT activity has been demonstrated in the striatum [146, 149], and elevated 3HAO activity in the brain [150]. An abnormal Trp metabolism has been revealed in the periphery (plasma) [151]. Increased KMO and decreased kynureninase activity have been observed in transgenic R6/2 mice [152]. Moreover, the 3HK levels were significantly and selectively elevated in the striatum, cortex and cerebellum in this model, starting at 4 weeks of age [153]. The levels of both 3HK and QUIN were enhanced in the striatum and cortex of the full-length HD models, YAC128 and Hdh(Q92) and Hdh(Q111) [153]. Intrastriatal administration of QUIN has been widely used as an animal model of HD, leading to an elevation of extracellular glutamate. Interestingly, this effect can be prevented by cannabinoid receptor agonists [32].

Genetic and pharmacological inhibition of KMO and genetic inhibition of TDO increase the level of the neuroprotective KYNA relative to the neurotoxic 3HK and ameliorates neurodegeneration in a *D. melanogaster* HD model [154].

Elevated levels of KYNA (or its analogues) or inhibition of KMO and TDO provide therapeutic possibilities for neuroprotection in HD [154-156].

4.3. Alzheimer's Disease

AD is the most prevalent neurodegenerative disorder, accounting for 60-70% of cases of dementia. The pathological hallmarks of the disease are the amyloid plaques and neurofibrillary tangles, which are clearly visible by microscopy in the brains of those afflicted by AD [157]. Excessive activation of NMDA receptor signalling is believed to contribute to the neuronal damage in AD [158], which is confirmed by neuroanatomical data, because the loss of neocortical neurons is restricted to the Glu-ergic neurons in layers III and IV [159] and the cortical and hippocampal neurons innervated by L-Glu [160]. This is supported not only by neuroanatomical observations, but also by the therapeutic effect of the low-affinity non-competitive NMDA receptor antagonist, memantine.

The relationship between AD and the KP is also indicated by other observed alterations [56] (Table **3**). The KP is up-regulated in the AD brain; the regulatory enzyme of the pathway, IDO, is abundant in AD as compared with controls, leading to increase in the excitotoxin QUIN [109]. Moreover, QUIN is co-localized in the cortex with phosphorylated tau [161] and induces tau phosphorylation in human primary neurons [161]. Alterations are also observed in the periphery; the serum level of 3HK was markedly increased in AD patients, but the Trp, KYNA, PIC and QUIN concentrations were similar to those in the controls [162]. The KYNA concentration was significantly decreased both in the plasma and in the red blood cells, but the levels of KYN and the activities of KAT I and KAT II remained unchanged [163]. In a mouse model of the disease, the IDO inhibitor coptisine ameliorated the cognitive impairment [164].

4.4. Multiple Sclerosis

MS, the most common chronic autoimmune/neurodegenerative demyelinating disorder of the CNS acording to Lucchinetti [165], emerges mostly in young adults and affects 2.5 million people worldwide. In a recent study, the standardized prevalence was found to be 83.7/100,000 and the female:male ratio in the MS population in Csongrád County, Hungary was 3.08 [166]. The clear role of a genetic predisposition has been suggested, together with unidentified environmental factors and autoimmune inflammatory mechanisms. The lifetime risk has been reported to be 1 in 400 [167], which makes MS potentially the most common cause of neurological disability in young adults.

The KP plays a pivotal role in regulating the balance between activation and inhibition of the immune system through the immunomodulatory effect of IDO [57]. The linkage between the kynurenine system and immunoregulation has been reviewed [56-57]. IDO has immunosuppressive action, and IDO-KP can serve as a negative feedback loop for Th1 cells [57], which can be important in MS therapy.

It may be presumed that not merely IDO plays a crucial role in MS, as QUIN and 3HK proved to be elevated in the more caudal

regions of the spinal cords of the animals in experimental autoimmune encephalitis (EAE), an animal model of MS [168-169] (Table **3**). Furthermore, the linkage of KP and MS and the therapeutic benefit of modulation of the cascade are strengthened by another EAE model study [170-171]. In that work, the KP metabolite cinnabarinic acid (an endogenous agonist of the type-4 metabotropic Glu receptor) suppressed EAE in mice [170-171]. Moreover, recent results indicated QUIN-induced oligodendrogliotoxicity in two cell lines [172], which could be attenuated by specific KP enzyme inhibitors and anti-QUIN monoclonal antibodies. This could be very important in MS, where the pathological hallmark is irreversible demyelination.

The levels of KYNA in the CSF of relapsing-remitting MS (RRMS) patients were significantly lower during remission [173]. By contrast, the KYNA levels in the CSF were elevated during acute relapse [174]. A recent study not only investigated the KP metabolite levels from the CSF, but was also the first comprehensive analysis of CSF kynurenine metabolites in MS patients in different disease stages in relation to neurocognitive symptoms. At the group level, MS patients did not show any difference in the absolute levels of the KP metabolites (Trp, L-KYN, KYNA and QUIN) as compared with the control group, but the stratification of the data according to the disease course revealed that both absolute the QUIN levels and the QUIN/L-KYN ratio were increased in RRMS patients in relapse, the secondary progressive MS patients showed a tendency to lower Trp and KYNA concentrations, and the primary progressive cohort displayed increased levels of all metabolites (similarly to the inflammatory neurological disease controls) [130, 175]. The depressed patients demonstrated higher KYNA/Trp and L-KYN/Trp ratios (mainly due to low Trp levels) [130, 175]. There was no linkage between the pattern of KP metabolites in RRMS patients and the neurocognitive symptoms [130, 175]. The study concluded that the clinical disease activity and differences in disease courses are correlated with the changes in KP metabolites [130, 175]. In the periphery, elevated levels of KYNA and KAT I and KAT II activities have been reported in the plasma and erythrocytes [176]. These changes may indicate a compensatory protective mechanism against excitatory neurotoxic effects.

It is questionable whether activation of the KP in MS is beneficial or detrimental. It may be beneficial in the early stages, because IDO activation can downregulate T cell proliferation. In contrast, prolonged activation of the KP may lead to chronically elevated levels of QUIN and other neurotoxins produced by perivascular macrophages, thereby contributing to further neurological deficits [177]. In an animal model of MS, the activation of IDO ameliorated [178-179], while the inhibition of IDO exacerbated EAE [177, 180], and anti-inflammatory metabolites of the KP ameliorated EAE [181]. The therapeutic aspects of the KP in MS and the role of the KP in the dialogue between the immune system and the CNS were well reviewed recently.

4.5. Amyotrophic Lateral Sclerosis

ALS is a rapidly progressive and fatal neurodegenerative disease with characteristic pathological features: degeneration of the upper (cortical) and lower (spinal and pontobulbar) motor neurons. Despite the fact that it is the most common motor neuron disease, ALS is rare. Its mean incidence in Europe is 2.8/100,000, while its mean prevalence is 5.40/100,000 [182]. Only 5-10% of the cases are classified as familial, which mainly inherited in an autosomal dominant manner [183-184], the remaining 90% being sporadic [185].

Glu excitotoxicity, damage by free radicals, a mitochondrial dysfunction, intracellular protein aggregation, excessive poly (ADP-ribose) polymerase activation, autoimmune inflammatory processes and the enhanced accumulation of intracellular Ca^{2+} are involved in the aetiology of the disease [184].

Currently only one effective mode of therapy exists (Riluzole, an anti-Glu agent similar to KYNA), which slowed the progression and possibly improved the survival in patients with bulbar onset in a double-blind placebo-controlled clinical trial [184, 186].

The role of Glu in ALS is not only supported by this therapeutic possibility; loss of a key Glu transporter (the Glu transporter-1 isoform responsible for keeping the extracellular Glu levels below neurotoxic), and increased extracellular Glu levels have also been described in both the sporadic and the familial form of ALS [187].

The oxidative degradation of Trp early in the pathway results in covalent cross-linking and the accumulation of human superoxide dismutase 1, one of the two major genetic contributors to ALS known to date [188] and therefore widely used in an animal model of ALS.

The linkage of the KP and ALS is additionally indicated by the alterations in the KP in ALS (Table **3**). Significantly increased levels of Trp, KYN and QUIN in the CSF and serum, and a decreased serum level of PIC have been measured in ALS samples, with enhanced microglial and neuronal IDO expression in the motor cortex and the spinal cord and elevated IDO activity in the CSF [189]. High KYNA levels were measured in the CSF in patients with a severe clinical status or with bulbar onset, whereas the serum KYNA levels were decreased in cases with a severe clinical status [190]. These changes are probably a part of the neuroprotective compensation. *In vitro* experiments with the NSC-34 cell line showed that KYNA may have anti-apoptotic features [191-192]. An animal model of the disease revealed changes in zinc-binding capacity [193-194], and PIC could therefore be a neuroprotectant in ALS because of its zinc chelator property. These findings provide strong evidence of the involvement of the KP in ALS, therefore possibly opening the way for new therapeutic opportunities in this fatal disease.

4.6. Migraine

Migraine, the most common type of primary headache, is a multifactorial recurrent brain disorder [195]. Its cumulative incidence has been reported to be 43% in women and 18% in men [196]. In 75% of the cases, the age at onset is less than 35 years [196]. Because of its high frequency, its economic importance should not be underestimated, in view of the costs of treatment, the loss of worktime and the decrease in productivity. The electrophysiological hallmark of the disease is cortical spreading depression (CSD), an excitatory slowly progressing wave of depolarization accompanied by a long-lasting suppression of neuronal activity and excitability in the cortex of the brain [197]. CSD is assumed to be the neurological basis of the aura phenomenon [198], which affects one-third of migrainers [199]. In the pathomechanism of migraine, genetic factors [200], peripheral sensitization of the trigemino-vascular system (caused by the changed cerebral blood flow and sterile neurogenic inflammation) [201-202], central sensitization of the caudal trigeminal nucleus [203], the activation of specific brain stem nuclei, called migraine generators (the dorsal raphe nucleus, the nucleus raphe magnus, the locus coeruleus and the periaqueductal grey matter) [204-206] and, not least, the development of CSD [207] are assumed. The common feature of these five processes is the role of Glu in each [208] and the importance of Glu in the pathomechanism is also indicated by the elevated Glu levels in the CSF during the attacks [209], and in the plasma (without aura) and in the platelets (with aura) in the headache-free periods [210], which may reflect persistent hyperexcitability [209]. Because of this common point, the therapeutic possibilities draw attention to the NMDA antagonist of the KP, KYNA. Elevated levels of KYNA or its analogues significantly attenuate the central sensitization of the caudal trigeminal nucleus [211-212] and alleviate the activation of the migraine generators [213] and primary and secondary trigeminal nociceptive neurons [214-215]; moreover, KYNA inhibits CSD both in the cerebellum and in the neocortex [216]. L-KYN or a synthetic KYNA analogue was also able to decrease nitroglycerine-induced calcitonin-gene related peptide

(CGRP) expression [212]. CGRP is one of the most investigated neuropeptides in research, especially because CGRP antagonists and monoclonal antibodies are of promise for the therapy of migraine [217-220]. Although increased KYNA levels have been found in the rat brain after triggered CSD, this is presumably an adaptive response for neuroprotection [56, 208]. KYNA additionaly alleviates the nociception caused by formalin and capsaicin in animal models [221-222]. The systemic administration of KYN attenuates the frequency of CSD in female rats, whereas in male rats this effect was observed only when probenecid was co-administered [223]. However, the administration of KYN with probenecid not only influences CSD, but also mitigates the central sensitization of the caudal trigeminal nucleus [211, 224]. After electrical stimulation of the trigeminal ganglia (migraine model), decreased KAT immunoreactivity was detected in the dural macrophages, Schwann cells and mast cells [56, 225], which leads to a reduced production of KYNA. These results indicate that kynurenine metabolites can influence the brainstem structures involved in the pathogenesis of migraine, and KYNA and its analogues may serve as a novel and useful therapeutic approach.

4.7. Schizophrenia

Schizophrenia is a disorder characterized by psychiatric symptoms and a cognitive dysfunction. Its pathology involves biochemical alterations in Glu neurotransmission (hypo-Glu-ergic hypothesis), which can cause secondarily altered dopamine homeostasis [226]. This Glu deficiency theory has been strengthened by genetic studies [227].

Investigations of the KP in schizophrenia revealed increased KYNA levels in the CSF and in post-mortem tissues [226, 228-230], whereas the level was lower in the blood of the patients [231] and in an animal model [232] (Table **3**). The KYNA level was elevated in the prefrontal cortex [226, 228], where a reduced metabolic function has been at the focus of interest in schizophrenia studies. Indeed, increased concentrations of this NMDAR antagonist can cause a hypo-Glu-ergic state in the brain [233-234]. The increased KYNA levels may be caused by reduced levels of the enzymes responsible for the synthesis in the other branches of the pathway. The activities of the enzymes, and the protein and mRNA levels of 3HAO and KMO proved to be reduced in the prefrontal cortex region in post-mortem samples, while those of IDO, KAT and quinolinic acid phosphoribosyltransferase were normal [235-236]. The 1q42-q44 chromosome region, where KMO is located, has been implicated in the disease aetiology [237-238]. Another genetic study supported the role of KMO in schizophrenia, in which the rs1053230 single nucleotide polymorphism was found to be strongly associated with increased CSF KYNA concentrations [234] in both controls and patients, but another, larger study failed to establish a significant association of KMO and schizophrenia [239]. This contradiction could be due to the different populations. Aoyama *et al*. used only the clinical diagnosis and no other clinical parameters, and they collected Japanese samples from different geographical regions. Interleukin-1 beta and IDO single nucleotide polymorphisms were studied together and a combination of alleles was associated with schizophrenia [240]. These results may indicate a slight genetic association and support the role of the KP in this disease.

In animal models of schizophrenia, elevated KYNA levels may be associated with cognitive deficits [70, 226]. The decrease of the extracellular Glu concentrations by KYNA was accompanied by the deteriorating performance of mice and rats in different cognitive tests, while the inhibition of KAT (which decreases the KYNA level) secondarily increases the release of Glu and improves the skills of the animals [226].

In summary, investigation of the KP is important in schizophrenia, and might be important in the future in other psychiatric diseases too (bipolar disorder and autism) [241-243]. In contrast with the diseases described above, the decreased Glu and increased KYNA levels may contribute to the development of schizophrenia.

5. POSSIBILITIES FOR NEUROPROTECTION BY MODULATING THE KYNURENINE PATHWAY

As discussed above, KYNA is a neuroprotective agent because of its broad-spectrum non-selective anti-Glu properties. Its neuroprotective action has been demonstrated against the neurotoxicity induced by kainate, ibotenate, QUIN or NMDA [244]. This metabolite of the KP is therefore of therapeutic potential, but unfortunately it has only a very limited ability to cross the BBB. For therapeutic exploitation, there are four main possibilities. One option is to use precursors of KYNA, L-KYN or its halogenated derivatives, which cross the BBB more readily (prodrug concept). A second possibility is to synthetize KYNA analogues which pass through the BBB more easily, but have at least the same neuroprotective effect as that of KYNA. A third option is to shift the KP towards the production of KYNA through the use of enzyme inhibitors. A fourth possibility is to make use of the innovations of nanotechnology, "packing the KYNA", which results in easier passage of the compound through the BBB (Fig. **2**).

5.1. Prodrug Concept

Preclinical studies have verified the efficacy of pretreatment with the neuroprotective L-KYN [245-246], which proved more effective when co-administered with probenecid in different disease models: epilepsy [247], migraine (L-KYN combined with probenecid and a novel synthetic KYNA derivative attenuated nitroglycerine-induced neuronal nitric oxide synthase in the rat caudal trigeminal nucleus [211-212]), PD [141] and AD [248]. Systemic L-KYN and probenecid administration displayed a protective effect against the behavioural and morphological alterations induced by toxic soluble amyloid beta (25-35) in the rat hippocampus [249]. However, the results of post-treatment were contradictory, as it was reported to be much less effective [246], possibly harmful [250] or possibly beneficial in animal ischaemia models [251].

Co-administration of L-KYN with probenecid may theoretically result in an elevation not only of KYNA, but also of neurotoxic kynurenines. However, the promising results in preclinical studies suggest that probenecid may predominantly lead to the elevation of the neuroprotective KYNA [252]. On the other hand, probenecid may also participate in several interactions with medications. Further research is therefore designed to overcome the limitations of this prodrug concept and influence the KP in a more specific way.

Halogenated derivatives of L-KYN (4-chlorokynurenine (AV-101) or 4,6-dichlorokynurenine) are transformed into 7-chlorokynurenic acid and 5,7-dichlorokynurenic acid, these compounds having increased affinity for the glycine co-agonist site of the NMDAR [253]. AV-101 is the most advanced L-KYN prodrug candidate for use as a neuroprotective agent [56]. Moreover, it may have therapeutic potential in epilepsy, HD and PD [56].

These results lend support to the existence of a critical link between the Trp metabolism in the blood and neurodegeneration, and provide a foundation for the treatment of neurodegenerative diseases.

5.2. The Metabolic Shift Concept

Another pharmacological approach is the use of KP enzyme inhibitors (Table **2**). Neuroprotection can be achieved by making a metabolic shift towards the neuroprotective KYNA instead of the neurotoxic 3HK, 3HAA and QUIN [56].

During the past two decades, many novel enzyme inhibitors have been developed which target KMO, kynureninase and 3HAO (Table **2**) to attain this metabolic shift [56].

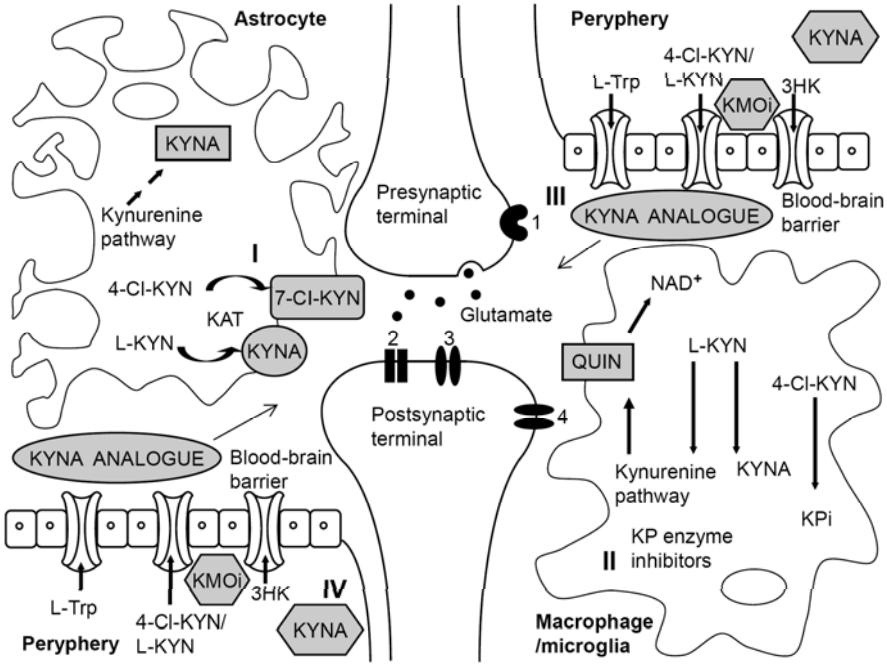

Fig. (2). Possibilities for neuroprotection in the KP
I: Prodrug concept. II: Metabolic concept. III: KYNA analogue concept. IV: Nanotechnology concept. 1: α7nACh receptor. 2: AMPA receptor. 3: NMDA receptor. 4: Extrasynaptic NMDA receptor.
From the periphery, only L-Trp, L-KYN and 3HK can be transported through the blood-brain barrier (BBB) to reach the central nervous system (CNS). In the CNS, the main sources of the neurotoxic QUIN are the microglias and the macrophages. This metabolite is an NMDA receptor agonist, which can largely over-activate these receptors and cause neuronal damage. In the astrocytes, the KP is not complete, because they do not possess KMO, and they therefore favour the formation of neuroprotective KYNA. In the prodrug concept, the administration of L-KYN and KMO inhibitors increases the availability of L-KYN within the CNS, resulting in increased KYNA concentration in the astrocytes. After release, KYNA exerts preferential inhibition on extrasynaptic NMDA and α7nACh receptors, but it does not influence the AMPA and the synaptic NMDA receptors. In the KYNA analogue concept, 4-Cl-KYN uses the same transporter and undergoes the same enzymatic mechanisms as L-KYN. In the astrocytes, 4-Cl-KYN is transformed into 7-Cl-KYNA. 4-Cl-KYN is a precursor of the 3HAO inhibitor, 4-chloro-3-hydroxyanthranilic acid. In the KYNA analogue concept, the KYNA analogues can cross the BBB more easily than KYNA, and enhance the KYNA concentration within the CNS. The enzyme inhibitors (inhibitors of KMO, 3HAO and kynureninase) concept is a promising pharmacological tool, shifting the pathway to the neuroprotective compounds. The nanotechnology concept is a new approach with which to enhance the neuroprotective metabolite concentrations within the CNS through easier transport across the BBB.
This is a modified figure version, the source can be found in Vecsei *et al*.: Kynurenines in the CNS: recent advances and new questions. Nat Rev Drug Discov [56].

Table 2. Enzyme inhibitors of the KP.

IDO inhibitors	Selective KAT II inhibitors
4-Amino-1,2,5-oxadiazole-3-carboximidamide	*S*-Adenosylhomocysteine
AC 12308	*(S)*-(4)-(Ethylsulfonyl)benzoylalanine
BTB 05536	4-Carboxy-3-hydroxyphenylglycine
Keto-indole derivatives	L-Cysteine sulphinic acid
2-Mercaptobenzothiazole	L-Aspartate
S-Benzylisothiourea derivatives	Quisqualic acid
Annulin A, B and C	**KMO inhibitors**
KM 00593	4-Aryl-2-hydroxy-4-oxobut-2-enoic acid derivatives
Garveatin A, C and E	(*m*-Nitrobenzoyl)alanine
NSC 401366	FCE 28833A (also known as PNU 156561)
4-Phenylimidazole derivatives	Nicotinylalanine
Berberin	UPF 648
Benzylthiol derivatives	S(+)-(*m*-Nitrobenzoyl)alanine
β-Carboline derivatives	Ro 61-8048 and related benzenesulfonamides

Table (2) contd….

Exiguamine A, B	**Kynureninase inhibitors**
6-Chloro-DL-tryptophan	Bicyclic L-kynurenine analogues
Hydroxyamidine derivatives	S-Aryl-l-cysteine S,S-dioxides
1-Methyl-DL-tryptophan	O-Methoxybenzoylalanine
1-Methyl-L-tryptophan	O-Aminobenzaldehyde
N-Methyl-L-tryptophan	3-Hydroxyhippuric acid
Methylthiohydantoin-DL-tryptophan	(*m*-Nitrobenzoyl)alanine
Selective KAT I inhibitors	Nicotinylalanine
D,L-Homocysteine	(4R)- and (4S)-dihydro-l-kynurenine derivatives
D,L-Indole-3-lactic acid	Desaminokynurenine derivatives
L-Glutamine	**3-HAO inhibitors**
3-Indolepropionic acid	4-Halo-3-hydroxyanthranilic acid derivatives
L-Phenylalanine	4,5- and 4,6-dihalo-3-hydroxyanthranilic acid derivatives
L-Tryptophan	

Table 3. Alterations in the KP in some neurological disorders.

Diseases	Alterations	Location	Refs
Parkinson's disease			
Homo sapiens	↓L-KYN, KYNA	frontal cortex, putamen, SNPC	[133]
Homo sapiens	↑3HK	putamen, SNPC	[133]
Homo sapiens	↑KAT II activity, KYNA	red blood cells	[137]
Homo sapiens	↓KAT I, KAT II activity, KYNA (tendency)	plasma	[137]
Mus musculus	↓KAT I decreased expression	substantia nigra	[134]
Rattus norvegicus	↓KYNA	cortex	[136]
Huntington's disease			
Homo sapiens early phase of the disease	↑QUIN, 3HK and poorly elevated KYNA	striatum	[56, 144]
Homo sapiens early phase of the disease	↓KYNA/QUIN, KYNA/3HK	striatum	[56, 144]
Homo sapiens late phase of the disease	↓KYNA	cortex, striatum, CSF	[146-147]
Homo sapiens	↑3HK	post-mortem brain tissue	[148]
Homo sapiens early phase of the disease, *Mus musculus*	↑3HK, KYNA, 3HK/KYNA	neostriatum	[145]
Homo sapiens	↓KAT activity	striatum	[146, 149]
Homo sapiens	↑3HAO activity	brain, striatum	[150]
Homo sapiens	↑L-KYN/Trp, IDO activity, L-KYN, ↓KAT activity, 3HK, 3HAA	blood	[151]

Table (3) contd….

Diseases	Alterations	Location	Refs
Mus musculus (R6/2 mice)	↑KMO activity, 3HK, ↓kynureninase	cortex, striatum, cerebellum	[152]
Mus musculus (R6/2 mice)	↑3HK	striatum, cortex, cerebellum	[153]
Mus musculus (YAC128, Hdh(Q92), Hdh(Q111))	↑3HK, QUIN	striatum, cortex	[153]
Alzheimer disease			
Homo sapiens	↑QUIN, IDO activity	hippocampus	[109]
Homo sapiens	↑3HK	serum	[162]
Homo sapiens	↓KYNA	blood (plasma, red blood cells)	[163]
Multiple sclerosis			
Homo sapiens remission	↓KYNA	CSF	[173]
Homo sapiens acute relapse	↑KYNA	CSF	[174]
Homo sapiens acute relapse, in relapsing-remitting MS	↑absolute QUIN, QUIN/L-KYN ratio	CSF	[130]
Homo sapiens secondary progressive MS	trend to lower Trp and KYNA	CSF	[130]
Homo sapiens primary progressive MS	↑Trp, L-KYN, KYNA or QUIN	CSF	[130]
Homo sapiens acute relapse	↑KAT I and KAT II activities	RBC	[176]
Homo sapiens acute relapse	↑KYNA	plasma, tendency in the RBC	[176]
Rattus norvegicus (EAE model)	↑QUIN	more caudal regions of the spinal cord	[168]
Rattus norvegicus (EAE model)	↑KMO activity, 3HK, QUIN	spinal cord	[169]
Amyotrophic lateral sclerosis			
Homo sapiens	↑Trp, L-KYN, QUIN	CSF, serum	[189]
Homo sapiens	↓PIC	serum	[189]
Homo sapiens	↑IDO expression	motor cortex, spinal cord	[189]
Homo sapiens	↑IDO activity	CSF	[189]
Homo sapiens severe clinical status/bulbar onset	↑KYNA	CSF	[190]
Homo sapiens severe clinical status	↓KYNA	serum	[190]
Migraine			
Rattus norvegicus after triggered CSD	↑KYNA	brain	[56, 208]
Rattus norvegicus after triggered CSD	↓KAT immunoreactivity	dural macrophages, Schwann cells, mast cells	[56, 225]
Schizophrenia			
Homo sapiens	↑KYNA	CSF, post-mortem tissues	[226, 228-230]
Homo sapiens	↑KYNA	prefrontal cortex	[226, 228]
Homo sapiens	↓KYNA, KYNA/KYN, KYNA/3HK, ↑3HK	blood (plasma)	[231]
Homo sapiens	↓3HAO and KMO activity, mRNA, protein, ↑KYNA	post-mortem prefrontal cortex	[226, 236]
Homo sapiens	↓KMO activity, mRNA levels, protein	post-mortem frontal eye field	[226, 235]
Rattus norvegicus	↓KYNA, neuroprotective ratio	social isolation rearing animal model	[232]
Rattus norvegicus	↑Trp, L-KYN, anthranilic acid, 3HAA, QUIN	social isolation rearing animal model	[232]

The early attempts were made with compounds that proved to be non-selective inhibitors, e.g. nicotinylalanine, but the later work was successful and combined therapy with prodrugs or analogues is now available [56].

Orally administered 3,4-dimethoxy-N- [4-(3-nitrophenyl)thiazol-2-yl]benzenesulfonamide was found to be a high-affinity inhibitor of KMO *in vitro* in the gerbil brain [254], but unfortunately it has rapid clearance. JM6 (3,4-dimethoxy-N-(4-(3-nitrophenyl)-5-(piperidin-1-ylmethyl)thiazol-2-yl)benzenesulfonamide), a novel, peripherally active KMO inhibitor prodrug, overcomes the problem of the rapid clearance and elevates the level of L-KYN in the blood, resulting in neuroprotection in animal models of HD and PD [255].

5.3. The Kynurenic Acid Analogue Concept

The synthesis of novel KYNA derivatives is a promising therapeutic approach for the development of new neuroprotective compounds [155, 256-257]. The most common analogues are halogenated (7-chlorokynurenic acid and 5,7-dichlorokynurenic acid), thio-substituted (thiokynurenates) or sugar derivatives (D-galactose-7-chlorokynurenic acid or glucosamine-kynurenic acid). The various chemical changes during the synthesis result in different beneficial features. The therapeutic advantages of the halogenated and thio-substituted derivatives are elevated affinity and selectivity for the glycine co-agonist site of the NMDARs, while the sugar components contribute to more facile passage through the BBB. Recent novel synthetic derivatives include KYNA amides, which are presumed to exert their effects preferably on NR2B subunit-containing NMDARs [258].

During the past decade, we have synthetized and tested a number of KYNA analogues [257], the most promising one being (N-(2-N,N-dimethylaminoethyl)-4-oxo-1H-quinoline-2-carboxamide hydrochloride [259], which is of proved neuroprotective value in animal models of cerebellar ischaemia [260] and HD [155].

5.4. Possibilities in Nanotechnology

The development of nanotechnology-based carrier systems offers novel promising technology for drug delivery into the brain [261]. Through the use of these carriers, therapeutic drug levels may be achieved in the brain, even for drugs which would otherwise not reach the CNS. This approach has been investigated to facilitate KYNA delivery into the brain by preparing micelles as nanoscale containers [262]: non-ionic surfactants were used to deliver KYNA, the central effects of which were proved in *in vivo* studies after peripheral administration too. However, further research is needed to develop biodegradable, biocompatible and non-toxic nanocarrier systems capable of promoting drug delivery into the brain without causing permanent damage to the BBB integrity.

6. CONCLUDING REMARKS

A growing body of evidence implicates alterations in the KP in aging and in many neurocognitive and neurodegenerative disorders (PD, HD, AD, MS, ALS, schizophrenia and migraine). NMDAR-mediated excitotoxicity, which causes neurodegeneration, occupies a central role in the pathophysiology of these diseases. Consequently, a pharmacological shift towards elevated concentrations of the neuroprotective KYNA may well be of therapeutic potential. There are currently four concepts through which to achieve elevated levels of KYNA: the use of more penetrable precursors; the synthesis of KYNA analogues, which can cross the BBB more easily; the utilization of specific enzyme inhibitors to shift the metabolic pathway towards the formation of KYNA; and the application of nanotechnology and “covered” KYNA.

This review has focused not only on the the linkage between neurological diseases and the KP, but also on the normal aging process. Continued exploration of the differences between normal aging and late-onset neurodegenerative disorders may promote a better understanding of both processes.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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