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Tryptophan, adenosine, neurodegeneration and neuroprotection

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Abstract This review summarises the potential contributions of two groups of compounds to cerebral dysfunction and damage in metabolic disease. The kynurenines are oxidised metabolites of tryptophan, the kynurenine pathway being the major route for tryptophan catabolism in most tissues. The pathway includes quinolinic acid – an agonist at *N*-methyl-D-aspartate (NMDA) receptors, kynurenic acid – an antagonist at glutamate and nicotinic receptors, and other redox active compounds that are able to generate free radicals under many physiological and pathological conditions. The pathway is activated in immune-competent cells, including glia in the central nervous system, and may contribute substantially to delayed neuronal damage following an infarct or metabolic insult. Adenosine is an ubiquitous purine that can protect neurons by suppressing excitatory neurotransmitter release, reducing calcium fluxes and inhibiting NMDA receptors. The extent of brain injury is critically dependent on the balance between the two opposing forces of kynurenines and purines.

Keywords Glutamate · NMDA · Ischaemia · Neurodegeneration · Neuroprotection

Introduction

It has long been recognised that hepatic encephalopathy is associated with organic brain damage and associated psychiatric symptoms, and is potentially fatal if untreated (Jalan *et al.* 2003; Matsusue *et al.* 2005). One of the dominant hypotheses has been that the accumulation of ammonia in the brain results in glial and neuronal disorganisation and ultimately cell death (Klejman *et al.* 2005), so that mechanistic

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emphasis has been placed upon the processes of ammonia accumulation, toxicity, removal and metabolism. In recent years several studies have indicated that ammonia toxicity is mediated via the activation of glutamate receptors which also respond to *N*-methyl-D-aspartate (NMDA), a conclusion largely based on the ability of NMDA antagonists to reduce ammonia toxicity in vivo or in cell cultures (Albrecht and Wegrzynowicz 2005; Klejman *et al.* 2005; Kosenko *et al.* 2003, 2004; Kitano *et al.* 2004).

Recent work by Rao *et al.* (2005a, b) has emphasised this possibility with the demonstration that ammonia accumulation activates the mitochondrial permeability transition pore, probably via NMDA receptors. This action is completely prevented by several antioxidant strategies including free radical scavenging with phenyl-t-butyl nitrone or vitamin E, or the inhibition of nitric oxide or superoxide activity.

Another aspect of NMDA receptor involvement was highlighted by Kosenko *et al.* (2003). This group reported that NMDA receptors were involved in the cellular ATP depletion and mortality of ammonia accumulation and they inhibited, via the formation of nitric oxide, the activity of glutamine synthetase. This direct modulation of ammonia metabolism, therefore, represents an important potential mechanism by which the activation of NMDA receptors could contribute to the progression of hepatic encephalopathy.

With the possibility that NMDA receptors could be involved in the cerebral dysfunction associated with hepatic encephalopathy, the question arises of how an overactivation of these sites could arise. One possibility is that the kynurenine pathway of tryptophan oxidation (Fig. 1) is induced, as this pathway includes the generation of compounds that can activate (quinolinic acid) or block (kynurenic acid) receptors for NMDA, and several compounds that have marked redox activity, such as 3-hydroxykynurenine and 3-hydroxyanthranilic acid (Stone 2001; Stone and Darlington 2002). This will be the subject of the first part of this review. The second part will consider the protective potential of purine nucleosides such as adenosine, part of the activity of which consists of modulating the activation of NMDA receptors (Norenberg *et al.* 1997; De Mendonca *et al.* 1995), although its own inhibitory and protective actions can be suppressed by NMDA receptors (Bartrup and Stone 1990; Nikbakht and Stone 2001; Shahraki and Stone 2004). There is, therefore, a level of interaction between NMDA and adenosine receptors, the balance of which may be critical in compromising brain function under pathological conditions.

Tryptophan oxidation via the kynurenine pathway

The first kynurenine pathway metabolite of tryptophan which was recognised as being neuroactive at the cellular level was quinolinic acid (Fig. 1). This compound depolarises neurons by activating NMDA receptors (Stone and Perkins 1981). As a result, it is also able to produce excitotoxicity (Schwarcz *et al.* 1983), and this realisation has led to quinolinic acid being implicated in a variety of central nervous system (CNS) disorders (see Stone 1993, 2001; Stone and Darlington 2002).

There has been some interest in the possibility that raised levels of quinolinic acid could account for the neurological symptoms associated with hepatic encephalopathy in humans or animal models (Moroni *et al.* 1986a, b). However, Heyes and his

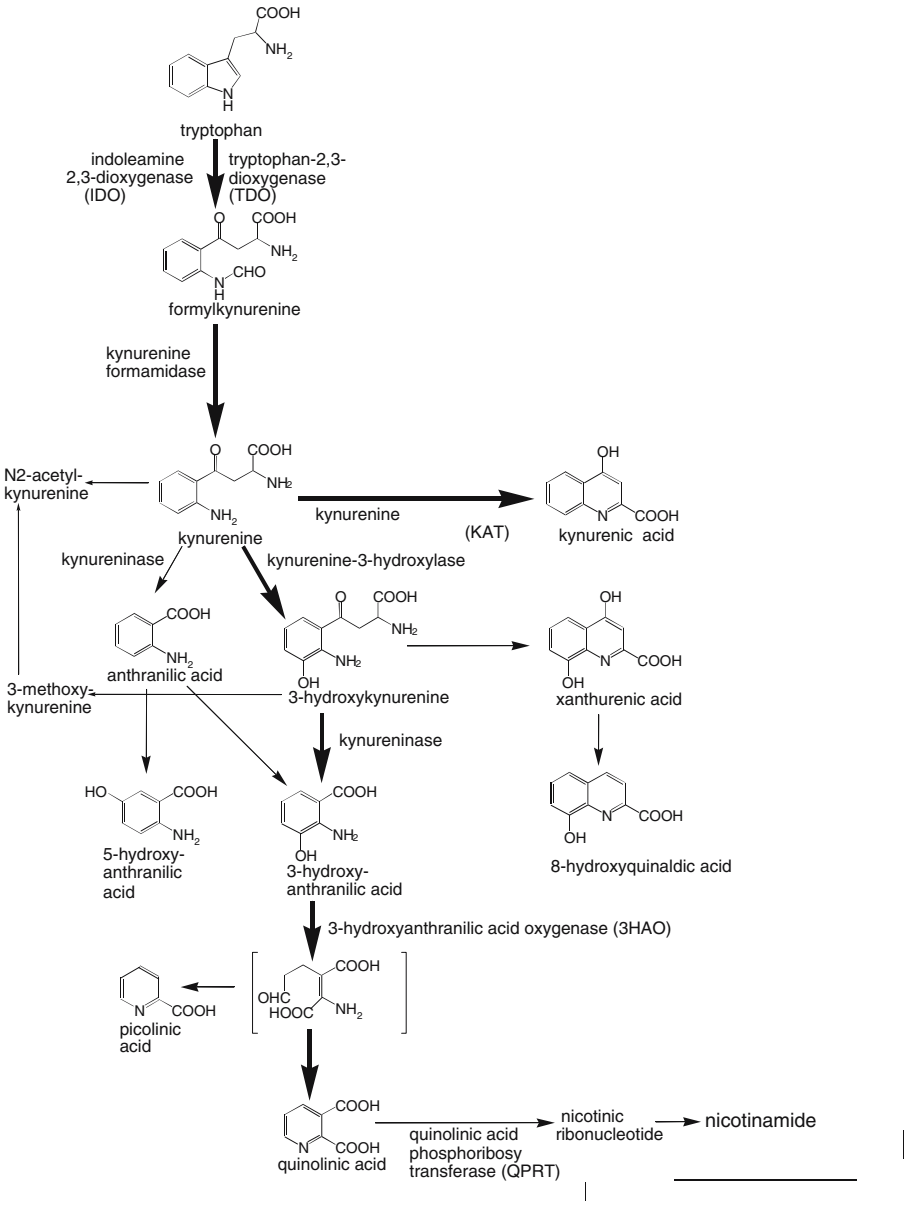

Fig. 1 A summary of the main components of the kynurenine pathway for the oxidative metabolism of tryptophan

collaborators have found that experimental models of hyperammonaemia, including the existence of portosystemic shunts are not associated with raised levels of quinolinic acid in the brain (Robinson *et al.* 1992; Bergqvist *et al.* 1995, 1996). Furthermore, although it was found that the levels of quinolinic acid in the brain of patients with hepatic encephalopathy were elevated compared with controls, it subsequently became apparent that this was the case only in patients dying with

acute disease and not chronic hepatic encephalopathy (Basile *et al.* 1995). This appeared to remove any obvious correlation between quinolinic acid levels and cerebral damage.

However, it remains possible that the difference between the acute and chronic conditions could lie in the kinetics of quinolinic acid production and removal. In the acute state this compound may be produced at such as rate that it overwhelms any removal process, whereas in the chronic disease, levels of quinolinic acid may rise sufficiently slowly that it can be removed. This possibility is strengthened by the fact that no specific removal or uptake process has been demonstrated for quinolinic acid, so that it's loss is largely via further metabolism or diffusion into the bloodstream.

Secondly, the concentrations of quinolinic acid causing cell damage do not need to be greatly elevated, and other, parallel, changes during a disorder such as hepatic encephalopathy may come into play. The amounts of quinolinate in the brain and cerebrospinal fluid (CSF) are normally less than 100 nM, but levels only slightly greater than this can cause neurotoxicity when cells are exposed for several hours (Kim and Choi 1987; Khaspekov *et al.* 1989; Galarraga *et al.* 1990) or weeks (Whetsell and Schwarcz 1989) with some neurones being damaged after exposure to only 100 nM quinolinic acid (Giulian *et al.* 1990, 1993). Concentrations of 350 nM for 5 weeks were shown by Kerr *et al.* (1995, 1998) to induce changes in the cellular cytoskeleton which in turn resulted in dendritic varicosities and damaged microtubules.

The pathological significance of quinolinic acid neurotoxicity may be partly dependent on its interaction with other factors. It has been shown, for example, that its toxic activity is enhanced by the presence of reactive oxygen or nitrogen species generated by the combination of xanthine and xanthine oxidase or the nitric oxide donor *S*-nitroso-*N*-acetyl-penicillamine (SNAP) (Behan and Stone 2002). Quinolinic acid itself can generate free radicals, as reflected in the ability of scavengers to reduce its neurotoxicity (Nakao and Brundin 1997; Nakai *et al.* 1999), partly as a result of Fenton reactions catalysed by the presence of iron (Rios and Santamaria 1991). The involvement of free radicals is supported by the finding that quinolinic acid-induced damage could be prevented by antioxidants such as melatonin and deprenyl (Southgate *et al.* 1998; Behan *et al.* 1999).

Sources of quinolinate

Of some relevance to the possible role of quinolinic acid in hepatic disorders is that the kynurenine pathway is induced in peripheral macrophages and CNS microglia in response to immune or inflammatory stimuli (Heyes *et al.* 1996; Espey *et al.* 1997; Pemberton *et al.* 1997). The levels of quinolinic acid can rise in some inflammatory disorders more than 50-fold, generating concentrations that are overtly toxic in their own right.

The systemic administration of lipopolysaccharide increases quinolinic acid immunoreactivity in rodent brain (Heyes *et al.* 1989) and lymphoid tissue within 24 h (Espey *et al.* 1995). The cells staining most intensely were identified as dendritic cells and macrophages and led to the proposal that quinolinic acid might represent an important agent in the regulation of immune cell activity or immuno-surveillance. Staining with an antibody to quinolinic acid has revealed the presence of quinolinic acid in immune system cells of all types (Moffett *et al.* 1994) and this

immunoreactivity was increased in monkeys infected with simian immunodeficiency virus (Namboodiri *et al.* 1996). In rats, quinolinic acid-immunoreactivity occurred in macrophages rather than microglia or neurones (Moffett *et al.* 1993, 1997).

Sung *et al.* (1997) demonstrated by immuno-electron microscopy that quinolinic acid was associated with the internal face of the plasma membrane of human peripheral blood monocytes and macrophages. An increased density of staining was seen upon treatment with kynurenine or interferon-γ, but quinolinic acid-positive particles remained attached to the cell membrane, raising the suggestion that these might reflect sites from which quinolinic acid could be released into the extracellular space. This hypothesis would fit well with the concept of quinolinic acid as the product of immune-activated cells in inflammatory conditions such as AIDS.

Human microglia, blood macrophages, and mixed cultures of human foetal brain cells can ordinarily convert tryptophan, kynurenine or 3-hydroxykynurenine into quinolinic acid even when unstimulated (Heyes *et al.* 1992). Treatment with interferon γ- induces the activity of indoleamine-2,3-dioxygenase (IDO), kynurenine-3-hydroxylase, kynureninase and 3-hydroxyanthranilic acid oxygenase, and increases kynurenine production sufficiently to reach >40 μM in these cells. The enhanced generation of quinolinic acid allows it to attain levels of 438 and 1410 nM in glia and macrophages respectively (Heyes *et al.* 1996). Human macrophages stimulated with tumour necrosis factor-α (TNF-α) or interferon-γ yielded large amounts of quinolinic acid, cellular concentrations reaching 10.3 μM after 72 h. Combinations of TNF-α and interferon-γ produced concentrations up to 16.7 μM, far exceeding the quinolinic acid concentrations known to be neurotoxic (Pemberton *et al.* 1997). The amount of quinolinic acid in the brain after immune stimulation can be prevented either by inhibitors of tryptophan metabolism or by the anti-inflammatory steroid dexamethasone, a compound able to suppress the activation of immune-competent cells (Saito *et al.* 1994).

Kynurenines, brain damage and hepatic encephalopathy

The spectrum of disorders in which brain damage may involve – to some extent – activation of the kynurenine pathway has been reviewed by Stone (2001), but a few examples here may suffice to convey some impression of the type of work performed to date.

Substantial increases in the production of several kynurenines can be produced by infection (Heyes *et al.* 1992), whether systemic or intracerebral. Quinolinic acid concentrations correlate well with markers of immune activation such as neopterin (Heyes *et al.* 1990, 1992). Septicaemia in non-human primates was associated with increases in serum and CSF quinolinic acid and kynurenine (Heyes and Lackner 1990). Mice infected with Herpes simplex virus type 1 develop paralysis which correlates closely with the increased concentration of quinolinate in the spinal cord, and with increased activity of IDO and kynurenine hydroxylase (Reinhard 1998). The levels of quinolinic acid can increase 40-fold over a few days in this condition.

Quinolinic acid levels rose 50-fold over the course of 7 days following the induction of cerebral ischaemia in gerbils, mimicking an ischaemic stroke (Heyes and Nowak 1990). This post-ischaemic rise, together with increased activity of the kynurenine pathway enzymes were limited in mice to brain regions experiencing an

interrupted blood supply (Saito *et al.* 1992), supporting the view that the quinolinic acid is of local origin. For reasons that remain unclear, there was no change in the activity of kynurenine aminotransferase with the result that the increased quinolinic acid: kynurenic acid ratio would exacerbate the neuronal damage. Activated microglia and macrophages may be at least partly responsible for these changes since quinolinic acid-positive microglia can be demonstrated in the brain following transient global ischaemia in the gerbil (Lees 1993; Baratte *et al.* 1998).

There is a delayed invasion by mononuclear phagocytes following experimental traumatic injury of the guinea-pig spinal cord. This results in raised concentrations of quinolinic acid, together with IDO activity, which can be maintained for several weeks (Blight *et al.* 1993, 1997; Popovich *et al.* 1994). When the kynurenine pathway was inhibited at the level of 3-hydroxyanthranilic acid oxygenase (Fig. 1), using the inhibitor 4-chloro-3-hydroxyanthranilate, there was a parallel decline in quinolinic acid levels and in the behavioural and motor deficits (Blight *et al.* 1995). This may suggest a potential avenue of therapy in humans, since accidental mechanical injury results in increased levels of quinolinic acid in the spinal cord which correlate well with symptom severity and mortality (Sinz *et al.* 1998; Bell *et al.* 1999).

Kynurenines, including quinolinic acid and kynurenic acid, and the free radical generators 3-hydroxykynurenine and 3-hydroxyanthranilic acid could, therefore, contribute to cerebral dysfunction via the modulation of NMDA receptors as is believed to occur in most of the disorders summarised above. In relation to hepatic encephalopathy specifically, Holt *et al.* (2002) have demonstrated raised levels of quinolinic acid in the brains of dogs with porto-systemic shunts, emphasising the possible role of the kynurenine pathway in the associated cerebral dysfunction. In addition, there are emerging alternative possible mechanisms of kynurenine-induced brain damage, some of which may be uniquely relevant to hepatic encephalopathy, as follows.

Nicotinamide

One consequence of NMDA receptor activation, or indeed the initiation of cellular damage by a variety of insults, is the activation of poly(ADP-ribose) polymerase with the depletion of nicotinamide adenine dinucleotide (NAD), a co-factor so essential for a variety of critical reactions that it's depletion leads to cell death (Kosenko *et al.* 2004). It is interesting to note, therefore, that a product of the tryptophan oxidation/kynurenine pathway is nicotinamide, produced from quinolinic acid (Fig. 1). Nicotinamide is being increasingly recognised as a neuroprotective compound, partly because of its replenishment of cellular NAD. It has been proposed that the generation of nicotinamide, and the subsequent restoration or maintenance of NAD levels is a major function of the kynurenine pathway acting as, paradoxically, a cellular protectant pathway.

Kynurenic acid

Kynurenic acid (Fig. 1) is an antagonist at several subtypes of glutamate receptor, including those responding to kainic acid or α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (Perkins and Stone 1982, see Stone 2001), although it has

its greatest potency as an antagonist at the co-agonist strychnine-resistant glycine site on NMDA receptors (Birch *et al.* 1988). It is this property which has led to kynurenate's being used as the lead compound for the development of glutamate antagonists for use against several central disorders (Stone 2000a, b).

Kynurenic acid is of particular interest in terms of hepatic encephalopathy, since ammonia inhibits its synthetic enzyme – kynurenine aminotransferase – in brain neurons and glia (Saran *et al.* 1998; Kocki *et al.* 2002). However, it is another paradox of the relationship between kynurenines and hepatic encephalopathy that, when measured directly in the brains of rats with the experimentally-induced disorder, levels of kynurenic acid were found to be increased, rather than decreased (Saran *et al.* 2004). It is possible that this results from a biochemical adaptation to the raised CNS ammonia levels, in an attempt to combat activation of NMDA and other glutamate receptors, and thus limit the brain damage caused. The short-term blockade of glutamate receptors could, however, contribute substantially to the coma and other symptoms of encephalopathy.

On the other hand since, as noted above, kynurenate blockade of NMDA receptors will result in a lowering of glutamine synthetase activity, it is possible that the increased kynurenic acid concentration in brain could be exacerbating the rise of ammonia levels, thus contributing to long-term cerebral dysfunction (Fig. 2).

Kynurenines and oxidative stress

In addition to the toxicity of quinolinic acid, mediated by the NMDA receptor, the kynurenine pathway includes another compound with significant neurotoxic potential—3-hydroxykynurenine (Fig. 1). This substance is a less potent toxin than quinolinic acid, and the neuronal damage produced seems to be mediated by free radicals and not glutamate receptors (Eastman and Guilarte 1989, 1990; Nakagami *et al.* 1996;

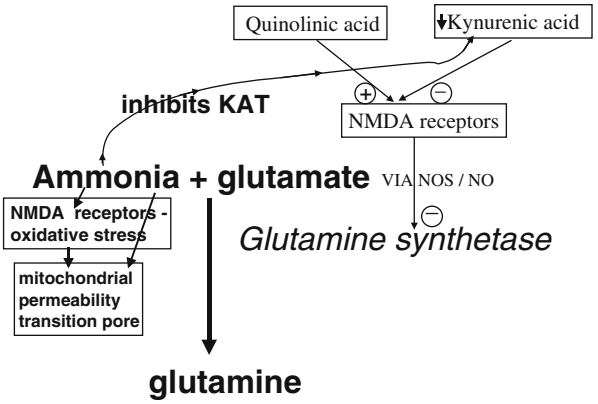

Fig. 2 Possible role of kynurenines in hepatic encephalopathy. Quinolinic acid, via NMDA receptors inhibits glutamine synthetase, thus slowing the removal of ammonia and potentiating tissue damage. Raised levels of kynurenic acid, as detected in the brain by Saran *et al.* (2004), block NMDA receptors and thus increasing glutamine synthetase activity, and may protect the brain. However, ammonia itself inhibits kynurenine aminotransferase (Kocki *et al.* 2002), the enzyme synthesising kynurenic acid, and will therefore reduce its protective activity. In effect, ammonia is enhancing its own toxicity by suppressing kynurenic acid formation

Okuda *et al.* 1996, 1998). 3-Hydroxykynurenine can be converted to quinoneimines with the accompanying generation of reactive oxygen species (Hiraku *et al.* 1995). The uptake of 3-hydroxykynurenine into cells is required for neurotoxicity, as damage can be prevented by blocking uptake into cells by competing large neutral amino acids (Okuda *et al.* 1998). Following immune activation or the administration of interferon-γ, the levels of 3-hydroxykynurenine are increased in the brains of mice (Saito *et al.* 1992). Levels are also elevated in cases of HIV infection, especially those associated with dementia (Sardar *et al.* 1995), infantile spasms (Yamamoto *et al.* 1994) and hepatic encephalopathy (Pearson and Reynolds 1991). It is possible that some of the deleterious actions attributed to 3-hydroxykynurenine are actually due to its metabolite 3-hydroxyanthranilic acid (Dykens *et al.* 1987, 1989), since the latter readily undergoes auto-oxidation with the formation of superoxide anions.

The activity of IDO has been measured in the post-mortem brains of AIDS patients (Sardar *et al.* 1995). Enzyme activity was increased significantly in tissue from those patients with dementia compared with tissue from controls or non-demented AIDS patients. The increased enzyme would lead to elevations both in quinolinate and 3-hydroxykynurenine. Raised levels of 3-hydroxykynurenine have also been reported in patients with Huntington's disease (Reynolds and Pearson 1989; Pearson and Reynolds 1992). This finding would be consistent with the demonstration in Huntington's disease brain of an increase in the activity of 3-hydroxyanthranilic acid oxygenase, one of the enzymes responsible for its removal (Schwarcz *et al.* 1988), if the raised levels of 3-hydroxykynurenine led to an induction of enzyme activity. Despite this possibility, however, there appears to be no change in the enzymes kynurenine aminotransferase and kynurenine-3-hydroxylase in the Huntington's disease brain (Pearson *et al.* 1995), leaving open the question of why kynurenic acid levels should be altered in this disorder.

Adenosine and neuroprotection

Another endogenous metabolite, adenosine, is released by a wide variety of cells when their metabolic status is compromised, especially when there is a mismatch between metabolic activity and oxygen supply. In addition to its roles as a precursor of ATP and cyclic AMP, adenosine acts on four subtypes of cell membrane receptors – A_1, A_{2A}, A_{2B} and A_3, and there is good evidence that several of these can have a protective effect against potential injury to the CNS. The activation of A1 receptors was among the first procedures shown to be protective (von Lubitz *et al.* 1989), an action resulting from the generally inhibitory nature of these receptors which induce direct hyperpolarisation of neurons, inhibition of glutamate release from excitatory neurons, and suppression of the rise of intracellular calcium levels which trigger neuronal damage. The extracellular concentration of adenosine is normally in the high nanomolar to low micromolar range in mammalian brain, but this can increase up to one thousand-fold following a hypoxic or ischaemic episode (Winn *et al.* 1979; Latini *et al.* 1999; Hagberg *et al.* 1987).

Indeed, the importance of endogenous adenosine as a natural neuroprotectant against such insults is strongly supported by demonstrations that antagonists at A1

receptors, including potent xanthines such as 8-cyclopentyl-1,3-dipropylxanthine, greatly increase the neuronal damage resulting from ischaemia or excitotoxins (Phillis 1995). There is, however, a time-dependency of these effects, in that A1 receptor activation must occur acutely in order to be neuroprotective. The effect on neuronal damage of A1 or A_{2A} receptor agonists and antagonists depends on whether the compounds are administered acutely or chronically (von Lubitz *et al.* 1995; Ongini *et al.* 1997, 2001), since an agonist administered chronically may produce an exacerbation of cell damage, for example, while acute treatment yields a protective action. The converse applies to antagonists. These inversions of protection are presumably the result of up- or down-regulation of receptor number or characteristics, or adaptive changes in their transduction systems, with chronic administration.

A1 receptors

Several A1 receptor agonists have been shown to protect neurones against damage following an ischaemic episode (Daval *et al.* 1989; Heron *et al.* 1994; Rudolphi *et al.* 1992; Tominaga *et al.* 1992; von Lubitz *et al.* 1999. The selective agonist R-phenylisopropyl-adenosine reduced the excitotoxic effects of quinolinic acid and kainic acid (Arvin *et al.* 1989; Connick and Stone 1989; MacGregor *et al.* 1993, 1996; MacGregor and Stone 1993). Indeed, A1 agonism represents one of the few approaches to reducing neuronal damage produced by the dopaminergic neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Lau and Mouradian 1993), raising the possibility of developing A1 receptor agonists for the treatment of Parkinson's disease.

Agonists at A1 receptors probably protect tissues partly by suppression of transmitter release, since both amino acid and amine transmission can be inhibited (Andine *et al.* 1990; Butcher *et al.* 1990; Michaelis *et al.* 1979; Spignoli *et al.* 1984). A1 receptors can also reduce calcium influx in neuronal and cardiac tissues (Scholz and Miller 1991), possibly secondary to the modulation of potassium conductances including the ATP-sensitive potassium channels in heart and hippocampal neurons (Hosseinzadeh and Stone 1998; Regenold and Illes 1990). The elevation of intracellular calcium levels is widely considered to represent the final common path of several injurious stimuli, and the lowering of intracellular calcium could be a key contributor to the mechanism of cell protection.

A_{2A} receptors

Agonists acting at A_{2A} receptors can protect against ischaemia (Sheardown and Knutsen 1996) and excitotoxins such as kainate (Jones *et al.* 1998a, b), although this is probably via a peripheral mechanism, since direct injections into the hippocampus of the selective agonist 2-[p-(2-carboxyethyl)-phenylethylamino]-5′-N-ethylcarboxamido-adenosine (CGS21680) failed to afford protection against kainic acid excitotoxicity. Antagonists at A_{2A} receptors, however, have proved to be an unexpected but potentially therapeutically valuable tool for neuroprotection (Ongini *et al.* 1997, 2001). The initial observation (Gao and Phillis 1994) that an A_{2A} antagonist could reduce brain damage caused by ischemia has been confirmed by

several other groups (Monopoli *et al.* 1998; von Lubitz *et al.* 1995). Using the kainate and quinolinic acid models of excitotoxicity (Jones *et al.* 1998a, b) we have reported that 4-(2-[7-amino-2-{2-furyl}{1,2,4}-triazolo{2,3-a}-(1,3,5}triazin-5-yl-amino]ethyl)phenol (ZM 241385), an antagonist which is 80-fold more active at A_{2A} than A_{2B} receptors, and around 1000-fold selective for A_{2A} versus A_1 receptors, protected the hippocampus against damage produced by kainate. Further support for the neuroprotective consequences of inhibiting A_{2A} receptors has arisen from studies with knockout models. Chen *et al.* (1999) have found that animals lacking A_{2A} receptors show relatively little neuronal damage following an episode of cerebral ischaemia. Blocking the A_{2A} receptors can also protect against dopaminergic neurotoxins such as MPTP, a result which has also been confirmed recently with the demonstration that toxicity due to MPTP is greatly reduced in mice lacking A_{2A} receptors (Pierri *et al.* 2005).

Receptor interactions and neuroprotection

A further area of interest is the existence of interactions between the various adenosine receptors. There is good evidence that A_{2A} receptors can inhibit the activation of, or the consequence of activating, A1 receptors. Thus, A_{2A} receptor agonists reduces neuronal sensitivity to the A1 receptor agonist N6-cyclopentyladenosine (O'Kane and Stone 1998), an interaction that may involve protein kinase C. Electrophysiological studies based on extracellular and intracellular recording methods have confirmed the inhibitory effect of A_{2A} receptors on A1 receptor activation (O'Kane and Stone 1998). The presence of an A_{2A} receptor antagonist should release, or 'unmask' A1 receptors, and allow the neuroprotective effect of the latter receptors to be seen. In a study in which we examined the effects of administering this combination of compounds to rats, examining the effects of neurotoxicity induced by glutamate receptor agonists, this explanation was invoked to account for the ability of an A1 receptor antagonist to reduce the neuroprotective effects of A_{2A} receptor antagonism (Jones *et al.* 1998a, b), the latter being presumed to have unmasked the neuroprotective effects of endogenous adenosine at otherwise inactive A1 receptors.

Another area in which receptor interactions are important in understanding the role of adenosine in neuroprotection is that of glutamate receptor modulation. Among our first observations in this area were that the inhibitory effect of adenosine on hippocampal population spikes, together with a parallel decrease of paired-pulse inhibition, were suppressed in magnesium-free medium, or by superfusing the slices with NMDA (Bartrup and Stone 1990). The interaction between NMDA and adenosine appeared to involve the enhancement of responses mediated by A_{2A} receptors, since NMDA did not modify the inhibitory effect of the selective adenosine A_1 receptor agonist N^6-cyclopentyladenosine, but did enhance the excitatory effect of CGS21680. Furthermore, the response to a mixture of NMDA and CGS21680 was prevented by the adenosine A_{2A} receptor antagonist ZM241385. Activating NMDA receptors, therefore, can suppress sensitivity to adenosine, probably via increased activation of adenosine A_{2A} receptors (Nikbakht and Stone 2001). However, since A_{2A} receptors can suppress the activation of A1 receptors, this may explain the inhibition of A1 receptors by NMDA.

Since many actions of NMDA are mediated by the production of nitric oxide (NO), we recently examined the possibility that NO might mediate this interaction (Shahraki and Stone 2004). As predicted, NO donors such as SNAP reduced the presynaptic inhibitory effect of adenosine selectively. A more detailed analysis of free radical effects lead to the conclusion that the presynaptic effects of adenosine can be inhibited by NO or superoxide, although neither of these species can account for the full extent of the reduction of adenosine responses by NMDA. The pharmacological importance of these results for neurodegeneration, however, lies in the fact that NO or other reactive oxygen species generated during reperfusion injury in the heart or brain may compromise the potential protective actions of endogenous adenosine. It would be valuable to inhibit or remove – by a suitable scavenger system – any reactive oxygen or nitrogen species generated under these conditions, as their removal should greatly enhance the neuroprotective activity of endogenous adenosine, and thus both reduce the amount of tissue injury and improve the potential for recovery.

Conclusion

The evidence summarised here strongly suggests an involvement of kynurenines in some degenerative diseases. Their generation by macrophages and monocytes activated by cellular damage places them in a potential position to cause or contribute significantly to cerebral dysfunction in the CNS in a range of disorders including hepatic encephalopathy. Another major endogenous metabolite, adenosine, also acts on cell membrane receptors with effects that may be generally protective. These systems may be inter-related, with activation of NMDA receptors by quinolinic acid possibly suppressing protection by adenosine receptors, leading to increased tissue damage. Modulation of either group of compounds by modifying their endogenous levels or using selective agonists or antagonists as appropriate might lead to novel therapeutic approaches to treating the symptoms and sequelae of hepatic encephalopathy and related disorders.

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