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An expanding range of targets for kynurenine metabolites of tryptophan

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ABSTRACT

The kynurenine pathway of tryptophan metabolism accounts for most of the tryptophan that is not committed to protein synthesis and includes compounds active in the nervous and immune systems. Kynurenine acts on the aryl hydrocarbon receptor, affecting metabolism of xenobiotics and promoting carcinogenesis. Quinolinic acid is an agonist at N-methyl-D-aspartate receptors (NMDAR), but is also pro-oxidant, has immunomodulatory actions and promotes the formation of hyperphosphorylated tau proteins. Kynurenic acid blocks NMDARs and $\alpha 7$ -homomeric nicotinic cholinergic receptors but is also an agonist at the orphan G-protein-coupled receptor GPR35. 3-hydroxykynurenine and 3-hydroxyanthranilic acid have pronounced redox activity and regulate T cell function. Cinnabarinic acid can activate metabotropic glutamate receptors. The aim of this review is to highlight the increasing range of molecular targets for components of the kynurenine pathway, in both the nervous and immune systems, in relation to their relevance to disease and drug development.

The kynurenine pathway

Apart from the tryptophan used in protein synthesis, most of this amino acid in mammals is oxidised along the kynurenine pathway. Only around 1% of tryptophan is used for the synthesis of 5-hydroxytryptamine (5-HT). For many years, most compounds along the pathway (Figure 1) were thought to have little biological activity until quinolinic acid was shown to be an agonist at glutamate receptors sensitive to NMDA [1] and kynurenic acid was found to be an antagonist at these and other ionotropic glutamate receptors [2]. These two compounds have been the focus of attention on the kynurenine pathway for over 30 years [3,4]. In parallel with work on the central nervous system (CNS), however, there has been growing interest in the role of kynurenines in the immune system, and the last few years have seen the identification of more molecular targets acted on by quinolinic acid, kynurenic acid or other components of the pathway. The key enzymes, indoleamine-2,3-dioxygenase (IDO) and kynurenine-3-monooxygenase (KMO) are also potential drug targets. The aim of this review is to highlight the increasing range of molecular targets now recognised in the nervous and immune systems in relation to their relevance to disease and drug development.

Kynurenine metabolites and their receptors in disease

Quinolinic acid

In addition to its ability to activate NMDARs selectively, quinolinic acid can generate reactive oxygen species (ROS). This activity can produce substantial oxidation of cellular lipids, especially in the presence of transition metal ions [5].

The axon-sparing neuronal loss produced by quinolinic acid *in vivo* may be due partly to formation of ROS [6] although it certainly also involves activation of NMDARs.

Acting on human primary astrocytes, excitotoxic concentrations of quinolinic acid can also promote the expression and secretion of some of the more potent chemokines and proinflammatory cytokines responsible for orchestrating the early phases of innate immune responses. In this context, quinolinic acid promotes the production of interleukin-1 β (IL-1 β) and monocyte chemoattractant protein-1 (MCP-1), as well as IL-8, Regulated on Activation, Normal T-cell Expressed and Secreted (RANTES) and several related chemokines and their receptors able to promote inflammatory responses [7,8] to a degree comparable with tumour necrosis factor- α (TNF- α) and interferon- γ (IFN- γ). This may indicate an ability of quinolinic acid to initiate inflammation within the CNS or to enhance it when it is partly established as part of a disease process such as Alzheimer's disease (AD).

The amyloid plaques found in the brains of patients with AD are associated with high concentrations of quinolinic acid [9] but the compound is also co-localised with hyperphosphorylated tau proteins which form the paired helical filaments in this disorder [10]. Quinolinic acid inhibits the phosphatase-mediated removal of phosphate from tau proteins, leaving hyper-phosphorylated tau protein.

Kynurenic acid

Two early studies of the anti-epileptic actions of kynurenic acid independently reported that its suppression of epileptiform bursts in

hippocampal slices could not be entirely explained by blockade of NMDARs [11,12] (Figure 2). However, a new receptor target was later identified as homomeric $\alpha 7$ -nicotinic cholinceptors ($\alpha 7$ NR), where kynurenic acid was a non-competitive antagonist [13]. The effect was observed initially in neuronal cultures, where kynurenic acid appeared more active as an antagonist of $\alpha 7$ NRs than NMDARs. However, this differential potency did not apply to neurones in more intact, multicellular preparations such as slices. A later examination of hippocampal interneurons confirmed that kynurenic acid could block $\alpha 7$ NR on these cells excited by exogenously applied agonists or synaptically released acetylcholine, although with a potency that was not fundamentally different from that which blocked NMDAR [14]. Thus, the sensitivity of $\alpha 7$ NR is probably dependent on experimental conditions and location, differing also between synaptic and extrasynaptic sites. Sensitivity may also change with age [15]. In addition, kynurenic acid produced endogenously within brain slices from kynurenine is better able to block NMDAR and $\alpha 7$ NR than kynurenic acid which is added exogenously [15], so that its physiological activity at this site may be underestimated.

AD. These data are especially relevant to the treatment of Alzheimer's disease. Agonists acting at $\alpha 7$ NR are particularly good at facilitating learning and memory processes in animal models and in patients with AD [16,17]. Conversely, a loss of cholinergic projections from the septum to the hippocampus or from nucleus basalis to the neocortex results in substantial deficits in learning, as does the administration of cholinceptor antagonists. Although there are relatively few studies of the kynurenine pathway in patients with AD, IDO is activated in the disease leading to a high kynurenine:tryptophan

ratio in blood [18, 19]. This would be expected to raise the endogenous levels of kynurenic acid which, by blocking glutamate and nicotinic receptors, could contribute to cognitive dysfunction.

However, the effects of compounds that inhibit KMO are not limited to increasing the levels of kynurenic acid. A recent study showed that KMO inhibition also produces a decrease in the levels of glutamate in a transgenic mouse model of Alzheimer's disease. This was associated with a reduction in the loss of synapses in the brain, with improved memory in a spatial learning task and reduced anxiety behaviour [20]. This would be consistent with the view that part of the neurodegeneration seen in Alzheimer's disease is caused by the excitotoxic effects of endogenous glutamate. Since KMO inhibition should also reduce the formation of quinolinic acid, it is possible that this NMDA agonist may also have contribute to the excitotoxicity in AD, but its role was not assessed directly in that study.

HD. There are many neurochemical similarities observed in the post mortem striatum of patients with HD and animal models produced by quinolinic acid injections [21,22], with additional aspects of motor function in common [23]. Patients also exhibit reduced levels of kynurenic acid in the brain [24], although 3HAA concentrations are raised, consistent with the increased concentrations of quinolinic acid found in the brains of animal models of HD [25,26]. In the most commonly used R6/2 mouse model of the disorder, KMO activity is increased and inhibition of the enzyme prolongs the life span of the animals as well as protecting neurons and synapses and suppressing microglial activation [20]. Recent clinical studies have obtained strong support for a role of kynurenines with the finding of highly significant correlations between the blood

concentrations of kynurenine and the number of DNA codon repeats (CAG) in the abnormally extended nucleotide sequence of the huntingtin gene [27].

Together these results are consistent with the view that the molecular aberration in HD is associated with altered kynurenine metabolism, which could account for at least some of the symptoms and progression of the disease.

Schizophrenia. In schizophrenia, the suppression of dopaminergic function by neuroleptic drugs can reduce the early, positive symptoms which are caused by overactivity of the ventral tegmental projections to the striatum and nucleus accumbens. Classical drugs have little effect on later, negative symptoms which are associated with underactivity of dopaminergic projections to prefrontal cortex [28]. Underlying these disturbances is a hypo-glutamatergic state [29] the induction of which, in animals, is widely used to model schizophrenic symptoms [30]. Thus, compounds that block NMDARs, such as phencyclidine, can induce many of the cardinal symptoms of schizophrenia such as a loss of pre-pulse inhibition [31]. A hypoglutamatergic state could be produced by raised levels of kynurenic acid, and several studies show up to five times the normal level of kynurenate in the cerebrospinal fluid (CSF) of schizophrenic patients [32,33]. The administration of kynurenic acid (directly or via its precursor, kynurenine), produces a reduction of extracellular dopamine concentrations, as seen in the prefrontal cortex in schizophrenia. Conversely, reduced kynurenic acid concentrations promote dopamine release in striatum [34] and hippocampus [35], which may account for the wide spectrum of cognitive dysfunction in schizophrenia. The mechanism of this effect is unclear at the cellular and network level, although it has been suggested that the interaction results from a blockade by kynurenic acid of glutamate or $\alpha 7$ NR on

dopaminergic nerve terminals or local astrocytes [36]. There is a diminished activation of $\alpha 7$ NRs in schizophrenia, and the administration of agonists acting at $\alpha 7$ NRs can reduce many of the positive and negative aspects of cognitive dysfunction in schizophrenia and animal models [37,38].

Slightly complicating this picture is a report that kynurenic acid may facilitate activity of AMPA receptors by modulating their desensitisation [39] and that it produces antagonism of AMPA when used at higher concentrations. To date, however, these results have not been confirmed and may represent, at best, a minor action of kynurenic acid.

Collectively these data suggest that the blockade of glutamate, NMDARs and $\alpha 7$ NRs by kynurenic acid could account for many of the learning and cognitive problems in AD and schizophrenia. Indeed, deletion of the enzyme which synthesises kynurenic acid – kynurenine aminotransferase II (KATII) – has a pro-cognitive effect in animals [40], supporting the view that even normal levels of kynurenate may have a limiting effect on cognitive function. In addition, the plasma concentration of kynurenic acid increases with age in humans and could contribute to age-related deficiencies in memory and cognition [41].

Alternative molecular targets for kynurenic acid

GPR35

Another target of kynurenic acid may be the erstwhile orphan G-protein-coupled receptor GPR35, at which kynurenic acid is one of the most potent endogenous agonists yet identified [42] (Figure 2). The highest levels of GPR35 are in the intestine where, in patients with inflammatory bowel disease, kynurenic acid levels are significantly greater than in control subjects [43]. The

receptor has been implicated in several aspects of gastrointestinal dysfunction including the development of gastric cancer [44]. Its role in the CNS is less clear although loss of GPR35 may underlie at least one form of mental retardation [45]. The agonist activity of kynurenic acid could therefore be important in the early development of the CNS. Indeed, recent data demonstrate that increasing kynurenic acid levels prenatally leads to marked changes in the expression of neurodevelopmental proteins in postnatal life [46].

Expression of GPR35 in immune cells occurs in neutrophils, monocytes, T cells and dendritic cells, but less so in natural killer (NK) cells and eosinophils. Amongst peripheral blood cells, GPR35 expression is greatest in circulating monocytes which, in the presence of kynurenic acid, bind firmly to endothelium, suggesting a role for this ligand-receptor combination in monocyte extravasation [47]. In monocytes, macrophages and glial cells, GPR35 interaction with kynurenic acid down-regulates the proinflammatory phenotype induced by bacterial lipopolysaccharides (LPS), notably reducing TNF- α and high-mobility group box 1 protein (HMGB1) [48] (Figure 2). A proposed intracellular mechanism for this effect is the lowering of intracellular calcium, mediated by GPR35-linked adenylate cyclase inhibition and reduced intracellular cAMP; a similar explanation has been advanced to explain reduced calcium-dependent release of glutamate from GPR35-expressing glia treated with kynurenic acid [42]. There is currently little information available about other immune system cells that express GPR35, except for invariant natural killer cells (iNKT) which, on specific stimulation by glycolipids (presented by antigen presenting cells) produce a large variety of cytokines and chemokines [49]; GPR35 engagement

by kynurenic acid downregulates IL-4 but not IFN- γ and probably has other actions yet to be identified.

Growth factors

Although the blockade of glutamate receptors by kynurenic acid may cause the cognitive dysfunction discussed above, the same blocking action can protect the brain against the excitotoxic effects of abnormally high glutamate receptor activation. This protective activity may be enhanced by effects on growth factors since kynurenic acid can increase the expression of nerve growth factor (NGF) in glial cells [50,51]. NGF is of special importance because of its regulation of proliferation and subsequent maintenance of cholinergic neurones in the CNS, and hence of relevance to AD and schizophrenia [52]. In contrast, kynurenic acid reduced the release of fibroblast growth factor-1 (FGF-1) in several different experimental models [53], so that its net effects on cell viability may depend on a balance of changes in different growth factors.

Although these results are exceptionally interesting for understanding the neuroprotective effects of kynurenic acid, therefore, work should be extended to other growth factors. For example, because kynurenic acid can enhance proliferation of some glial cells, it would be of value to examine the expression and release of gliotropic factors as well as brain-derived growth factor (BDNF).

A kynurenine receptor?

A most surprising discovery has been that kynurenine itself – a compound regarded as being almost devoid of biological activity – can act at the aryl hydrocarbon receptor (AHR) [54] (Figure 3). The AHR is a cytosolic

transcription factor which is the primary binding site for the potent cellular toxin 2,3,7,7-tetrachlorodibenzo-p-dioxin, (often known as 'dioxin'). The receptor is a component of the 'xenobiotic response element' which is important in the detection of foreign substances. The AHR acts on a range of major metabolising enzymes including phase I and phase II enzymes such as CYP1A1, CYP1A2 and CYP1B1 and gives animals the ability to detect and respond to a wider range of xenobiotics and toxins than would otherwise be possible. The AHR appeared early in evolution and exists in a variety of species. Kynurenine may be the primary natural, endogenous ligand at the AHR, promoting protection of the organism, reducing illness triggered or caused by chemicals, and even prolonging survival [54,55]. This view is supported by work in which the AHR has been deleted, leaving animals with physiological aberrations and slowed development [56,57].

The AHR may be associated with fundamental aspects of cell biology including the proliferation and differentiation of cells early in embryonic development, especially in the blood and lymphoid tissues as well as neurons. This would explain a requirement for the AHR in tissue formation [58]. In vertebrates, the role of AHR in development extends to the maturation of cells in the immune and nervous systems. Expression of AHR has been demonstrated in both innate and adaptive immune cells and, with few known exceptions, ligand engagement determines anti-inflammatory and tolerogenic cell phenotypes. Gene knock-out studies indicate that macrophages with intact AHR produce fewer proinflammatory mediators on stimulation with LPS or silica than those lacking AHR [59,60].

Dendritic cells (DCs) present antigens to naïve T cells and are a crucial link between innate and adaptive immunity; whether DCs exhibit a predominantly immunostimulant or immunosuppressive phenotype determines T cell responses. Immunostimulants such as LPS promote the expression of the AHR in DCs, and this expression is in turn required for the induction of IDO [61]. Furthermore, co-cultures of AHR(-/-)DCs and naïve T cells suppressed differentiation of the latter into T_{reg} cells, while addition of kynurenine to this system restored differentiation into anti-inflammatory T_{reg} cells and reduced differentiation into the highly inflammatory Th17 cells [55]. Thus, kynurenine acts on DCs to produce a powerfully anti-inflammatory action (Figures 3, 4). Whether this effect of kynurenine is also mediated through the AHR remains unclear.

In the adaptive immune system, AHRs are also constitutively expressed on naïve CD4⁺ T cells, and on AHR-kynurenine engagement differentiate into tolerizing Foxp3⁺ T_{reg} cells, (which exert a constant restraining influence over both Th1 and Th2 helper cell populations) rather than to the pro-inflammatory Th17 cells [62,63]. One result of this is to promote self-tolerance, reducing the development of autoimmune disorders. The effect is potentiated by the activation (by kynurenine) of AHRs on DCs, an action which inhibits DC maturation and - because these are major antigen presenting cells - further inhibits immune surveillance. This also reduces tumour recognition, and thus, together with its propensity for increasing cell proliferation, AHR activation by kynurenine promotes tumour survival, growth, migration and metastasis [64].

Since kynurenine is generated when IDO or TDO are activated in pro-inflammatory microenvironments by mediators such as IFN- γ or TNF- α , the

discovery of AHR as a kynurenine or kynurenic acid receptor may help to provide the sought-after link between chronic tissue inflammation and the induction of cancer. The future prospects for integrating the biology of kynurenines in the nervous and immune systems with carcinogenesis, with the kynurenine pathway emerging as an important new target for drug development, is immensely exciting.

Finally, it should be noted that, in addition to kynurenine, kynurenic acid may also be an agonist at the AHR with nanomolar potency [65], able to induce expression of the multi-functional and tumour-associated cytokine IL-6 (Figures 3, 4).

The 3-hydroxy compounds

Both 3-hydroxykynurenine (3-HK) and 3-hydroxyanthranilic acid (3HAA) (Figure 1) show significant cellular toxicity. The neurotoxicity of 3-HK is mediated primarily through its production of ROS, which initiate apoptosis [66]. The toxicity is probably produced at an intracellular site because the compound must be taken up by the large neutral amino acid transporter to exhibit toxicity. As with other redox active compounds, 3-HK and 3HAA acid they show pro-oxidant or anti-oxidant activity, depending on the local oxidative environment, and thus regulate the oxidative status of tissues. Given the acknowledged importance of ROS in tissue function and pathology, fluctuations in concentration of 3-HK or 3-HAA could play a significant role in the initiation, progress or remission of diseases involving oxidative stress, which includes many neurodegenerative CNS disorders.

3-HAA also inhibits nitric oxide synthase in macrophages [67] and can readily be nitrosylated to oxadiazole compounds, a property shared with 3-HK [68]. These behaviours could seriously compromise the biological functions of NO and merit further investigation.

Certainly, the levels of 3-HAA can change dramatically. In a study of patients newly diagnosed with osteoporosis, plasma levels of 3-HAA were less than 10% of those in control subjects. Over two years' treatment with standard drugs, this level rose to control values in parallel with significant improvements in bone density [69]. Intriguingly, this leap in plasma 3-HAA concentrations was accompanied by the converse change in anthranilic acid, another kynurenine metabolite whose origin, metabolism and biology remain largely unexplored. A similar reversal in the ratio of 3-HAA and anthranilic acid has been discovered in patients with Huntington's disease (HD), stroke and chronic brain injury [70].

Cinnabarinic acid is a metabolite of 3-HAA formed by its oxidative dimerisation. This compound is able to induce apoptosis of T cells with a potency about ten times that of 3-HAA itself [71], and it may, therefore, be the compound responsible for some of the effects hitherto attributed to 3-HAA. In addition, cinnabarinic acid activates mgluR4 [72], raising the possibility that it may have relevance to the development or treatment of several CNS disorders, especially Parkinson's disease [73].

A wider role in the immune system

In addition to the effects that kynurenines have on immune function via the AHRs, there is increasing evidence for more generalised actions on the immune system. The inhibitory effect of IFN- γ on the growth and proliferation of

Toxoplasma parasites cultured with fibroblasts results from its activation of the first enzyme in the kynurenine pathway – IDO [74]. The activation produced a suppression of cell proliferation which was restored by adding tryptophan, giving rise to the 'tryptophan depletion' hypothesis which posits that the activity of IDO reduces the local concentrations of tryptophan, which in turn limits protein synthesis to rapidly dividing cells.

That observation marks the start of interest in kynurenine effects in the immune system. A second landmark discovery was that inhibition of IDO, using 1-methyl-tryptophan, produced a loss of embryos in pregnant rats [75]. The proposed explanation was that the placenta normally upregulated IDO to maintain low tissue concentrations of tryptophan, thus inhibiting the activity and proliferation of maternal T cells that would normally detect and destroy the allogeneic foetus. By inhibiting IDO, therefore, this tryptophan depletion could not be induced and T cell attack proceeded successfully to destroy the foetus. This pioneering work diversified rapidly into investigating the links between raised levels of IDO and immunotolerance in both transplantation and cancer [76] (Figure 4).

Much of the immune tolerance to tumours is particularly attributed to the proliferation of regulatory T cells (T_{reg} cells) expressing the Foxp3+ transcription factor [77]. These cells depress the activity of aggressive T cell populations including CD8+ cytotoxic (anti-tumour) cells, DCs and NK cells. IDO activation in a sub-population of DCs initiates a positive feedback cycle leading to an expansion in the numbers of Foxp3+Treg cells by promoting their differentiation from naïve CD4+ T cells, a change which is greatly enhanced in the presence of transforming growth factor- β (TGF- β) and IL-6. These T_{reg} cells then act back

on DCs to induce further IDO [78] (Figure 4). Also, 3-HAA stimulates the production of TGF- β , which further potentiates T_{reg} cell formation. Overall, the increased numbers of Foxp3⁺Treg cells, involving the expression of IDO activity, suppresses immune function and generates a pronounced anti-inflammatory effect. This is further enhanced by a direct inhibition of Th1 cells by 3-HAA [79] (Figure 4).

In addition to stimulating TGF- β production, 3-HAA acts directly upon Th1 cells to suppress their pro-inflammatory activity, but has no discernible action on Th2 cells [78-80] although IDO activation overall may promote Th2 function [81]. These two T cell populations normally exist in a delicate balance, with Th1 cells generating IFN γ helping to sustain macrophage activation and release the powerfully pro-inflammatory TNF- α as well as other deleterious substances including ROS. The combination of these Th1-induced factors is anti-microbial but also tends to attack allogeneic cells, producing rejection of tissue allografts and foetal resorption or abortion. Th2 cells generate IL-4 which acts as a brake on the activation of macrophages by IFN γ , thus imposing an anti-inflammatory restraint on the system and contributing to graft retention and foetal protection [82, 83]. The preferential inhibition of Th1 cells, therefore, confers on 3-HAA an overall immunoprotective influence [82].

In fact, IDO activation may not be the only trigger for this cascade. IFN- γ and other pro-inflammatory cytokines also induce kynurenine-2,3-dioxygenase (KMO) and kynureninase so that, as long as kynurenine is available, the levels of 3-HK, 3HAA and quinolinic acid generated by DCs will be sufficient to regulate the activity of immune system cells [84]. The resulting state of immune

tolerance (tolerogenesis) seems to be produced by the kynurenine metabolites rather than by tryptophan depletion.

Although IDO is widely distributed in many tissues, the closely related enzyme tryptophan-2,3-dioxygenase (TDO) is largely confined to the liver. It also converts tryptophan to kynurenine and its subsequent metabolites and will therefore reduce T cell activity and immune surveillance, thus increasing the possibility of tumour formation as discussed above for IDO. In contrast to IDO, the activity of TDO is induced by glucocorticoids [85,86]. and, because the secretion of these steroids occurs in response to stress, this link may contribute to the greater incidence of cancer resulting from chronic stress, for which TDO inhibitors might present a potential treatment [87,88].

Kynurenine metabolites help to regulate secretion of the tolerogenic Human Lymphocyte Antigen-G (HLA-G) [89]. In patients with HD, blood levels of this antigen correlate significantly with the levels of kynurenine metabolites in the blood. There is also a strong correlation between tryptophan metabolism and the size of the abnormally extended huntingtin protein which is believed to cause the disorder [27], supporting the increasing evidence for a significant pathological role for kynurenines in Huntington's disease [22].

Kynurenines and drug development

The discovery that kynurenine-derived metabolites of tryptophan could modulate the level of glutamate receptor activation focussed early interest on their potential roles in neurodegenerative disorders in which over- or under-activity of those receptors could produce excitotoxicity and neurodegeneration, or a general suppression of excitatory neurotransmission respectively. As this

review indicates, some of those original thoughts may still be highly relevant in disorders such as AD and HD, where compounds that inhibit KMO in particular could slow the rate of neuronal loss. In schizophrenia, the contrary situation is encountered, with raised kynurenic acid levels that could be normalised by development of selective inhibitors of KAT II [21]. The pro-cognitive actions of KAT inhibition have been adequately confirmed by the finding that deletion of KAT II results in a similar degree of cognitive enhancement and memory function [40]. The potential value of the kynurenine pathway for the development of new drugs acting in disorders such as these, in which a degree of neuronal damage is involved, has been discussed previously [90]

In addition, the identification of a range of molecular targets such as GPR35, with potential roles in inflammatory disorders, raises the possibility of developing new generations of anti-inflammatory compounds based on the chemical structure of kynurenic acid. Similarly, as knowledge develops of the actions performed by the AHR, the recognition of kynurenic acid as the possible natural ligand raises an entirely new means of viewing the possible pharmacological regulation of xenobiotic metabolism.

Finally, the parallel work that has developed since the early 1980s of the actions of kynurenines in the CNS and their effects in the immune system seem to be moving closer towards an integrated view of their interaction. That may in turn result in the development of compounds that can regulate changes in the processes of CNS neurotransmission directly, but which can also modify the development and progression of inflammatory reactions that increasingly seem to underlie chronic CNS disorders such as AD and HD, but may also be relevant to conditions such as multiple sclerosis (MS) [91] and infection-induced

dementias [92]. This is certainly a pathway that is likely to become more intriguing in the future.

Concluding remarks

Although the links between tryptophan metabolism to kynurenines and to 5-HT should not be forgotten, future research might benefit greatly from an increasing attention on the oxidative metabolism of tryptophan along the kynurenine pathway. The potential sites for interference may be under- or over-activated by their ligands, mutated genetically or modified epigenetically and should be regarded as druggable targets for pharmacological development with therapeutic value in a range of disorders in the nervous and immune systems.

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Legends

Figure 1

A summary of the main compounds which constitute the kynurenine pathway for the oxidative metabolism of tryptophan. The pathway is usually referred to in this way after the initial stable product of tryptophan oxidation, kynurenine, which was originally isolated from canine urine in the nineteenth century and named to reflect this.

Figure 2

The major cellular and molecular targets of kynurenic acid. The blockade of NMDA receptors was the first specific site of action to be identified [2], followed nearly 20 years later by blockade of $\alpha 7$ nicotinic receptors [13]. Increasing interest is being shown in a range of sites in the immune system with potential importance in the regulation of immune tolerance and cancer suppression.

Figure 3

Potential sites at which kynurenine, for long regarded as biologically inactive, may act to regulate the balance of cells produced in the immune system.

Figure 4

The first enzyme in the kynurenine pathway, indolamine-2,3-dioxygenase (IDO) plays a key role in regulation of the immune system by virtue of its activation by mediators such as interferon- γ . In addition to the effects of kynurenic acid and kynurenine itself, some features of the kynurenine pathway on the balance of inflammatory status are mediated by 3-hydroxykynurenine and 3-hydroxyanthranilic acid (3HAA).

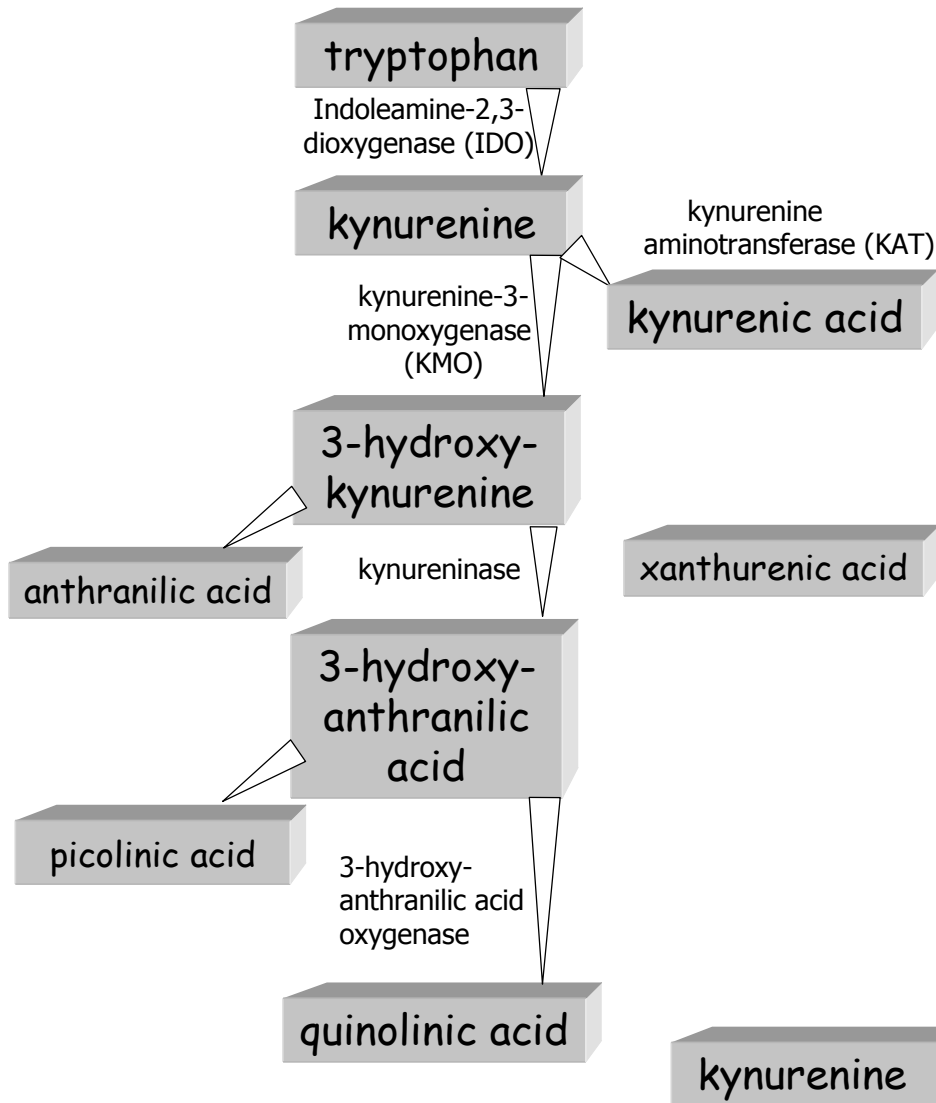


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Figure 2

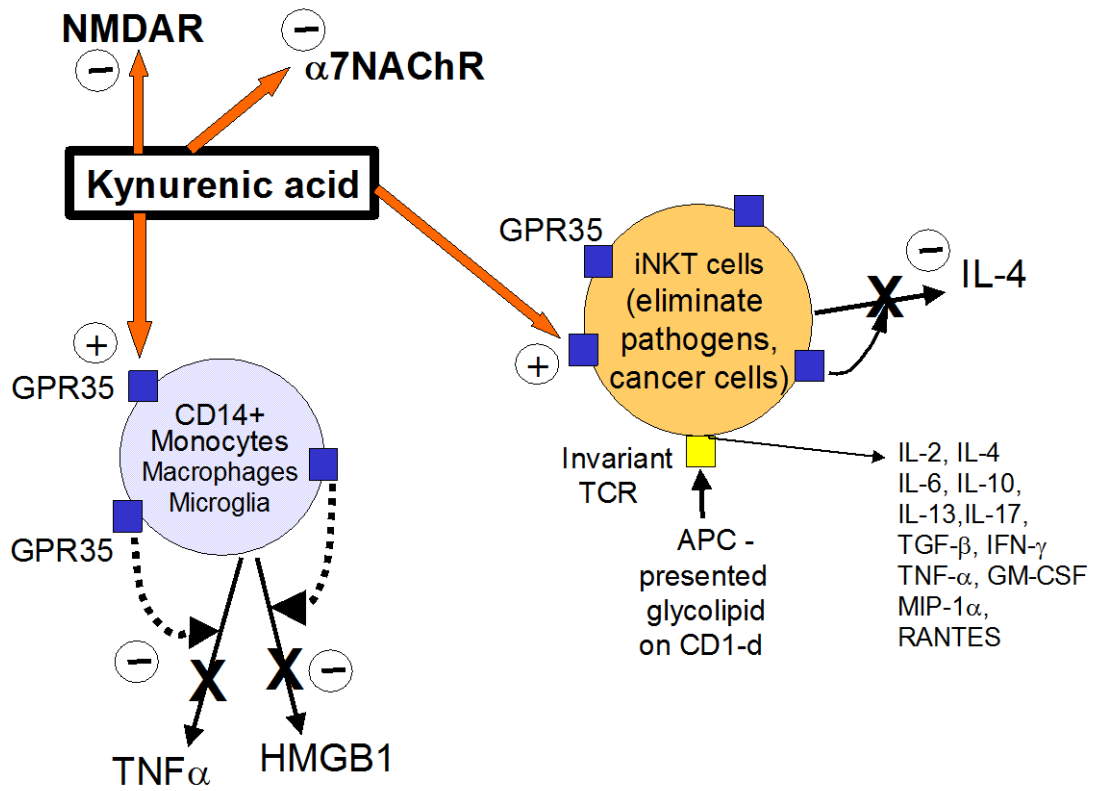


Figure 3

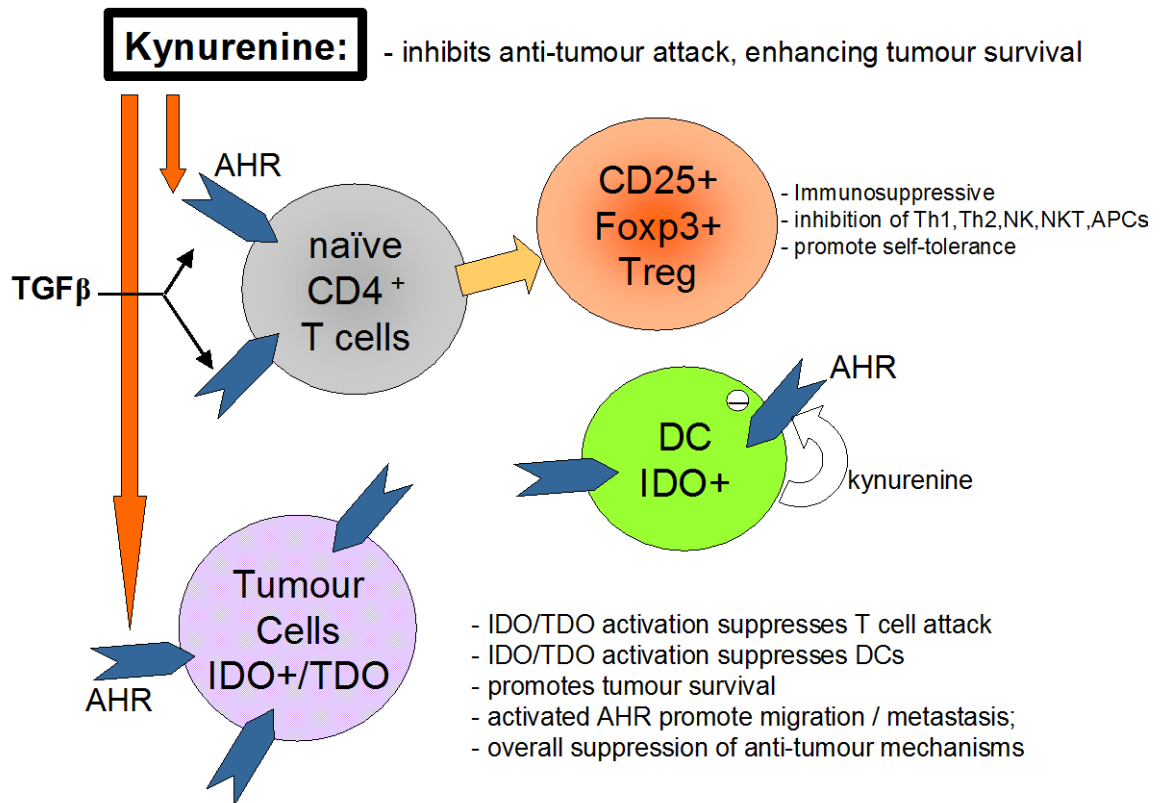
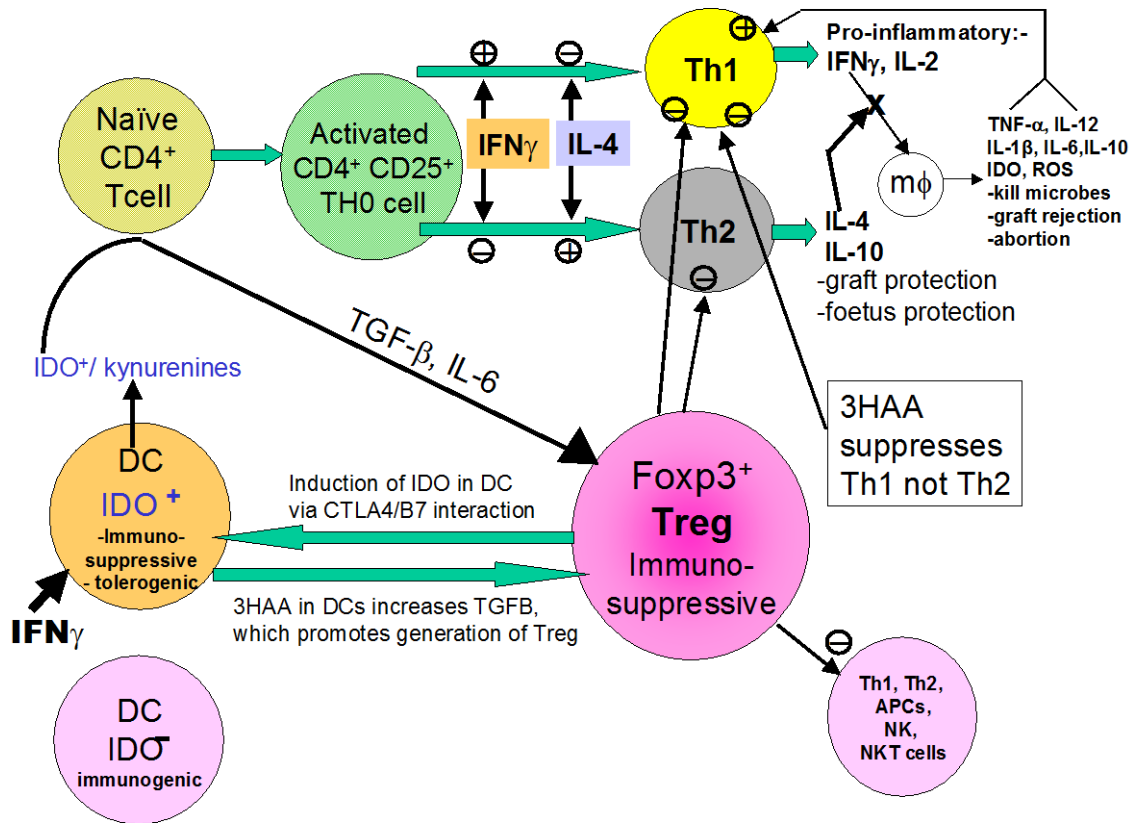


Figure 4



Abbreviations

α 7NR:	α 7-nicotinic cholinceptors
AHR:	aryl hydrocarbon receptor
AMPA:	α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
CD8+ :	cytotoxic (anti-tumour) T cells
CSF :	cerebrospinal fluid
DC:	Dendritic cells
GPR35:	G-protein-coupled receptor 35.
3-HAA	3-hydroxyanthranilic acid
3HK:	3-hydroxykynurenine:
HLA-G:	Human Lymphocyte Antigen-G
HMGB1	:high-mobility group box 1 protein
IDO:	indoleamine-2,3-dioxygenase
IL-1 β :	Interleukin-1 β
IFN- γ :	interferon- γ
iNKT:	invariant natural killer cells
KAT:	kynurenine aminotranferase
KMO:	kynurenine-3-monoxygenase
LPS:	bacterial lipoloyasaccharides
MCP-1:	monocyte chemoattractant protein-1
NK:	natural killer cells
NMDAR:	N-methyl-D-aspartate receptors
RANTES:	Regulated on Activation, Normal T-cell Expressed and Secreted
ROS:	reactive oxygen species
TDO:	tryptophan-2.3-dioxygenase

TGF- β : transforming growth factor- β

Th1, Th2 T-helper cell populations

TNF- α : tumour necrosis factor- α