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Kynurenines in the CNS: from endogenous obscurity to therapeutic importance

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Abstract

In just under 20 years the kynurenine family of compounds has developed from a group of obscure metabolites of the essential amino acid tryptophan into a source of intensive research, with postulated roles for quinolinic acid in neurodegenerative disorders, most especially the AIDS-dementia complex and Huntington's disease. One of the kynurenines, kynurenic acid, has become a standard tool for use in the identification of glutamate-releasing synapses, and has been used as the parent for several groups of compounds now being developed as drugs for the treatment of epilepsy and stroke. The kynurenines represent a major success in translating a basic discovery into a source of clinical understanding and therapeutic application, with around 3000 papers published on quinolinic acid or kynurenic acid since the discovery of their effects in 1981 and 1982. This review concentrates on some of the recent work most directly relevant to the understanding and applications of kynurenines in medicine.

Keywords: Kynurenine; Kynurenic acid; Quinolinic acid; Tryptophan; Neurodegeneration; Neuroprotection; Excitotoxicity

Contents

Abbreviations: 5HT, 5-hydroxytryptamine; AIDS, Acquired immunodeficiency syndrome; CSF, Cerebrospinal fluid; GABA, Gamma-amino-butyric acid; GV150526A, 3-[2-[(phenylamino)carbonyl]ethenyl]-4,6-dichloroindole-2-carboxylic acid; HIV, Human immunodeficiency virus; L689 560, 2-carboxy-5,7-dichloro-4-[[(*N*-phenylamino)-carbonyl]amino]-1,2,3,4-tetrahydroquinoline; L695 902, 4-hydroxy-3-(carboxymethyl)-quinoline-2(1H)-one; L701 252, 4-hydroxy-3-(cyclopropylcarbonyl)-7-chloroquinoline-2(1H)-one; L701 324, 4-hydroxy-7-chloro-3-(3-phenyloxy)phenyl-quinoline-2(1H)-one; MDL 100 748, 4-[(carboxymethyl)amino]-5,7-dichloroquinoline-2-carboxylic acid; MDL 29 951, 3-(4,6-dichloro-2-carboxyindole-3-yl)propionic acid; MDL 104 653, 3-phenyl-4-hydroxy-7-chloroquinoline-2(1H)-one; NADPH, Nicotinamide adenine dinucleotide phosphate; NCR-631, 4,6-dibromo-3-hydroxyanthranilic acid; NMDA, *N*-methyl-D-aspartate; PNU156561, (= FCE28833A) 3,4-dichlorobenzoylalanine; QPRT, Quinolinic acid phosphoribosyltransferase; Ro-61-8048, 3,4-dimethoxy-*N*-[4-(3-nitrophenyl)thiazol-2-yl]-benzenesulphonamide; RPR 104632, 6,8-dichloro-[2-(2H)-[(3-bromophenyl)methyl]-1,2,4-benzothiadiazine-1,1-dioxide-3-carboxylic acid; SC49648, 6-chloro-2-carboxyindole-3-acetic acid; SHR, Spontaneously hypertensive; SIV, Simian immunodeficiency virus; TNFα, Tumour necrosis factor-α; ZD9379, 7-chloro-4-hydroxy-2-(4-methoxy-2-methylphenyl)-1,2,5,10-tetrahydropyridazino[4,5b]quinoline-1,10-dione.

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1. Quinolinic acid and neuronal function

Until 1981 quinolinic acid was believed to be a physiologically inactive metabolite of tryptophan; a mere intermediate along the kynurenine pathway (Fig. 1) in the synthesis of the essential co-factors nicotinic acid and nicotinamide adenine dinucleotide. The potential physiological and pharmacological significance of quinolinic acid was recognised with the discovery of its ability to activate selectively the subpopulation of neuronal glutamate receptors sensitive to *N*-methyl-D-aspartate (NMDA) (Stone and Perkins, 1981). The result

of this activation was an excitation of neurones reflected in an increase in the firing rate (Stone et al., 1989). The study of analogues with agonist activity (Stone, 1984) and of differences in the sensitivity of neurones to quinolinic acid (Perkins and Stone, 1983a,b) subsequently led to the proposal of NMDA receptor subtypes (Stone, 1993b) which has been confirmed by later molecular biology.

It had previously been proposed that glutamate receptors might be involved in mediating neuronal damage in some clinical neurodegenerative disorders, following the finding that kainic acid could cause an axon-sparing lesion of the striatum (Coyle and Schwarcz, 1976; McGeer and McGeer, 1976). A massive efflux of glutamate occurs from neurones and glia following hypoxia, ischaemia or hypoglycaemia, reach-

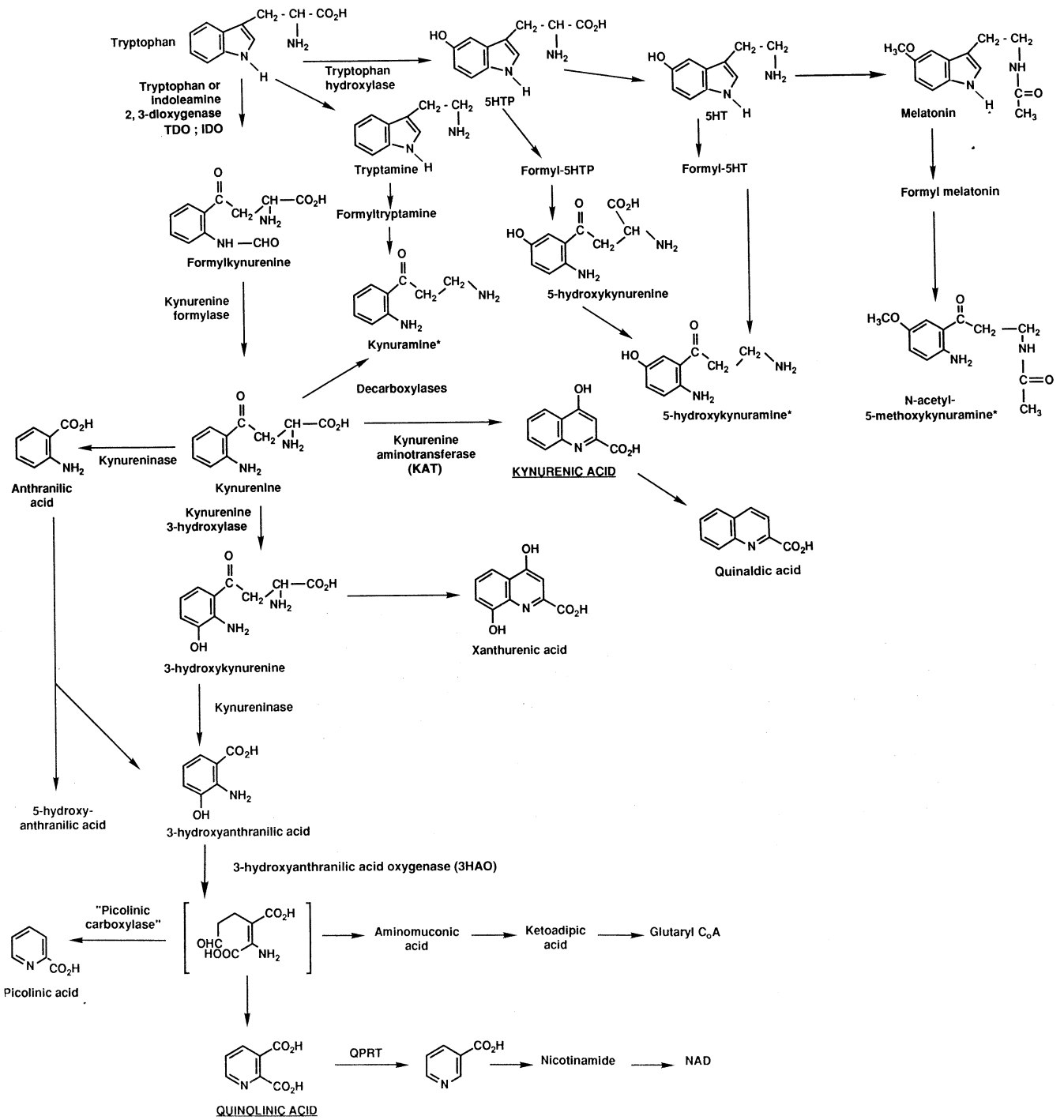

Fig. 1. The kynurenine pathway of tryptophan metabolism. The conversion from tryptophan to kynurenine is performed by tryptophan-2,3-dioxygenase in the liver, and by indoleamine-2,3-dioxygenase in most other tissues.

ing concentrations likely to be neurotoxic and giving rise to the 'excitotoxicity' hypothesis that overstimulation of glutamate receptors could account for neuronal damage (Olney, 1969). The population of NMDA receptors attracted the maximum attention in this regard since activation of these was associated with a substantial increase of calcium influx into the target neurones. Calcium is intimately involved in excitotoxicity, since this ion entrains a series of events leading to neuronal damage. As an NMDA receptor agonist, quinolinic acid similarly proved able to cause neuronal death following direct intracerebral administration (Schwarcz et al., 1983; Stone et al., 1987) or when applied to neurones in culture (Kim and Choi, 1987).

As quinolinic acid remains the only known endogenous compound able to activate selectively receptors for NMDA, it has attracted a wealth of interest in attempts to define the extent of its physiological roles and its possible involvement in a variety of pathological states. There is strong evidence now that quinolinic acid may play a very significant pathological role in generating the dementia which often accompanies the acquired immunodeficiency syndrome (AIDS) and there is sufficient suggestive evidence in many other disorders to justify further work.

In addition, the kynurenine pathway is the metabolic route to kynurenic acid (Fig. 1), another endogenous compound which has become a universal tool for the study of amino acid receptors since the original description of its ability to block glutamate receptors by Perkins and Stone (1982). The kynurenine pathway has consequently become a serious inspiration for new drug development by academic and commercial groups seeking a novel approach for the modulation of glutamate receptor activity. The compounds which are now being produced as derivatives of kynurenic acid are being tested primarily as drugs for use in the treatment of epilepsy and as inhibitors of the neuronal damage which follows cerebral insults such as head trauma and strokes.

Much of the early literature on kynurenines has been reviewed (Stone and Connick, 1985; Stone and Burton, 1988; Stone, 1989, 1993a,b) and the purpose of this review is to concentrate on more recent work, especially that which is relevant to the possible clinical and applied therapeutic significance of kynurenines in medicine.

1.1. Pathological roles of quinolinic acid

1.1.1. The acquired immunodeficiency syndrome (AIDS)

"Dementia due to human immunodeficiency virus (HIV) is the commonest cause of dementia in children, young adults and middle-aged people" according to a recent review by Nath and Geiger (1998). Up to 20% of AIDS patients experience marked CNS involvement, with cognitive decline, motor dysfunction and behavioural abnormalities (Power and Johnson, 1995). The prognosis for patients with neuro-AIDS is especially poor. Although there are several hypotheses for the involvement of causative agents in neuro-AIDS, there is a particularly strong case for believing that the excitotoxin quinolinic acid may have special relevance to the development of CNS dysfunction and damage in the AIDS-dementia complex.

1.1.2. Human studies

There is strong evidence that the activation of NMDA receptors is critical in the production of brain damage in AIDS (Lipton, 1998). The extensive literature which has arisen on the possible involvement of quinolinic acid in the pathogenesis of the AIDS-dementia complex has been reviewed by Chao et al. (1996). In patients with AIDS-dementia complex the levels of quinolinate in the CSF were increased up to 20-fold, and were correlated with the severity of the cognitive and motor dysfunctions exhibited by these patients (Heyes et al., 1989b, 1991; Martin et al., 1992). Levels in the brain itself may increase to levels 300 times greater than those in the CSF in patients infected with HIV (Fig. 2) (Heyes et al., 1998). Zidovudine treatment reduced the amount of quinolinic acid in parallel to the neurological improvements. In a later study the elevated levels of kynurenine and quinolinic acid in the serum and CSF of HIV-1 infected patients were shown to correlate with the amounts of 2-microglobulin and neopterin as indicators of immune activity. The concentration of quinolinic acid in CSF in this sample of patients was increased approximately 60-fold (6000%) compared with controls, with an increase in the ratio of quinolinate:kynurenate of 20-fold. Interestingly, there was no correlation between the levels of quinolinic acid, kynurenine or kynurenate in the CSF and the serum: CSF albumin ratio, indicating that the central changes were not simply the result of a defective blood-brain barrier (Heyes et al., 1992a).

Increases in CSF quinolinic acid levels are not confined to adult patients, but have been also found in children. In 40 children with symptomatic HIV-1 infection, quinolinate was elevated four-fold in the CSF (55.8 nM compared with controls of 14.9 nM) and treatment with zidovudine reduced this level to normal values. Patients with HIV-1 associated encephalopathy had even higher quinolinate levels (79.6 nM), the highest amounts being found in patients dying less than 3 years after baseline assessment (Brouwers et al., 1993).

When the amount of quinolinic acid in the post-mortem brain tissue of AIDS patients was measured, the levels were found to average 23 pmols/10 mg of tissue, compared with control brain tissue levels averaging less than 1 pmol/10 mg (Achim et al., 1996).

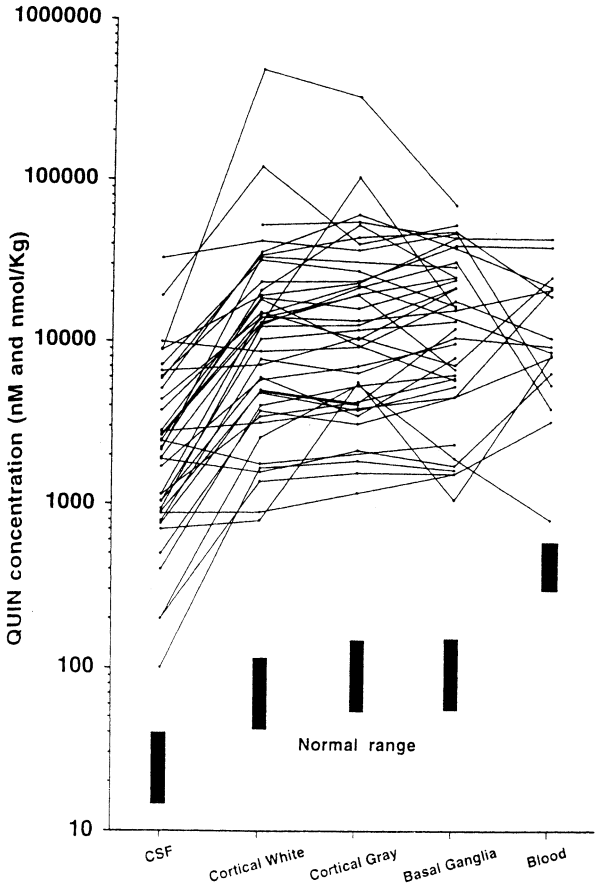

Fig. 2. In control human subjects, quinolinic acid levels ranged from 15 to 35 nM in CSF (mean 22.1 ± 2.1 nM), 51–141 in basal ganglia (72 ± 26 pmol/g), 35–135 pmol/g in cortical white matter (75 ± 12 pmol/g) and 42–161 pmol/g in cortical grey matter (81 ± 20 pmol/g). Substantially higher QUIN levels were found in HIV-infected patients in CSF (3789 ± 888 nM, $P < 0.01$), basal ganglia ($20\,942 \pm 2959$ pmol/g, $P < 0.01$), cortical white matter ($25\,397 \pm 11435$ pmol/g, $P < 0.01$) and cortical grey matter ($26\,292 \pm 8615$ pmol/g, $P < 0.01$). Serum quinolinic acid levels were 451 ± 78 nM in controls and $16\,847 \pm 3358$ nM in HIV-infected patients ($P < 0.01$). The lines connect sample quinolinic acid values for each individual HIV-infected patient. Statistical comparisons were made by one-way ANOVA, Dunnett's t-test after transformation to the logarithm, and the Kruskal–Wallis test (reproduced with permission from Heyes et al., 1998).

Although less work has been performed on the various components of the kynurenine pathway other than quinolinic acid, Sardar and Reynolds (1995) have shown an increase in the amount of the first extra-hepatic enzyme of the kynurenine pathway — indoleamine-2,3-dioxygenase
(indoleamine-2,3-dioxygenase) (Fig. 1). Activity of this key enzyme increased significantly in the brains of patients with AIDS-dementia complex as compared with the non-demented patients. The serum kynurenine:tryptophan ratio in seronegative control subjects has been measured as 36.6, whereas this increases to 117 in AIDS patients with CNS involvement, consistent with the rise in brain quinolinate being the result of increased tryptophan metabolism along the kynurenine pathway (Huengsberg et al., 1998). An inverse relationship was noted between the kynurenine:tryptophan ratio and the severity of the AIDS.

It should be noted that changes of CSF or brain quinolinate are not simply a consequence of general brain deterioration, as little change of CSF tryptophan, quinolinate or kynurenate have been detected in Huntington's disease, Alzheimer's disease, complex partial seizures, depression, anorexia or schizophrenia. One of the few positive reports has claimed a trend towards a decreased level of kynurenine and 3-hydroxykynurenine in all the regions of the Alzheimer's disease brain (Baran et al., 1999). Kynurenic acid levels in the striatum were double those of the control brains and were associated with increased amounts of kynurenine aminotransferase 1. The authors propose that the raised levels of kynurenic acid could block NMDA receptors sufficiently to contribute to the learning and cognitive disorders in Alzheimer's disease.

1.1.3. Animal studies

The levels of quinolinic acid have been measured in monkeys infected with simian equivalents of HIV (Heyes et al., 1990a, 1992b; Coe et al., 1997). After infection with the pathogenic form SHIV(89.6P), the levels of quinolinic acid in the CNS increased dramatically, while this did not occur with the non-pathogenic construct SHIV(HXBc2) (Coe et al., 1997). In humans and a series of macaques, Heyes et al., (1991), Heyes et al. (1992b), Rausch et al. (1994) demonstrated a clear relationship between the CSF levels of quinolinic acid in infected monkeys and the degree of neurological impairment. In some cases, quinolinic acid levels increased up to 400-fold above basal levels (Heyes et al., 1998), with the greatest amounts occurring in those animals which deteriorated most quickly. The changes were associated with increased activity of indoleamine-2,3-dioxygenase (Saito et al., 1991). Most rhesus monkeys with simian immunodeficiency virus (SIV) infection studies by Rausch et al. (1994) showed CNS dysfunction including motor and/or cognitive impairments. These animals also had elevated levels of quinolinate in the CSF.

In one study, rhesus monkeys were infected with SIV and studied over 2.5 years. Three animals were virus negative at 5 weeks, and remained healthy with CSF quinolinate levels of < 100 nM. The virus-positive animals showed CSF quinolinate levels of 153–565 nM, associated with clinical symptoms of SIV infection (Jordan and Heyes, 1993).

Mice infected with the LP-BM5 murine leukaemia virus develop an immunodeficiency syndrome. Blood and brain tissue from such animals contained elevated

levels of quinolinic acid from 2 weeks post-infection and with a maximum at 16 weeks. A non-pathogenic but equivalent strain of virus caused no change of quinolinic acid, while antiviral treatments reduced the viral load and quinolinic acid concentrations in parallel (Nagra et al., 1994; Sei et al., 1996).

1.1.4. Toxicity of quinolinic acid levels in HIV infection

Although the amounts of quinolinate in the brain rarely exceed 1 μM, even with the increased production in AIDS, these levels *would* be sufficient to cause significant neuronal damage either by direct activation of NMDA receptors or via the release of endogenous glutamate (Connick and Stone, 1988, 1989). There is an inverse relationship between the time for which cells are exposed to quinolinic acid and the effective toxic concentration (Kim and Choi, 1987). Micromolar concentrations are toxic after several hours (Kim and Choi, 1987; Khaspekov et al., 1989; Galarraga et al., 1990) and submicromolar concentrations can produce neurotoxicity in culture if maintained for several weeks (Whetsell and Schwarcz, 1989) with some neurones being killed on exposure to only 100 nM quinolinic acid (Giulian et al., 1990, 1993). Kerr et al. (1995, 1998) have examined the effects of quinolinic acid on human central neurones in culture. When present at concentrations of 350 nM for 5 weeks, quinolinic acid caused a loss of cell density and of microtubule-associated protein. Many cells were found to be swollen with dendritic varicosities and damaged microtubular assemblies. As these concentrations are comparable with those found in AIDS patients, this result emphasises the potential contribution of chronically elevated quinolinate to the damage sustained in neuro-AIDS.

1.1.5. Sources of quinolinate in AIDS and other inflammatory disorders

The normal brain does possess all the component enzymes and metabolites of the kynurenine pathway (Guidetti et al., 1995), with an increased flux through this pathway seen after a cerebral insult. Most forms of tissue damage, including damage to the brain, are accompanied by an inflammatory reaction with activation of monocytes and macrophages peripherally and the activation of microglial cells and invasion by activated macrophages in the CNS. There is abundant evidence that the kynurenine pathway is up-regulated in these cells in inflammatory states, with activated macrophages and microglial cells producing quinolinic acid in addition to other cytotoxins (Espey et al., 1997). 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., 1992e). Treatment with interferon-γ induces an increase in the activity of indoleamine-2,3-dioxygenase and has been shown to increase kynurenine production sufficiently to reach >40 μM in these cells, and to increase quinolinic acid levels in glia and macrophages to 438 and 1410 nM, respectively (Heyes et al., 1996). High activities of kynurenine-3-hydroxylase, kynureninase and 3-hydroxyanthranilic acid oxygenase were measured in interferon-γ stimulated macrophages. MT2 macrophages and N11 microglial cells can be induced to express indoleamine-2,3-dioxygenase, and kynurenine 3-hydroxylase and nitric oxide synthase activities after stimulation with interferon-γ (Alberati-Giani et al., 1996; Alberati-Giani and Cesura, 1998). Lipopolysaccharide increased indoleamine-2,3-dioxygenase activity further in glia. Human macrophages stimulated with tumour necrosis factor-α (TNFα) or interferon-γ yielded large amounts of quinolinic acid, cellular concentrations reaching 10.3 μM 72 h after treatment with interferon-γ. Combinations of TNF 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 generation of neurotoxic amounts of quinolinic acid by immune-activate cells in the CNS as a result of local or generalised inflammatory stimuli is, therefore, highly feasible (Heyes et al., 1992c; Alberati-Giani et al., 1996; Alberati-Giani and Cesura, 1998).

Even treatment of mice with a general immune activator such as bacterial lipopolysaccharide or pokeweed mitogen is able to raise the activity of indoleamine-2,3-dioxygenase in the lung more than 100-fold (Saito et al., 1992b), eliciting speculation that the normal rate-limiting function of this enzyme may then be superseded by more distal enzymes such as kynureninase or 3-hydroxyanthranilic acid oxygenase (Fig. 1).

Indirect evidence that quinolinic acid might be an important neurotoxic product of virus-infected immune cells was produced by Giulian et al. (1990, 1993). The envelope glycoprotein gp120 of HIV type-1 was found to stimulate the release of neurotoxic, heat stable, non-protein factors from human blood monocytes. A key finding was that the toxicity of these factors on ciliary ganglion cells or rat spinal neurones was blocked by antagonists acting at NMDA receptors. This group also noted that spinal neurones are especially sensitive to the toxic effects of quinolinic acid, with 40–60% of rat spinal neurones being killed on exposure to only 100 nM quinolinic acid. In a similar study, Brew et al. (1995) measured quinolinic acid production by macrophages infected with macrophage-tropic isolates from patients with AIDS-dementia complex, Quinolinic acid production was found to be related directly to the viral load. Since cell-free isolates also increased the quinolinic acid production by macrophages, this group concluded that infection with HIV was itself sufficient to enhance kynurenine metabolism.

It has been proposed that, in AIDS, quinolinic acid may be one of the more important of the inflammatory toxins (Kerr et al., 1997). Human macrophages infected with isolates from AIDS patients were shown to cause more toxicity to human neuronal cultures than did macrophages treated with 6-chloro-D-tryptophan to suppress kynurenine synthesis. This result indicates that the activated macrophages present in AIDS patients are capable of generating enough quinolinic acid to cause neuronal damage. Infection with HIV-1 has been shown directly to cause human monocytes to generate quinolinic acid, especially when also activated by endotoxins such as bacterial lipopolysaccharides or by interferon-γ (Nottet et al., 1996).

Beagles et al. (1998) have calculated that, in the rat, 85% of the quinolinic acid present in the extracellular fluid of the brain arises from the blood. Systemic administration of bacterial endotoxin increased blood quinolinic acid levels 10.2-fold, and brain extracellular levels 18.5-fold. In patients with various forms of neurological dysfunction associated with inflammation, the levels of quinolinic acid in the brain increased up to 60-fold (Fig. 3) compared with patients whose illnesses did not involve inflammation (Heyes et al., 1992c) and correlate locally with the extent of inflammation (Heyes et al., 1998). During a locally induced brain inflammatory response (local application of endotoxin) the amount of quinolinic acid in brain tissue increased 246-fold and increased in the extracellular space 66-fold. These increases were attributed partly to an increased local rate of synthesis and partly to a reduced efflux from the brain into blood (Beagles et al., 1998). On the other hand, Heyes et al. (1998) have concluded that more than 98% of the brain quinolinic acid in HIV-infected patients is generated locally within the CNS. That much of this quinolinic acid arises from immune-activated macrophages is indicated by procedures which reduce parallel to the number of systemic macrophages and the rise of cerebral quinolinic acid produced by an intrastriatal injection of lipopolysaccharide (Koennecke et al., 1999). The difference between these two sets of data emphasises the dramatic impact which central inflammatory cells can have on the brain concentration of quinolinic acid.

1.1.6. Modulation of quinolinic acid release

A recent discovery of interest has been that kappa opioid receptors modulate the release of quinolinic acid from microglial cells in culture (Chao et al., 2000). The effect is associated with a suppression of the neurotoxic effects of supernatants from HIV-infected microglia, consistent with the concept that quinolinic acid is primarily responsible for that toxicity. These results raise the possibility of using kappa opioids or other ligands to diminish the release of inflammatory mediators and quinolinic acid, reducing the severity of neuronal damage due to HIV.

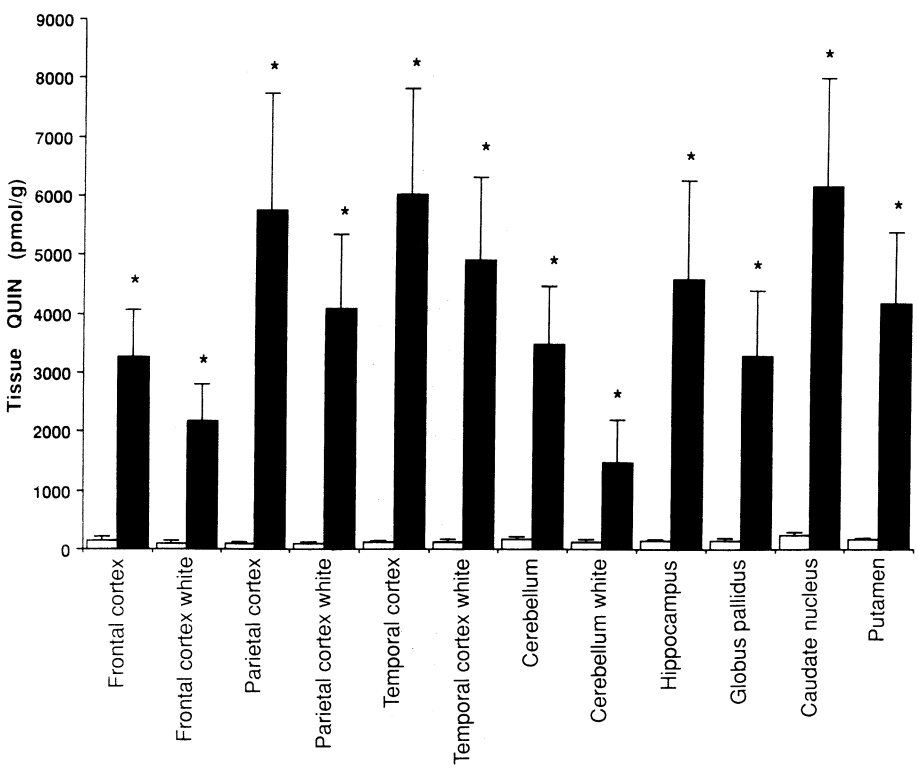

Fig. 3. Regional brain QUIN concentrations in patients with non-inflammatory ($n = 11$; open bars) and inflammatory neurological disease ($n = 6$; closed bars). Values presented are mean ± 1 S.E.M. $^*P < 0.0001$ versus controls (reproduced with permission from Heyes et al., 1992c).

1.1.7. 3-Hydroxykynurenine

A related kynurenine, 3-hydroxykynurenine, is also neurotoxic and may be involved in the neuronal damage in neuro-AIDS (see below).

1.1.8. Immunomodulation

Why *should immune-competent cells produce quinolinic acid*? One possibility is that quinolinic acid plays an important role in normal immuno-surveillance. Strong direct evidence for the immune cell origin of quinolinic acid came from the use of a quinolinic acid antibody which revealed the presence of quinolinic acid in immune system cells of all types (Moffett et al., 1994a) and this immunoreactivity was increased in monkeys infected with SIV (Namboodiri et al., 1996). Systemic immune stimulation was later found to induce the presence of quinolinic acid in choroid, vascular and meningeal cells (Moffett et al., 1994b). Quinolinic acid-immunoreactivity occurs in macrophages rather than microglia or neurones (Moffett et al., 1993, 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).

Systemic administration of lipopolysaccharide increases quinolinic acid immunoreactivity in the brain (Heyes et al., 1989a) 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. Sung et al. (1997) later 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. It is now clear that extracellular kynurenines are metabolised by the lymphoid tissues (Moffett et al., 1998) rather than the liver as had been thought. While the significance of this is uncertain, this observation emphasises the close relationship which exists between the kynurenine status and immune function.

In parallel with the developing interest in the role of kynurenines in immune function, there has been a growing realisation that the generation of nitric oxide is also of crucial importance in mediating cell function and phagocytic efficiency. It appears that these two pathways are intimately linked. Thomas et al. (1994) have demonstrated that nitric oxide can inhibit reversibly the activity of indoleamine-2,3-dioxygenase and that, conversely, inhibition of nitric oxide synthase leads to the induction of the oxygenase enzyme. However, this relationship appears to apply only in macrophages, since it does not occur in microglial cells (Alberati-Giani and Cesura, 1998). 3-hydroxyanthranilic acid also inhibits the expression of nitric oxide synthase (Sekkai et al., 1997), presenting another route by which an increased flu along the kynurenine pathway could modulate the generation of nitric oxide.

1.2. Huntington's disease

1.2.1. Quinolinic acid

There are striking similarities between the effects of quinolinic acid and Huntington's disease, which have led many to propose a causative role for quinolinic acid in this disorder. Quinolinic acid lesions of the striatum in monkeys produce dystonia and dyskinesia closely resembling those of human Huntington's disease (Storey et al., 1994; Burns et al., 1995) and those effects can be suppressed by lesions of the pallidum (Joel et al., 1998).

Quinolinic acid lesions are associated with the induction of the huntingtin gene in rats, which can appear within 6 h of quinolinic acid treatment (Tatter et al., 1995; Carlock et al., 1995). Whereas it might have been predicted that animals or humans with Huntington's disease would be more susceptible than controls to the toxic effects of quinolinic acid, the converse appears to be true. Despite normal levels of NMDA receptors, R6/1 mice (a model of Huntington's disease produced by the expression of exon 1 of the human Huntington's disease gene) are resistant to quinolinic acid striatal toxicity (Hansson et al., 1999). It will be of great interest to establish the reasons for this counter-intuitive observation and to translate those reasons into the study of human Huntington's disease.

When quinolinic acid was infused chronically into the striatum of rats, the treatment induced deficits of spatial learning in a radial arm water maze, leading the authors to propose that chronically raised quinolinic acid could induce the related deficits seen in Huntington's disease (Shear et al., 1998a). When acute intrastriatal injections were used and the animals studied in a range of behavioural paradigms together with a crude histological assessment, the authors concluded that quinolinic acid provided a good model of the earlier symptoms of Huntington's disease (also see Bordelon and Chesselet, 1999), while 3-nitropropionic acid produced more severe effects which could be a model for the later symptoms (Shear et al., 1998a,b).

The distribution of changes in the levels of glutamate, GABA and other amino acids produced by quinolinic acid is similar to that seen in Huntington's disease (Ellison et al., 1987; Storey et al., 1992; Nicholson et al., 1995). Among the earliest studies were those of Beal et al. (1986, 1989a) who reported that quinolinic acid lesions caused a depletion of transmitters such as GABA and substance P from striatal spiny cells with no change of dopamine levels. A paradoxical 3–5-fold increase was noted in the number of somatostatin and neuropeptide Y cells due to the apparently selective preservation of a class of medium-sized aspiny neurones in which these peptides were colocalised, together with the enzyme nicotinamide-adenine dinucleotide phosphate (NADPH)-diaphorase. The large cholinergic aspiny neurones were also spared. An important distinction was made from other excitotoxins such as kainate and ibotenate which killed all neurones indiscriminately. Overall the pattern of cell loss was closely similar to that seen in Huntington's disease (Beal et al., 1986, 1989a,b, 1991a,b). A similar pattern of selective neuronal damage resembling Huntington's disease has been demonstrated in cell and organotypic striatal cultures when incubated with quinolinic acid (Koh et al., 1986; Koh and Choi, 1988) and in primates after intracerebral injections of quinolinic acid (Beal et al., 1989a).

The preservation of NADPH-diaphorase cells in Huntington's disease and following quinolinic acid lesions has been confirmed by several groups, again using either in vivo or in vitro methods (Koh et al., 1986; Koh and Choi, 1988; Beal et al., 1991a; Qin et al., 1992; Bazzett et al., 1993, 1994).

There is also a degree of consensus from experimental studies in vivo and in vitro that cholinergic cells are resistant to damage by quinolinic acid and other NMDA receptor agonists (Ferrante et al., 1987; Koh and Choi, 1988; Norman et al., 1991; Forloni et al., 1992; Rugg et al., 1992; Qin et al., 1992; Figueredo-Cardenas et al., 1994; Mackenzie et al., 1995; Maeda et al., 1997 Figueredo-Cardenas et al., 1998). The main dissenters from this view are Susel et al. (1991), Yamada et al. (1990) who reported a decrease of cholinergic markers after chronic intracerebral quinolinic acid administration.

The main area of controversy is that of peptide transmitters. The neurones containing colocalised somatostatin and neuropeptide Y are preserved in Huntington's disease striatum. Beal et al. (1986, 1989b) reported a depletion of substance P neurones with the preservation or relative increase of somatostatin and neuropeptide Y containing cells. While this result has been replicated (Storey et al., 1992), others have claimed that these neurones are vulnerable to quinolinic acid damage (Boegman et al., 1987; Davies and Roberts, 1987; Boegman and Parent, 1988; Forloni et al., 1992; Qin et al., 1992; Figueredo-Cardenas et al., 1994, 1998). Such resistance is difficult to understand, however, given the recent evidence that tachykinins can protect against quinolinic acid induced damage in cultures (Calvo et al., 1996). The implication may be that intracellular stores of tachykinins increase sensitivity to quinolinic acid, whereas activation of tachykinin receptors leads to protection. Alternatively, interpretation of these findings may lie in the dynamics of quinolinic acid levels in the brain. For example, Maeda et al. (1997) found no loss of somatostatin cells after seven daily intracerebroventricular administrations of quinolinic acid but a decrease after 14 days continuous administration via a minipump. In cultures of cortical neurones quinolinic acid increased the messenger RNA for somatostatin, though not for neuropeptide Y (Patel et al., 1995).

The loss of enkephalinergic neurons from the external pallidum is greater than, and occurs earlier than, the loss of substance P containing neurons in the internal pallidum both in the hours immediately following a quinolinic acid lesion in rats and in Huntington's disease itself (Bordelon and Chesselet, 1999). This finding not only strengthens the quinolinic acid model as a valid reflection of neurodegeneration in Huntington's disease, but also supports the view that quinolinic acid may be involved in the neuronal damage responsible for the human condition.

The levels of neurotensin are increased in the striatum of Huntington's disease and after quinolinic acid lesions (Masuo et al., 1990). There is also a decrease in the number of enkephalin-immunoreactive neurones both in Huntington's disease and after quinolinic acid lesions (Beal et al., 1991a; Roberts et al., 1993)

Somatostatin/neuropeptide Y containing neurones lack calcium binding proteins. Figueredo-Cardenas et al. (1994, 1998) have pointed out that although the presence of such proteins is probably not an absolute determinant of neuronal vulnerability to damage, one of them — calbindin — may offer limited protection. This view would help to explain the apparently greater vulnerability to the damage of neurones deficient in calbindin in Huntington's disease.

Indeed in Huntington's disease striatal neurones show an increase of calbindin-immunoreactivity. In postmortem samples from control subects, calbindin occurs in neuronal somata and proximal dendrites. In Huntington's disease this protein is found in second and third order dendrites and spines. In rats treated with intrastriatal quinolinic acid, the surviving spiny neurones around the lesion core show calbindin distribution similar to Huntington's disease samples. In striatal cultures, 2–6 h of exposure to quinolinic acid increased the length of dendrites exhibiting calbindin-immunoreactivity (Huang et al., 1995). That this effect was mediated through NMDA receptors was shown by its blockade after treatment with antagonists. One im-

plication of these studies is that the neurones may up-regulate their content of calbindin in an attempt to protect against the presence of quinolinic acid.

A population of aspiny neurones containing GABA and parvalbumin is also spared by NMDA receptor agonists such as quinolinic acid and in Huntington's disease (Waldvogel et al., 1991; Qin et al., 1992; Storey et al., 1992).

Overall, there is a large body of evidence indicating major similarities between the neurochemistry and histopathology of Huntington's disease and the effects of damage inflicted by quinolinic acid. The outstanding problem with implicating quinolinic acid in the neuropathology of Huntington's disease, is that the levels are unchanged in the CSF of affected patients as compared with controls (Reynolds et al., 1988; Schwarcz et al., 1988b; Heyes et al., 1992c). If quinolinic acid is involved in the neuronal damage, it may be that the localised concentrations are higher and more variable than gross CSF levels can indicate, perhaps with higher levels generated in the region of synaptic specialisations and amino acid receptors, or that the effects of normal levels of quinolinic acid are potentiated by raised levels of, for example, reactive oxygen species (see below).

1.2.2. Kynurenic acid

Increased activity of the kynurenine pathway should produce increased amounts of the amino acid antagonist kynurenic acid (Perkins and Stone, 1982; see Stone 1993a) in addition to increased quinolinic acid. However, the activity of the kynurenate synthesising enzymes, kynurenine aminotransferase I and II do not seem able to compete with the direct pathway to quinolinic acid when in competition for their kynurenine substrate when this is elevated as a result of increased indoleamine-2,3-dioxygenase or tryptophan-2,3-dioxygenase activity. The result is that when the kynurenine levels are raised, increases in kynurenate are substantially less than the increases in quinolinic acid, raising the ratio of the toxic quinolinic acid to the protective kynurenic acid (e.g. Heyes et al., 1990a).

The levels of kynurenic acid in the caudate nucleus are reduced in Huntington's disease. Both isoforms I and II of kynurenine aminotransferase are also reduced in the Huntington's disease striatum, with a three-fold increase in the Km value for the enzyme (Jauch et al. 1995). There is, therefore, an apparently selective impairment of kynurenic acid synthesis in the Huntington's disease striatum, possibly due to the absence of an activator or cofactor for kynurenine aminotransferase.

Although the levels of quinolinic acid itself do not appear to be elevated in Huntington's disease (Reynolds et al., 1988; Schwarcz et al., 1988b; Heyes et al., 1992c) there is good evidence that its antagonist, kynurenic acid, is changed. There is evidence both for a reduction in kynurenic acid in the Huntington's disease striatum (Beal et al., 1990, 1992) and for an increase (Connick et al., 1989), although the latter work involved only four brain samples. However, activity of the enzyme 3-hydroxyanthranilic acid oxygenase is elevated in Huntington's disease (Schwarcz et al. 1988a). This would have the effect of diverting tryptophan metabolism away from kynurenic acid formation, leaving neurones potentially more vulnerable to damage by glutamate or quinolinic acid. Despite these reported changes in the brain parenchyma, the CSF levels of kynurenic acid do not appear to change in Huntington's disease (Heyes et al., 1992c).

Yu et al. (1999) have recently reported an analysis of the kynurenine aminotransferase gene which could lead to an examination of its role in changing the levels of kynurenic acid in Huntington's disease.

1.2.3. 3-Hydroxykynurenine

3-hydroxykynurenine may also be involved in the pathogenesis of Huntington's disease (see below). Raised levels of 3-hydroxykynurenine have been reported in patients with Huntington's disease (Reynolds and Pearson, 1989; Pearson and Reynolds, 1992) and this would be consistent with the increased activity of 3-hydroxyanthranilic acid oxygenase which has been demonstrated in this disorder (Schwarcz et al. 1988a). However, Pearson et al. (1995) failed to detect any difference in the activities of 3-hydroxykynureninase and kynurenine aminotransferase in the brain of Huntington's disease patients compared with controls, consistent with earlier results (Beal et al., 1990; Beal, 1992).

1.2.4. Immune function and Huntington's disease

Since much of the disturbed kynurenine pathway metabolism in AIDS appears to be related to the presence of activated immune cells, which can generate high levels of quinolinic acid and kynurenic acid, Leblhuber et al. (1998) have sought to define whether altered immune activity also exists in Huntington's disease. It was found that plasmas tryptophan levels were less in Huntington's disease patients than controls, and that the lower levels were associated with the greatest loss of cognitive function. Interestingly, the lowest levels were found in those five patients who died within 1 year of the study. Other immune system makers supported the conclusions that a disorder of the immune system may occur in Huntington's disease to an extent which could account for some of the deterioration of brain function.

1.3. Parkinson's disease

The levels of 3-hydroxykynurenine are elevated in the

putamen and substantia nigra of brains from patients with Parkinson's disease. The ratio of kynurenine to 3-hydroxykynurenine is also reduced from control levels of 24.8–10.3 in the substantia nigra, with similar changes in the frontal cortex and putamen (19.5–6.3) (Ogawa et al., 1992). This would imply not only an increased synthesis of the toxic compound 3-hydroxykynurenine, but also a smaller proportion of kynurenine being available for the synthesis of kynurenic acid. The combination of effects could contribute to the susceptibility of neurones to damage.

1.4. Cognitive decline of ageing

If infused subchronically (for 2 weeks) into the cerebral ventricles, quinolinic acid produces memory deficits in animals accompanied by a loss of neurones selectively in the basal forebrain (Misztal et al. 1996). This situation resembles that believed to underlie the cognitive decline associated with ageing and, since the CSF and brain levels of kynurenines (Gramsbergen et al., 1992; Wada et al. 1994) including quinolinic acid (Moroni et al., 1984) are increased with advancing age, it is possible that quinolinic acid could mediate that decline.

The importance for cognition of the kynurenic acid sensitive glycine-2 site on the NMDA receptor (Birch et al., 1988) is emphasised by the report that the antagonist properties of kynurenic acid against NMDA could be reduced not only by serine, glycine and D-cycloserine, but also by the reputedly cognition-enhancing drugs aniracetam and oxiracetam. This finding raises the possibility that accumulation of endogenous kynurenic acid could contribute to cognitive decline and its receptor might be an appropriate target for new drug development able to improve cognition by reducing receptor blockade by kynurenate (Pittaluga et al. 1995; Pittaluga et al., 1997). The view that increases of kynurenic acid concentration could underlie cognitive decline is, of course, supported by the finding that kynurenine and kynurenic acid levels increase with age in rats (Moroni et al., 1988; Gramsbergen et al., 1992; Wada et al., 1994). It has been shown directly by Ohno et al. (1994) that blockade of the glycine-2 receptor by kynurenic acid or 7-chlorokynurenic acid interferes with working memory (Steele and Stewart, 1993). On the other hand, there is evidence that kynurenic acid can improve recognition memory (Hlinak and Krejci, 1995).

Although there are no significant changes in the levels of quinolinic acid in the brains of patients with Alzheimer's disease (Mourdian et al., 1989), or amyotrophic lateral sclerosis (motoneurone disease) (Krieger et al., 1993) there is an increase in the amount of kynurenic acid, a change which could cause reduced excitatory neurotransmission (Baran et al., 1999).

1.5. Infections of the CNS

Mice infected with *Herpes simplex* virus type 1 develop paralysis with increased levels of quinolinic acid. The increase of quinolinate seen in the spinal cord parallels the degree of paralysis in these animals, with a 40-fold increase being seen after 7 days. Infection is also accompanied by an increased activity of indoleamine-2,3-dioxygenase and kynurenine hydroxylase (Reinhard, 1998).

The levels of quinolinic acid in the CSF of children with a range of bacterial infections of the CNS are increased dramatically. The levels correlate with markers of immune activation such as neopterin (Heyes et al. 1995), leading the authors to propose that not only is quinolinic acid a useful marker of immune system activation, but that it may contribute to central dysfunction and degeneration in children with CNS inflammation.

In rhesus macaques, septicaemia was associated with increases in both serum and CSF quinolinic acid and kynurenine. The former was elevated about 10-fold in the serum and 30-fold in the CSF (Heyes and Lackner, 1990) with lesser but highly significant changes of kynurenine.

As would be expected of an antagonist at glutamate receptors in the brain, kynurenic acid is neuroprotective and reduces the degree of neuronal damage observed in the brain in a rat model of meningitis from group B streptococci (Leib et al. 1996).

1.5.1. Poliovirus

Seventeen days after the intraspinal inoculation of macaques with poliovirus the activity of indoleamine-2,3-dioxygenase was increased 36-fold and the concentration of quinolinic acid in the cord was increased in proportion to the degree of inflammation, neurological damage and the severity of motor paralysis (Heyes et al., 1992d). Sections of spinal cord from infected animals were shown to have the ability to convert tryptophan into quinolinic acid. In the CSF of macaques infected with poliovirus, 6-chloro-tryptophan reduced the formation of kynurenine and kynurenic acid from tryptophan (Naritsin et al. 1995).

1.5.2. Lyme borreliosis (Lyme disease; infection with *Borrelia burgdorferi*)

Although neurological dysfunction is common in Lyme disease, invading organisms are rarely encountered in the CNS, raising the possibility of mediation by substances associated with the inflammatory response. The levels of quinolinic acid are raise significantly in the CSF of Lyme disease patients with CNS involvement, and those levels correlate strongly with the invasion of the CNS by leucocytes (Halperin and Heyes, 1992). The levels found averaged 325 nM (range up to almost 1000

nM) compared with control values of 21 nM (range up to 45 nM) and representing an increase of around 20-fold. The probable origin of quinolinic acid from inflammatory cells has been discussed above.

Reinhard et al. (1994) have provided an extensive listing of the many other infectious diseases in which changes in the levels of kynurenines have been demonstrated.

1.5.3. Malaria

Infestation of mice with cerebral malaria produces a rapid 40-fold increase of brain IDO activity with a 15-fold increase of kynurenine levels and a doubling of the quinolinic acid:kynurenic acid ratio (Sanni et al., 1998). These changes could implicate the neurotoxicity of kynurenines in the brain damage occurring in cerebral malaria in mice and, conceivably in humans.

1.6. Ischaemia

It is well recognised that brain damage occurs following a period of cerebral ischaemia. In a gerbil model of brief ischaemia, lasting only 5–15 min, no change was seen in quinolinic acid levels during the first 24 h, but a delayed increase was observed in which quinolinic acid levels rose to 50-fold their basal value after several days (Heyes and Nowak, 1990; Saito et al., 1993) (Fig. 4). No changes occurred in the blood or in areas of brain with an uninterrupted blood supply (Saito et al., 1992a). The raised amount of cerebral quinolinic acid was almost certainly, therefore, generated locally, a view supported by the demonstration that intracisternally applied tryptophan was converted to quinolinic acid in damaged but not normal areas of brain. These changes were accompanied by increased activity of all the kynurenine metabolic enzymes except kynurenine aminotransferase. The resulting ischaemia-induced rise in the ratio of quinolinic acid to cerebral kynurenic acid levels may contribute to the amount of brain damage, since kynurenic acid or its close analogues are able to decrease ischaemia damage is several models (Wood et al., 1993).

Macrophages enter the CNS after ischaemia and infiltration into the CNS parallels the biochemical changes after ischaemia (Saito et al. 1993). Similarly, the increases in the amount of quinolinic acid in different brain regions correlates with the sensitivity of those regions to ischaemic damage. Lees (1993) has proposed that microglia and macrophages may contribute to delayed neuronal death seen after cerebral ischaemia, probably by secreting quinolinic acid as discussed above. Direct evidence for this has been obtained by Baratte et al. (1998) who have observed quinolinic acid-positive microglia in the brain at 4 and 7 days following transient global ischaemia in the gerbil.

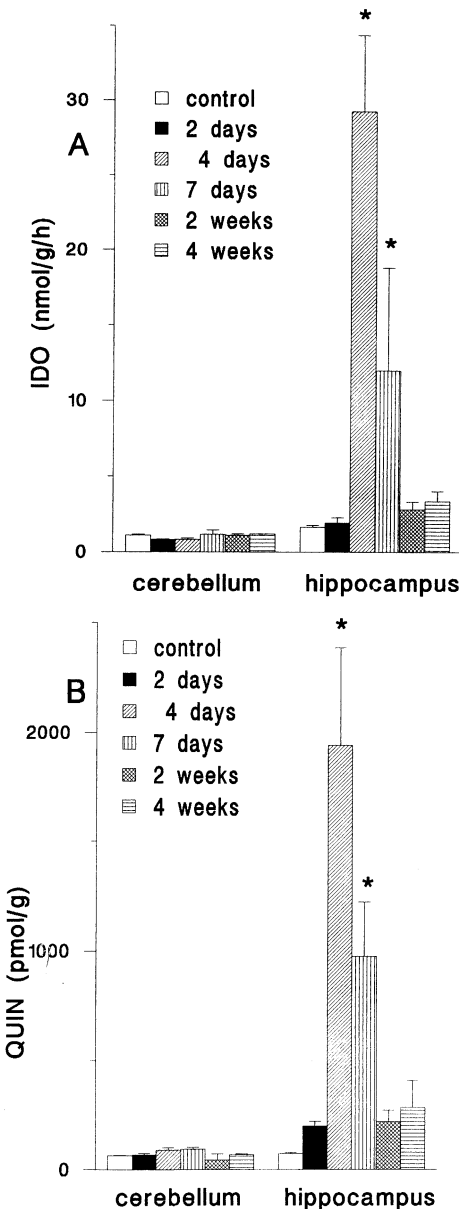

Fig. 4. Regional brain IDO activity (A) and QUIN concentrations (B) 2, 4, 7, 14 and 28 days following 10-min bilateral carotid occlusion (four or five gerbils per group; mean ± S.E.M.). Note the marked and sustained responses in the hippocampus, which shows the most severe neurodegeneration and inflammatory lesions compared with the cerebellum, in which blood flow is preserved and where no neuropathologic changes are evident. $*P < 0.05$ compared with controls (reproduced with permission from Saito et al., 1993).

A further study relevant to this question is that of Behan and Stone (2000), who have investigated the contribution of kynurenines to the neuronal damage produced by the excitotoxin kainic acid. Treatment of rats with *m*-nitrobenzoylalanine, an inhibitor of kynurenine-3-hydroxylase (see below) both intrahippocampally and intraperitoneally, was able to partially prevent the hippocampal damage produced by local administration of kainate (Fig. 5), despite the fact

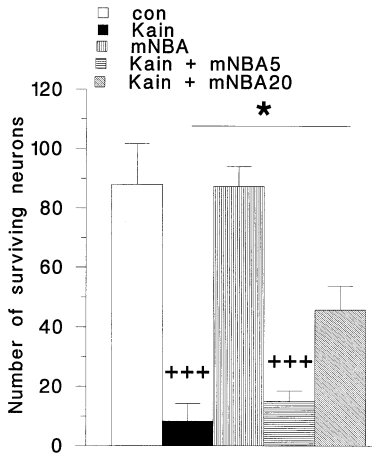

Fig. 5. Histograms summarising the number of neurons surviving after treatment with kainic acid 2 nmols (Kain) administered either alone or together with an intrahippocampal (5 or 20 nmols) and systemic injection of mNBA. Results are shown as mean ± S.E.M. Analysis was performed by ANOVA followed by the Student–Newman–Keuls test for multiple comparisons, $*P < 0.05$; $**P < 0.01$ compared with kainic acid alone; $++P < 0.01$; $+++P < 0.001$ compared with control; $n = 3$; (reproduced with permission from Behan and Stone, 2000).

that the induction of kynurenine pathway enzymes in the rat brain by toxic or immune activation is appreciably less than in mice or gerbils (Heyes et al., 1997). Since the protective effect could not be reversed by glycine (Fig. 6), the authors proposed that the mechanism involved was that of reducing quinolinic acid formation rather than increasing kynurenic acid, a

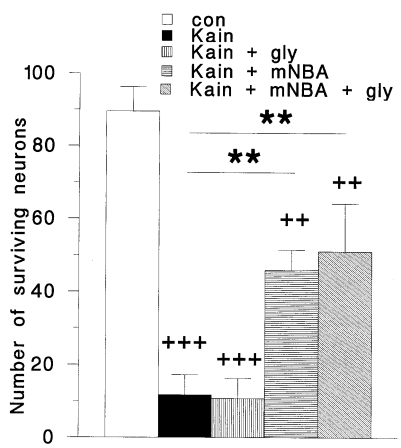

Fig. 6. Histograms summarising the number of neurons surviving after treatment with kainic acid 2 nmols (Kain) administered either alone or together with combined treatments with kainic acid, mNBA and glycine (25 nmols). Results are shown as mean ± S.E.M. Analysis was performed by ANOVA followed by the Student–Newman–Keuls test for multiple comparisons, $*P < 0.05$; $**P < 0.01$ compared with kainic acid alone; $++P < 0.01$; $+++P < 0.001$ compared with control; $n = 4$; (reproduced with permission from Behan and Stone, 2000).

conclusion consistent with the weak inhibitory activity of m-nitrobenzoylalanine against kynureninase. In mice, Chiarugi and Moroni (1999) have shown that inhibitors of kynurenine-3-hydroxylase (*m*-nitrobenzoylalanine and Ro61-8048) can suppress quinolinic acid generation after chronic but not acute treatment in immune-stimulated animals.

1.6.1. Hypoxia at birth

Kazda et al. (1998) have recently addressed a related problem-that of the susceptibility of the neonate to seizures and hypoxic brain damage. Measuring the levels of several kynurenines in umbilical vessels and amniotic fluid during normal labour and caesarean sections, this group found an increased placental transfer of tryptophan from mother to foetus during labour, together with an increased formation of kynurenines by the foetus. If the levels of quinolinic acid rise sufficiently, neurones in the CNS may be at greater risk from excitotoxic damage either produced by quinolinic acid itself, or by a combination of the quinolinic acid with increased glutamate release during hypoxia. The danger posed to the foetus by kynurenines during development is emphasised by the demonstration that quinolinic acid can pass across the intervening barriers to gain access to the foetal brain, causing significant damage (Beskid, 1994a,b). One might, therefore, be tempted to suggest that any elevation of tryptophan or kynurenine levels in the mother should be minimised during pregnancy.

However, a more important consideration is likely to be the balance between the quinolinic and kynurenic acid levels. Walker et al. (1999) have shown that the amounts of kynurenic acid are high in the brain and CSF of foetal sheep, but that these levels fall around the time of birth. Most dramatically, these authors found that chronic restriction of umbilical blood flow (days 120–140 of gestation) produced a fall in kynurenic acid levels in the hypothalamus and hippocampus. This fall could increase the susceptibility of the brain to any additional hypoxic or ischaemic insult imposed at the time of parturition. Potentially, therefore, the risk of hypoxic brain damage at birth could be reduced by the administration of kynureninase or kynurenine-3-hydroxylase inhibitors which, as noted below, should raise the levels of endogenous kynurenic acid.

A related study by Munoz-Hoyos et al. (1998a,b) has found that the circadian variations in the excretion of kynurenines is significantly less in prematurely-born human neonates and in those suffering foetal distress. While the significance of this is not yet clear, the results do emphasise that changes of tryptophan metabolism may be associated with foetal development and birth.

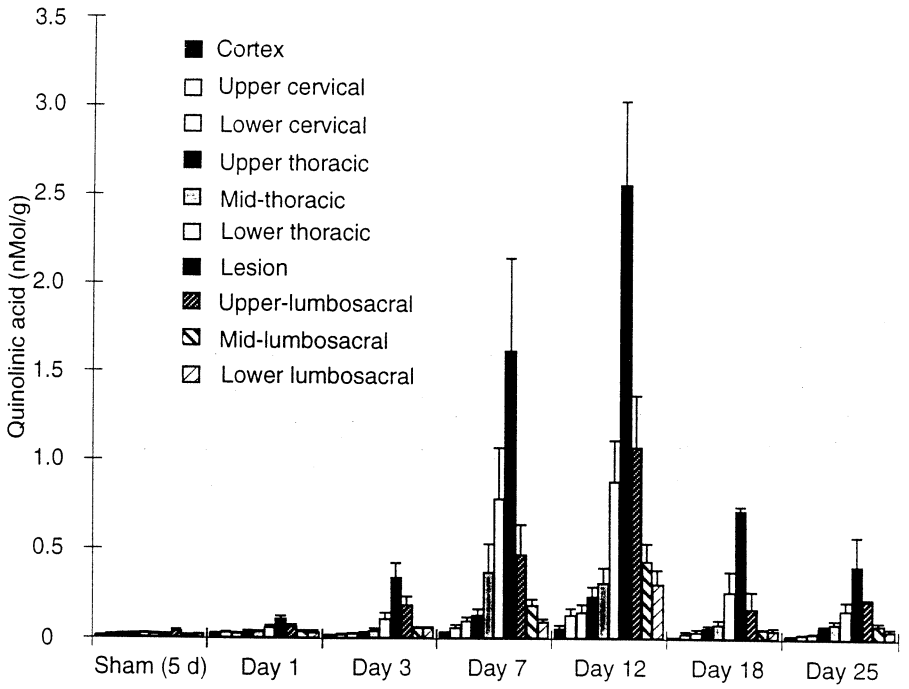

Fig. 7. Spatio-temporal distribution of quinolinic acid concentration changes following spinal cord injury in guinea-pigs. Samples were collected 1, 3, 7, 12, 18 and 25 days following compression of the thoracic spinal cord. Sham animals received the same surgical procedures as the injured animals, except that the spinal cord was not compressed, and samples were collected 5 days after surgery. Values presented are mean ± S.E.M. (error bar). Reproduced with permission from Blight et al. (1997).

1.7. Traumatic injury

Experimental compression injury of the spinal cord causes delayed damage coincident with invasion by mononuclear phagocytes and the appearance of increased amounts of quinolinic acid, though with marked species differences. In rats, quinolinate increased up to 10-fold at 7 days after injury, whereas in guinea-pigs, quinolinic acid was increased one day after compression injury, with a 100-fold increase after 12 days (Fig. 7) (Blight et al., 1997). Levels remained elevated after 25 days. At the injury site, activity of indoleamine-2,3-dioxygenase was also increased, although no changes in indoleamine-2,3-dioxygenase or quinolinic acid were detected in uninjured regions of cord (Blight et al., 1993, 1997). Similar results were reported by Popovich et al. (1994), with an emphasis placed on the role of secondary changes of quinolinic acid associated with the inflammation and macrophage infiltration consequent upon injury. The increased amounts of quinolinic acid were maintained for 21 days after damage to the rat spinal cord. The importance of quinolinic acid was emphasised by the demonstration that 4-chloro-3-hydroxyanthranilate (an inhibitor of 3-hydroxyanthranilic acid oxygenase) attenuated both the increase in quinolinic acid and the functional deficits in traumatised animals (Blight et al. 1995).

Following traumatic brain injury in humans there is an increase of up to 50-fold in the level of quinolinic acid in the cerebrospinal fluid of some patients, from control values of less than 50 nmols/l to a mean of 463 nmols/l (Sinz et al., 1998). The levels correlated with mortality resulting from the cerebral insult. This would account for the earlier finding by Smith et al. (1993a,b) that treatment of animals with kynurenic acid resulted in improved neurologic outcome measures, 2 weeks after fluid-percussion brain injury. The surprising aspect of this latter observation is that a single injection of kynurenic acid, 15 min after application of the cerebral insult was sufficient to protect the brain. An increase of CSF quinolinic acid has recently been detected in children suffering form severe traumatic brain injury (Bell et al., 1999). The levels of quinolinic acid were correlated with mortality rate, and support the concept that centrally-mediated inflammatory processes, involving the generation of quinolinic acid, may contribute to both trauma and mortality.

1.8. Epilepsy

1.8.1. Human studies

There have been no differences reported in the concentration of quinolinic acid in epileptic foci and non-focal areas of the human brain (Heyes et al. 1990c). Indeed, the levels of quinolinic acid may be reduced in the CSF of patients with complex partial seizures (Heyes et al. 1990c; Heyes et al., 1994). However, there is a loss of quinolinic acid phosphoribosyltransferase

activity in tissue from the epileptic focus of human patients compared with tissue from non-epileptic individuals (Feldblum et al., 1988). The levels may be as low as 10% of controls, raising the possibility that the absence of this enzyme could result in increased levels of quinolinic acid in some cells or cellular compartments in the epileptic focus which might not be detectable during an overall analysis of tissue content.

There is no difference between normal and seizure-prone individuals in the CSF levels of kynurenic acid (Yamamoto et al. 1995) except for those people with West syndrome, in whom the levels were reduced. The most important of the three convulsant kynurenines, therefore, may be 3-hydroxykynurenine, the levels of which increase dramatically during vitamin B6 deficiency. The levels may rise up to 213-fold to around 200 μM (Guilarte et al. 1988), concentrations at which 3-hydroxykynurenine can displace benzodiazepine binding and prevent its enhancement by GABA. It is possible, therefore, that 3-hydroxykynurenine could be responsible for the seizures which accompany B6 deficiency (Sharma and Dakshinamurti, 1992).

The concentration of kynurenic acid is lower than normal in the CSF of patients with infantile spasms, with the possibility that the motor disorder is due to reduced antagonism of endogenous excitants such as glutamate or quinolinic acid (Yamamoto et al., 1994). There are also differences in the diurnal rhythms of kynurenine excretion pattern between control subjects and patients with seizures, further differences being noted between patients with seizures of febrile and epileptic origin (Munoz-Hoyos et al., 1997). The significance of these findings remains to be established but may indicate a role for kynurenines in the genesis and severity of convulsant disorders.

1.8.2. Animal studies

Several of the kynurenines, including kynurenine itself, quinolinic acid and 3-hydroxykynurenine, can produce seizures when administered intracerebrally, (Lapin, 1978, 1989). These seizures are not due to antagonism of the inhibitory transmitter GABA (Stone, 1986) but may involve the production of nitric oxide, as inhibitors of NO synthase reduce quinolinic acid seizures and the administration of the NO synthase substrate L-arginine increases them (Nakamura et al. 1995).

Increased amounts of quinolinic acid have been reported in the brains of epileptic E1 mice (Nakano et al. 1993) in which there is also an increase of up to 17-fold of the activity of 3-hydroxyanthranilic acid oxygenase (Nakano et al. 1992, 1993; Eastman et al. 1994) and its gene (Nakagawa et al., 1998). These findings, together with increased levels of kynurenine in these animals (Suzuki and Mori, 1992), raise the possibility of a contribution of kynurenines to their epileptic state.

It is possible to increase the levels of endogenous kynurenic acid to values at which it exerts anticonvulsant activity. Nicotinylalanine is an inhibitor of kynurenine hydroxylase and kynureninase and administration to rats increases cerebral kynurenic acid levels up to 13-fold above control values when measured in the hippocampal extracellular fluid of rats (Connick et al., 1992; Russi et al., 1992; Carpenedo et al., 1994). These changes are sufficient to induce sedation and to suppress convulsions due to maximal electroshock stimulation or in seizure-susceptible animals such as DBA/2 mice (Russi et al., 1992; Carpenedo et al. 1994).

Seizures are associated with a subsequent gliosis with increased cerebral activity of kynurenine metabolic enzymes (Du et al. 1993). The increased formation of quinolinic acid in these circumstances could, therefore, contribute to the kindling of later seizures. Certainly the administration of kynurenic acid is able to reduce the rate of kindling (Thompson et al. 1988) as are other antagonists acting at the same glycine-2 receptor. The levels of kynurenic acid are raised in the brain and plasma of kindled rats, especially in areas such as the nucleus accumbens which are known to be involved in kindling (Loscher et al., 1996). Such a change could reflect an adaptation in the brain to combat the increased kindling-induced excitability of neurones.

In vitro studies have confirmed that kynurenic acid can suppress the electrophysiological signs of seizure activity in brain slices (Stone, 1988; Brady and Swann, 1988; Scharfman and Ofer, 1997). Interestingly, the potency of kynurenic acid was different when tested against electrophysiological epileptiform activity induced by different agents, and when compared with the standard antagonist at NMDA receptors, 2-amino-5-phosphonopentanoic acid. These studies led to the proposal, made independently by two separate groups, that the seizure suppressant effect of kynurenic acid might involve a novel receptor, possibly even one not related to the antagonism at glutamate receptors (Stone, 1988; Brady and Swann, 1988).

1.8.3. High pressure neurological syndrome (HPNS) and hyperbaric oxygen

Both quinolinic acid and kynurenine lower the threshold for eliciting the seizures which characterise the HPNS in animals, whereas kynurenic acid, as expected, raises it (Wardley-Smith et al. 1989). Imbalance between these kynurenines could, therefore, contribute to the genesis of this problem. A related high-pressure problem is that of seizures which may result from the use of hyperbaric oxgen. Dang et al., (1998) have found that oxygen at about 5 atm induced an initial stimulation of 3-hydroxyanthranilic acid oxygenase, with an increased generation of quinolinic acid, and a later inhibition of the enzyme. The initial activation could contribute to the lowering of seizure threshold.

1.9. Olivopontocerebellar atrophy

Although no increase of quinolinic acid has been demonstrated in this disorder, the activity of the enzyme responsible for metabolising quinolinic acid, quinolinic acid phosphoribosyltransferase (QPRT), is increased 92% in the cerebellum of affected individuals (Kish et al. 1991). As the authors note, this may be an adaptive response to compensate for a high rate of production of quinolinic acid, and would account for the failure to detect measurable changes of quinolinic acid itself.

1.10. Spinal muscular atrophy

In cases of infantile spinal muscular atrophy, kynurenine levels are reduced in the central nervous system, and are correlated with disease severity (Takeuchi et al., 1994). As yet, however, it is unclear how this is related to the pattern or balance of the different neuroactive kynurenines, and whether the changes are sufficient to account for any of the symptoms of this disorder.

1.11. Multiple sclerosis

Experimental autoimmune encephalitis is an autoimmune animal model of human multiple sclerosis. In Lewis rats inoculated with myelin basic protein, encephalitis developed in 12 days. The levels of quinolinic acid increased in caudal regions of spinal cord, those increases occurring before the appearance of neurological symptoms. The amount of quinolinic acid in the brain, serum and liver remained unchanged. Treatment with dexamethasone prevented both the increase of quinolinic acid levels and the development of symptoms (Flanagan et al. 1995).

1.12. Tourette's syndrome

The plasma concentration of kynurenine has been found to increase in patients with Tourette's syndrome (Dursun et al. 1994; Rickards et al. 1996). The amounts of tryptophan and neopterin were similar in Tourette's patients and healthy controls, suggesting that activation of the immune system was not involved in these changes (Dursun et al. 1994; Rickards et al. 1996). It is clearly important to establish whether the raised kynurenine is associated with the predicted increase of quinolinic acid in these patients, and whether the plasma changes are reflected in the brain or CSF.

1.13. Encephalopathies

A distressing combination of congenital encephalopathy with hypertonia, mental deficiency and deafness has been studied by Cheminal et al., (1996). Most patients die before the age of ten years. When reported, the only biochemical abnormality which could be detected was a massive increase of blood kynurenine levels (up to 213 mols per mmol creatinine) which were reached only during periods when the patients were comatose (normal levels less than 10 mols per mmol creatinine) or following a protein load. If this defect in tryptophan handling is indeed the primary error in these patients, they provide the clearest evidence to date of the potent deleterious consequences which could result from a disturbance of kynurenine metabolism.

1.13.1. Hepatic encephalopathy

There is evidence for an increase in the central levels of quinolinic acid in human and animal models of hepatic encephalopathy. Moroni et al. (1986a,b) were the first to demonstrate an increase in the CSF, though this has been disputed by Bergqvist et al., (1996). Increased amounts of quinolinic acid, up to seven times those of control animals, have been reported in the brain, CSF and plasma of rats with stage IV hepatic encephalopathy. No change was noted in the activity of extrahepatic indoleamine-2,3-dioxygenase, although activity of the hepatic enzyme tryptophan-2,3-dioxygenase was increased. The results suggest that quinolinic acid is produced peripherally and then crosses the blood-brain barrier in end stage liver failure.

Basile et al. (1995a) have measured quinolinic acid in human postmortem brain or plasma during encephalopathy with acute or chronic liver failure. The amount of quinolinic acid in plasma was increased significantly in stage I encephalopathy with acute failure, and stages II and III with chronic failure. Quinolinic acid levels in the brain were increased only with acute failure and were always lower than the plasma levels. The results were interpreted to suggest that quinolinic acid enters brain across a permeabilised blood-brain barrier, probably damaged by the metabolic disorder associated with liver failure. The finding of raised quinolinic acid only in the brains of patients dying of acute, not chronic, liver failure suggest that it may have more relevance to the former condition (Basile et al., 1995b).

1.14. Hyperammonaemia

Children with congenital hyperammonaemia exhibit cognitive deficits and neurological abnormalities. CSF levels of quinolinic acid were found to be raised up to ten-fold in this condition, especially in those patients in coma. A similar increase in neopterin concentrations suggested a correlation with immune system activation in this latter group (Batshaw et al. 1993). In rodents, hyperammonaemia tends to increase tryptophan uptake into the brain, a result which could lead to the increase in quinolinic acid.

1.15. Hypoglycaemia

During a period of insulin-induced hypoglycaemia in rats, the striatal extracellular level of quinolinic acid increased significantly (Westerberg et al., 1990). The authors noted that a limited but maintained elevation of quinolinic acid could account for the damage experienced by vulnerable striatal neurones. Greater increases were seen when the tissue content of quinolinic acid was measured (Heyes et al., 1990b), although this was not accompanied by any change of extracellular levels measured in the hippocampus.

1.16. Control of blood pressure

Immunochemical examination shows kynurenine aminotransferase-immunoreactivity in the medulla and cord, in glia and neurones (Kapoor et al., 1997). The areas with highest levels are those involved in cardiovascular control-ventral medulla, nucleus ambiguus, nucleus tractus solitarius and intermediolateral column of the cord but the levels are significantly lower, by about 50%, in genetically hypertensive rats (SHR strain) than in normotensive Wistar Kyoto animals (Kapoor et al., 1998). This probably accounts for the reduced levels of kynurenic acid which have also been detected in the medulla and spinal cord of SHR rats. More specifically, it appears that SHR rats lack one of the two isoforms of kynurenine aminotransferase known as kynurenine aminotransferase-1b (Kapoor et al., 1998). It has been found that the sensitivity of cardiovascular control neurones to locally applied glutamate is increased (Kapoor and Kapoor, 1998), a phenomenon which could be due to the reduced amount of local kynurenic acid (Kapoor et al. 1994, 1997). Together these observations raise the possibility that elevated blood pressure could result at least in part from a disorder of kynurenine metabolism in the brain leading to a lack of kynurenic acid and increased local sensitivity of neurones to the excitatory neurotransmitter glutamate.

1.16.1. Lipid metabolism

Interferon-γ suppresses the oxidation of low density lipoprotein by human blood mononuclear cells. Although the mechanism and significance remains unclear, the conversion of tryptophan to kynurenines, especially 3-hydroxyanthranilic acid, is involved in, and apparently required for, this inhibition (Christen et al., 1994). It is possible that the kynurenines function as inhibitors of the enzymes responsible for the oxidation of lipid. Evidence is also available that 3-hydroxyanthranilic acid acts synergistically with -tocopherol as an antioxidant (Thomas et al., 1996).

1.17. Systemic lupus erythematosus

In patients with systemic lupus erythematosus and associated neuropsychiatric dysfunction, the levels of quinolinic acid in the CSF are increased more than 6-fold from control levels of 38.2–232.5 nM (Vogelgesang et al., 1996). A most interesting feature of this change, however, is that it does not correlate with the density of white cells present in the CSF, suggesting either that it arises largely from sources within the brain parenchyma or from the blood. In either case, however, the levels could, if maintained for several days or weeks, cause significant damage to central neurones.

1.18. Glutaric aciduria

Glutaric aciduria type I is an autosomal recessive disorder with severe motor dystonia and degeneration in the cortex, cerebellum and striatum. The condition arises from a lack of glutaryl-CoA dehydrogenase which is part of the biosynthetic pathway from kynurenine to acetyl-CoA. The absence of enzyme will, therefore, tend to cause an accumulation of kynurenine metabolites including quinolinic acid, and it has been proposed that this could be responsible for the CNS symptoms (Heyes, 1987).

On the other hand, a reduced traffic along the kynurenine pathway could also raise the levels of kynurenic acid. Richter et al. (1996) have shown that a raised level of kynurenic acid occurs in the forebrain, cerebellum and brainstem of genetically dystonic hamsters. The amounts of kynurenic acid were normal when the animals reached 70 days of age and the dystonia had disappeared. The blockade of glutamate receptors in key motor areas of the brain could, therefore, contribute to the dystonic symptoms in these amimals.

1.19. Vitamin B6 deficiency

Vitamin B6 is an essential cofactor for several of the kynurenine pathway enzymes and deficiency of the vitamin is associated with reduced flux along the pathway to quinolinic acid. There is a resulting accumulation of the intermediates including kynurenine and 3-hydroxykynurenine. The toxicity of the latter could contribute to neuronal loss occurring with chronic B6 deficiency (van de Kamp and Smolen, 1995).

1.20. Eosinophilia-myalgia syndrome

The eosinophilia-myalgia syndrome in some subjects consuming tryptophan is associated with elevated levels of quinolinic acid and kynurenine in the CSF which are higher than in control subjects, asymptomatic users of tryptophan and steroid-treated patients with this syn-

drome. The raised quinolinic acid may be the result of enhanced tryptophan metabolism, which is increased in this condition although the mechanism is unclear (Silver et al., 1992).

1.21. Analgesia and morphine withdrawal

Surprisingly little work has been performed on the role of kynurenines in pain perception, but Heyliger et al. (1999) have found that tryptophan, kynurenic acid, kynurenine, quinolinic acid and other metabolites of kynurenine possess weak analgesic properties after systemic administration. Changes in the central levels of kynurenines could, therefore, contribute to alterations in pain sensitivity in disorders such as multiple sclerosis.

Kynurenic acid prevents the development of morphine tolerance and withdrawal symptoms (Rasmussen et al. 1991), an effect which may be related to the observation that kynurenate, even when administered peripherally, reduces the positive rewarding effects of the opiate in a conditioned place preference paradigm or when seen as a facilitation of intracranial self-stimulation (Marek et al., 1991; Bespalov et al. 1994). Kynurenic acid also attenuates the development of tolerance to morphine (Marek et al., 1991). Conceivably, the liability of individuals to develop tolerance and dependence to morphine and other agents could be determined in part by the levels of kynurenines in the brain.

1.22. Feeding

It has been noted that there is a decrease in the amount of kynurenic acid, with an increase in the quinolinic acid:kynurenic acid ratio, in patients with anorexia (Demitrack et al., 1995). Conversely the kynurenic acid analogue, 7-chlorokynurenic acid, enhances feeding behaviour, an effect mediated through the NMDA receptor as it is reversed by the glycine2-site agonist D-serine (Sorrels and Bostock, 1992). The level of kynurenic acid in the brain could, therefore, be one determinant of feeding activity.

1.23. Psychiatry: anxiety, depression and schizophrenia

1.23.1. Anxiety

The plasma concentration of kynurenine is increased in subjects given an anxiogenic dose of caffeine (25 mg/kg), or in patients with clinically diagnosed anxiety. The levels decline to normal on pharmacological treatment. Similarly, the administration of kynurenine to animals provokes behaviours considered to reflect anxiety (Orlikow and Ryzov, 1991; Orlikov et al., 1994). It is not clear, whether any of these are relevant to the aetiology and treatment of anxiety in humans. An increase of kynurenine would be expected to lead to a rise of kynurenic acid both peripherally and centrally, but the direct administration of a kynurenic acid analogue into the rat hindbrain induced anxiolysis as revealed by plus-maze performance and a raised threshold for aversive electrical stimulation (Matheus et al., 1994). A marked anxiolytic activity of kynurenic acid has also been shown using a variety of anxiogenic agents in a light-dark paradigm (Lapin, 1998). Kynurenic acid proved able to prevent the anxiogenic activity of leptazol, caffeine and yohimbine. There may, therefore, be a role for kynurenines in anxiety, but the nature of that role remains unclear. There may also be value in exploring carefully the possible use of kynurenic acid analogues as anxiolytic agents.

1.23.2. Depression

As early as 1974, and before any awareness of the neuronal activity of kynurenines, Mangoni noted a positive correlation between depression scores and the amount of the kynurenine metabolite xanthurenic acid in the urine of depressed patients. He noted that the antidepressants imipramine and tranylcypromine inhibited the kynurenine synthetic enzyme tryptophan-2,3-dioxygenase in the liver and proposed that such an inhibition would lead to more tryptophan becoming available for conversion to 5-hydroxytryptamine, explaining the value of these antidepressants. More recently it has been claimed that depressed patients exhibit a lowered level of plasma kynurenine which increases to control values on treatment (Orlikov et al. 1994), though this would run counter to the findings of Mangoni (1974).

An area of psychopharmacology which has as yet received almost no attention is the role of kynurenines in the actions of antidepressant drugs. Current explanations of the mechanism of action of clinically used drugs are unsatisfactory, though it has been recognised that some of the most effective agents are those which decrease the uptake and removal of the transmitter 5HT. However, any pharmacological manipulation which alters the amount of 5HT in neurones or glia will alter secondarily the activity of its synthetic enzymes and the balance of metabolites in the synthetic pathway. A change in the amount of tryptophan in cells will alter the amount available for the synthesis of kynurenines. The effects of a range of antidepressants, especially those affecting 5HT, should, therefore, be examined on the activity and concentrations of the components of the kynurenine pathway.

1.23.3. Schizophrenia

Of a series of metabolites measured, Issa et al. (1994) found that 3-hydroxykynurenine gave the best indication of clinical response to neuroleptic treatment in schizophrenia. There may, therefore, be value in exam-

ining further the possible role of kynurenines in schizophrenia, especially since quinolinic acid lesions of the ventral striatum of rats have the effect of suppressing prepulse inhibition, an attention disorder characteristic of schizophrenia (Kodsi and Swerdlow, 1994).

Although a large volume of evidence suggests a role for glutamate receptors in the aetiology of schizophrenia, there is no abnormality in plasma kynurenine levels in schizophrenic patients. However, it has recently been shown that a single injection of amphetamine reduced the levels of kynurenic acid in the young rat striatum, as a result of which the sensitivity of the animals to the neurotoxic effects of NMDA is substantially increased (Poeggeler et al., 1998; Rassoulpour et al., 1998). Since repeated administration of amphetamine is known to induce a psychosis closely resembling that of schizophrenia, it is possible that schizophrenia itself could involve a decline of kynurenic acid levels with a secondary hyperactivation of NMDA receptors and a loss of neurones in limbic regions of the brain.

1.24. Miscellaneous disorders

A number of disorders have received passing attention in the literature, and do not merit detailed consideration. For example, although the significance is unclear, the levels of quinolinic acid in the CSF are raised in children with hydrocephalus or with cerebral tumours (Heyes et al., 1995). Conversely, the levels of kynurenic acid are elevated three-fold in cortical regions of patients with Down's syndrome, raising the possibility that, together with the greater potency of endogenously generated kynurenate, it may be partly responsible for the poor mental performance of these patients (Baran et al., 1996).

1.25. Mechanisms of damage by quinolinic acid

The implications of quinolinic acid secretion by activated cells of the immune system are considerable, since there is evidence for a potentiation between cytokines and activation of glutamate receptors. The potentiation may be mediated by nitric oxide (Kim et al., 1997). Interleukin-1 is known to enhance the excitatory effects of NMDA receptors and the neurotoxic effects of activating NMDA receptors. In addition, the neurotoxic effects of activated macrophages are reduced by antagonists at NMDA receptors (Ma et al., 1997).

In addition to direct toxic effects on neurones, quinolinic acid can induce progressive mitochondrial dysfunction, which may be a contributory factor in neurodegeneration (Bordelon et al., 1997). The neurotoxicity produced by quinolinic acid may also depend at least partly on the formation of reactive oxygen species, since its neurotoxic activity can be prevented by spin-trap reagents such as α-phenyl-*t*-butylnitrone (Nakao and Brundin, 1997) and free radical scavengers (Nakai et al., 1999). In synaptosomes from rat brain the basal amount of lipid peroxidation was increased by up to 256% in the presence of quinolinic acid 100 μM. These results were supported recently by additional demonstrations that quinolinic acid-induced lipid peroxidation and neuronal damage could both be prevented by antioxidants such as melatonin (Southgate et al., 1998; Behan et al., 1999; Cabrera et al., 2000) and deprenyl (Behan et al., 1999) (Figs. 8 and 9).

A role of free radicals generated by quinolinic acid is further supported by data showing that the quinolinic

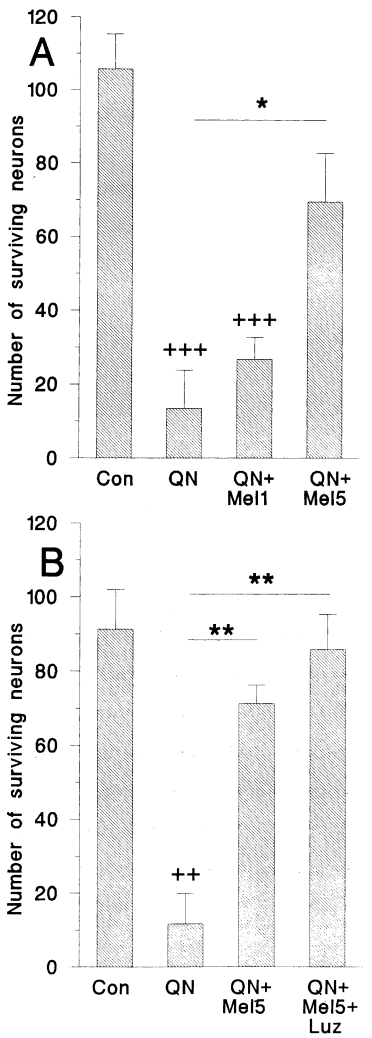

Fig. 8. Histograms summarising the number of neurons surviving after treatment with quinolinic acid 120 nmols (QN) or combined treatments with quinolinic acid and melatonin (1 or 5 nmol + 2 × 20 mg kg^{-1} i.p.) (histogram A) or combined treatments with quinolinic acid 120 nmols, melatonin 5 nmol + 2 × 20 mg kg^{-1} i.p. and luzindole 1 nmol (histogram B). Four animals were used in each group. Results are shown as mean ± S.E.M. Analysis was performed by ANOVA followed by the Bonferroni test for multiple comparisons, $*P < 0.05$; $**P < 0.01$ compared with quinolinic acid alone ($n = 4$); $++P < 0.01$; $+++P < 0.001$ compared with control; (reproduced with permission from Behan et al., 1999).

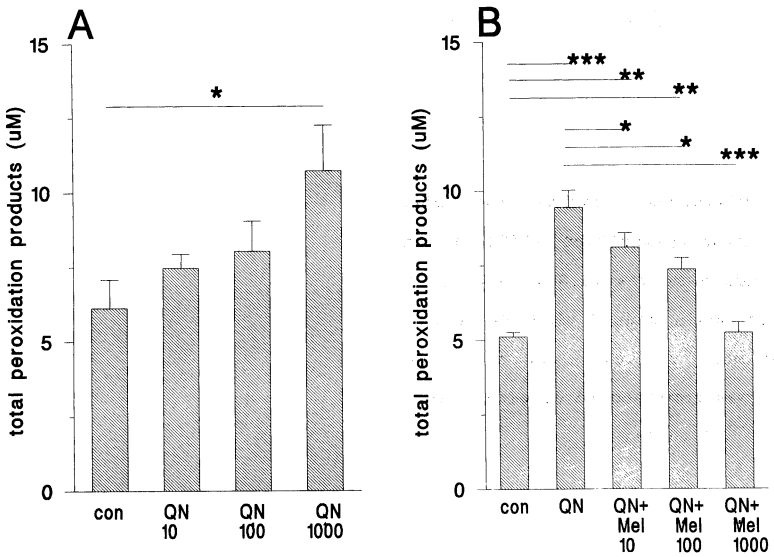

Fig. 9. Histograms summarising the total concentration of malondialdehyde and 4-hydroxynonenal after incubation of hippocampal tissue with quinolinic acid at 10, 100 or 1000 M (histogram A) or with quinolinic acid 1000 μM together with melatonin at 10, 100 or 1000 μM (histogram B). Results are shown as mean ± S.E.M. Analysis was performed by ANOVA followed by the Dunnett test for comparisons with control data (A) or the Bonferroni test for multiple comparisons (B). Four animals were used in each group. $*P < 0.05$; $**P < 0.01$; $***P < 0.001$ for the differences indicated by the bars; (reproduced with permission from Behan et al., 1999).

acid-induced peroxidation was inhibited by nitroarginine but potentiated by L-arginine. This finding suggests that NO, a free radical itself and a precursor of potent toxic radicals such as peroxynitrite, may contribute to the activity of quinolinic acid (Rios and Santamaria, 1991; Santamaria et al., 1997). The same group has shown that inhibition of nitric oxide synthase can prevent the neurotoxic activity of quinolinic acid (Perez-Severiano et al., 1998), supporting the involvement of nitric oxide-derived free radicals in the damage. In an extension of this idea, Kalisch et al. (1999) have found that nitric oxide seems to mediate the damaging effects of quinolinic acid on enkephalinergic neurons in the rat striatum, but not the loss of neurons containing NADPH-diaphorase. This may be related to the nitric oxide synthase activity of the latter enzyme, but may also indicate different mechanisms for quinolinic acid-induced neuronal damage on subpopulations of cells.

1.25.1. 3-Hydroxykynurenine

With the developing interest in the kynurenine pathway, it was noted that another component, 3-hydroxykynurenine, was also neurotoxic. The dose required is about four times that of 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; Okuda et al., 1996, 1998). This idea is supported by the fact that 3-hydroxykynurenine can be converted to quinonimines with the accompanying generation of reactive oxygen species (Hiraku et al., 1995). The uptake of 3-hydroxykynurenine into cells is required for neurotoxicity, as the inhibition of its uptake by competing large neutral amino acids prevents damage (Okuda et al., 1998). The levels of 3-hydroxykynurenine are increased in the brains of mice following immune activation or administration of interferon-γ (Saito et al., 1992b). They are also elevated in some disease states including HIV infection, especially in those cases associated with dementia (Pearson and Reynolds, 1991; Sardar et al., 1995), infantile spasms (Yamamoto et al., 1994) and hepatic encephalopathy (Pearson and Reynolds, 1991).

The activity of the first enzyme in the synthetic pathway from tryptophan to quinolinate, indoleamine-2,3-dioxygenase has been measured in the post-mortem brains of AIDS patients (Sardar and Reynolds, 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 been reported in patients with Huntington's disease (Reynolds and Pearson, 1989; Pearson and Reynolds, 1992). This would be consistent with the increased activity of 3-hydroxyanthranilic acid oxygenase (Schwarcz et al. 1988a) in this disorder.

It is possible that some of the deleterious actions attributed to 3-hydroxykynurenine are actually due to its metabolite 3-hydroxyanthranilic acid, since the latter readily undergoes auto-oxidation with the formation of superoxide anions (Dykens et al., 1987, 1989).

2. Therapeutic applications of kynurenines

There are at least two ways in which therapeutic agents are being developed based on a modulation of the kynurenine pathway. One approach has been to use analogues of kynurenic acid as antagonists at glutamate receptors. A second has been to inhibit the activity of those enzymes responsible for synthesising quinolinic acid, an action which also diverts kynurenine metabolism towards kynurenic acid. Inhibition of kynurenine hydroxylase results in a decrease in the levels of endogenous quinolinic acid and an increase of kynurenic acid. The change in the balance of these, away from the excitotoxin and towards the neuroprotectant, is predicted to have anticonvulsant and neuroprotective properties in stroke (Pellicciari et al., 1994; Varasi et al. 1996). Some of these approaches are reviewed in greater detail elsewhere (Stone, 2000a,b).

2.1. Kynurenic acid

With the recognition that glutamate receptors may be involved in regulating neuronal excitability and possibly even their viability after cerebral insults, there arose a widespread ambition to develop glutamate antagonists which might be of value in the treatment of stroke damage and neurodegenerative disorders of the brain. The NMDA receptor is the receptor via which glutamate is most able to elevate the intracellular concentrations of calcium to an extent which can cause long-term changes of synaptic function such as long-term potentiation (LTP) but which, if maintained or repeated, can lead to neuronal death. The discovery that kynurenic acid was an antagonist at amino acid receptors (Perkins and Stone, 1982) presented a lead compound which has been used as the basis for developing several series of chemically related agents as potential drugs. Kynurenic acid is able to antagonise glutamate receptor activation in rodents and primates (Stone and Perkins, 1984) and may distinguish subpopulations of kainate receptors (Stone, 1990). The value of kynurenic acid is that it is able to antagonise actions mediated by both the NMDA and the non-NMDA groups of glutamate receptors although most interest has centred around its more potent activity at the strychnine-resistant glycine site on the NMDA receptor. Interestingly, kynurenine itself can act as an agonist at this site (Stone, 1991).

Kynurenic acid itself can pass across the blood–brain barrier (Scharfman and Goodman, 1998; Salvati et al., 1999) and its glutamate antagonist activity is probably responsible for its ability to prevent brain damage following anoxia (Simon et al., 1986), ischaemia (Germano et al., 1987; Salvati et al., 1999). These facts have led to the development of several series of compounds with potential therapeutic value in the treatment of strokes, epilepsy (Rowley et al., 1993; Moore et al. 1993; Nichols and Yielding, 1993) and neurodegenerative disorders.

2.1.1. Kynurenic acid antagonists as therapeutic agents

Several groups have used the kynurenate structure (1, Fig. 10) to model features of the glycine-2 receptor site as a prelude to the development of more active agents (Manallack et al., 1990; Stone, 1992). Harrison et al. (1990), Leeson et al. (1991a,b), Leeson et al., (1992), Leeson et al. (1993), Carling et al. (1992, 1993), Bigge (1993) have discussed the structural requirements of modifying the basic kynurenate structure to maintain or improve NMDA receptor blockade, examining in a series of papers the relative importance of different portions of the molecule, or exploring different approaches to their modification. Some of these chemical developments have been reviewed by Salituro et al. (1993). A major advantage of the kynurenic acid molecule is that its bicyclic structure confers lipid solubility which allows penetration through the blood-brain barrier (Scharfman and Goodman 1998).

Among the first attempts to improve on the biological activity of kynurenic acid were molecules with minimal changes in the kynurenate nucleus, but a range of substituents on the molecule (Frey et al., 1988; Leeson et al. 1991a,b; Moroni et al., 1991; Baron et al., 1990, 1992; Foster et al., 1992; Smith et al., 1993a,b). Simple substitution of halogen atoms, for example, yielded the potent analogue 5,7-dichlorokynurenic acid (2, Fig. 10) (Baron et al., 1990). The dichloro fomula has been retained in many of the analogues developed subsequently.

Replacement of the 4-hydroxy group of kynurenic acid with acetic acid or similar substituents (3, Fig. 10) allowed further increase in potency (Carling et al., 1992). This change led to the examination of amido substituents in the 4-position, with potent analogues such as, (4, Fig. 10) (MDL 100 748) and (5) (L689 560) (Harrison et al., 1990; Leeson et al., 1991a,b, 1992; Baron et al., 1992). In a different approach several groups showed that a series of kynurenate analogues with a 3-phenyl substituent resulted in lipid soluble compounds which retained potent activity at the glycine-2 site (McQuaid et al., 1992a; Chapman et al., 1995). One of the compounds produced from this strategy was MDL 104 653 (6, Fig. 10). The insertion of sulphur in the 4-position of the kynurenate nucleus has produced active compounds such as (7, Fig. 10)(RPR104632; Boireau et al., 1996).

Carling et al. (1993) made the interesting observation that in a series of 3,4-dihydroquinolones and tetrahydroquinolines, those with a nitro-substituent in the 3-position were all active as selective antagonists at the NMDA/glycine site provided they bore a bulky grouping at position 4. The compound with no 4-substituent proved to be one of the most effective broad spectrum

antagonists of NMDA and AMPA receptors known at the time (8, Fig. 10). The observation allowed the authors to propose the importance of steric hindrance at the 4-position for permitting activity at the AMPA site

Salituro et al. (1990, 1991, 1992), Gray et al. (1991), Baron et al. (1992), Hood et al. (1992), Rowley et al. (1992), Rao et al. (1993), Noe et al. (1996) demonstrated the activity of a series of kynurenate analogues in which the 6-membered nitrogen-containing ring was replaced by a 5-carbon ring to provide a series of indole analogues. The simplest of these compounds included (9, Fig. 10) (SC49648; Rao et al., 1993) but a range of substituents has been employed with the most effective products being (10, Fig. 10) (MDL29 951; Salituro et al., 1990; Baron et al., 1992). Expansions of the 3-substituent retained activity (Rowley et al., 1992) and included the potentially valuable clinical compound (11, Fig. 10) (GV150526A; Glaxo, 1993). Modifications of the indole nucleus were found generally to parallel

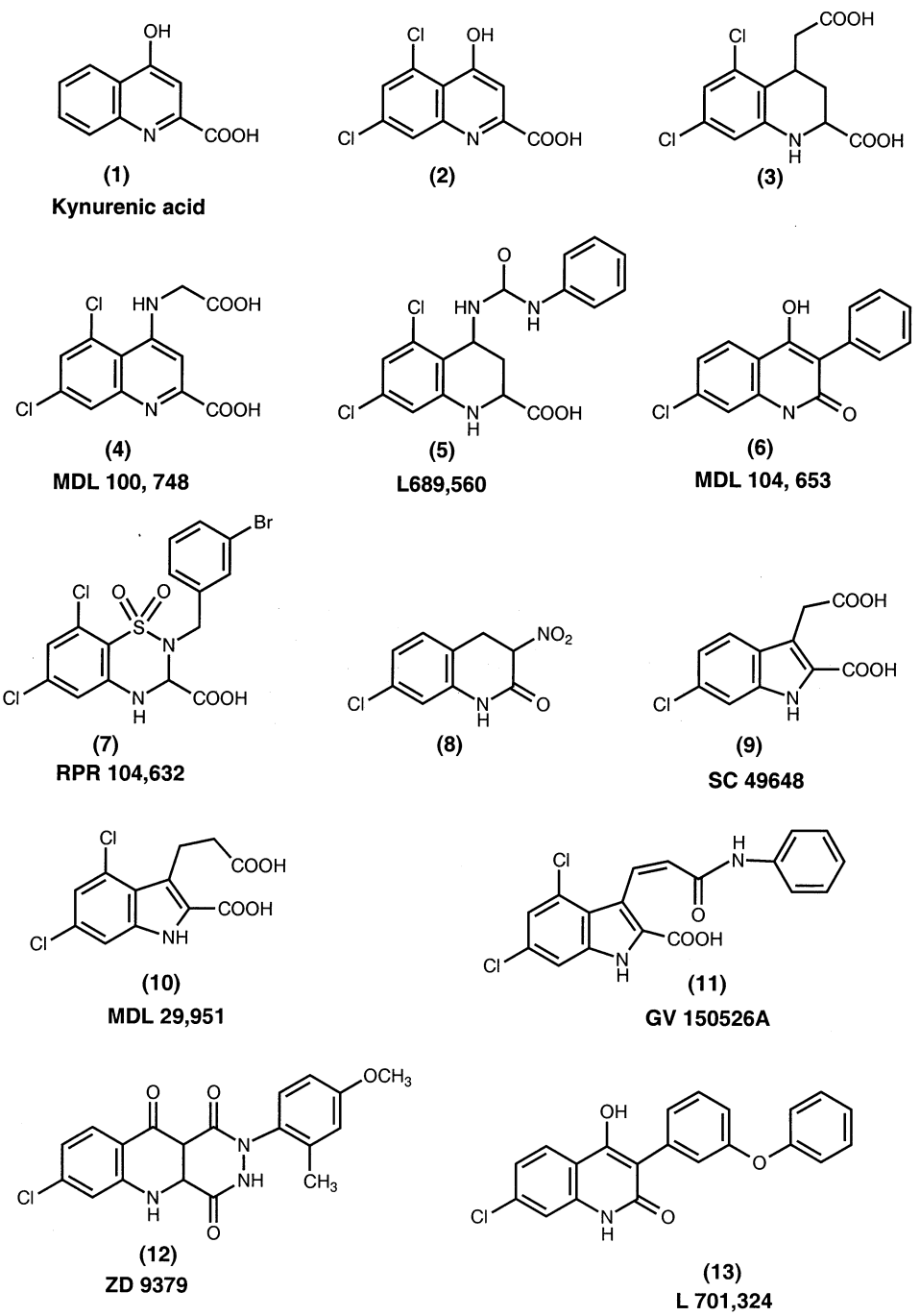

Fig. 10. Structures of some of the kynurenic acid analogues which have been developed as glutamate receptor blockers.

those of the kynurenate nucleus (Gray et al., 1991; Salituro et al., 1991).

Attempts have been made to combine features from several of the earlier series, with the demonstration of activity in molecules possessing heterocyclic substitutions. These cyclic substituents have been incorporated into the kynurenate nucleus or included in side chains (Leeson et al., 1992) or attached to the quinoxaline nucleus (McQuaid et al., 1992b). A different approach has been to cyclise the 2- and 3-substituents and then substitute on the third ring. This has yielded a range of compounds including (12, Fig. 10) (ZD9379; Zeneca Limited, 1995).

Other groups which have synthesised compounds based upon kynurenic acid include Jimonet et al. (1994), Cai et al. (1996a,b), Keana et al. (1995). The most recent developments have included more complex substituents in the 3-position of the kynurenate nucleus (13, Fig. 10) (L701 324; Bristow et al., 1996) or its indole-based derivatives (Siegel et al., 1996; Merrell Pharmaceuticals, 1996; Hoechst Marion Roussel, 1996), or inclusion of the nitro grouping (Cai et al., 1996a). Compound L701 324 (13) has a marked neuroleptic profile in rodent models. In view of the evidence for a role of glutamate receptor dysfunction in schizophrenia (Tamminga, 1998), this compound may prove promising as a candidate antipsychotic in Man.

Recent attention has shifted in some companies to the B ring of the kynurenate base molecule, with activity at glutamate receptors being evident in compounds in which the ring is replaced by a substituted 5-membered ring (Rhone-Poulenc Rorer, 1996; Merck GmbH, 1996). Conversely, enlargement of the nitrogenous ring of kynurenate into a seven-membered ring has produced benzazepinedione compounds with activity at the NMDA receptors.

An entirely different approach has been to examine agents acting as prodrugs to deliver kynurenic acid into the brain (Moore et al., 1993). For example, L-4-chlorokynurenine is transported into brain and is there converted into 7-chlorokynurenic acid. Similarly 4,6-dichlorokynurenine is taken into brain and converted to 5,7-dichlorokynurenic acid (Hokari et al., 1996).

These various developments have culminated in the patenting of several agents for the treatment of CNS disorders in which an abnormality of glutamate receptor function has been implicated, including head injury, strokes, schizophrenia and epilepsy. Particular excitement has been generated by agents which show activity after systemic administration and may therefore be useful in the prevention or slowing of neurodegenerative disorders. The pharmacology of some of these has been discussed by Kulagowski (1996), Kulagowski and Leeson (1995), Warner et al. (1995), Priestley et al. (1996), Ilyin et al. (1996), Kretschmer et al., (1997), Wood and Hawkinson (1997), Hawkinson et al. (1997). Some of these agents have progressed towards the stage of clinical trials for stroke and head injury and include L-695 902, L-687 414 and L-701 324 (13) (Merck GmbH, 1996), GV150526A (11) (Glaxo, 1993), ACEA1416 and ACEA 1021 (CoSensys/Ciba-Geigy; Weber and Keana, 1994), SM-18400 (Sumitomo) and ZD9379 (12) (Zeneca Limited, 1995).

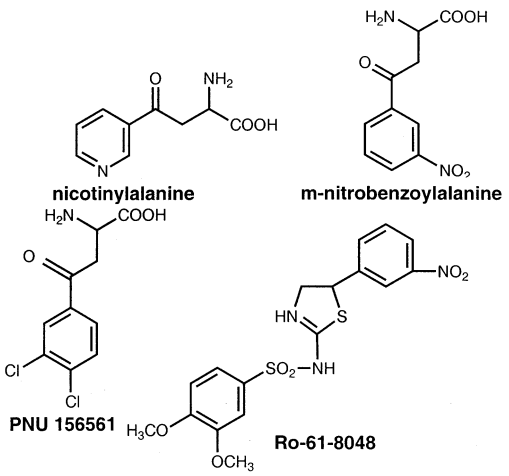

Fig. 11. Structures of compounds which inhibit enzymes of the kynurenine pathway.

2.1.2. Modulators of kynurenic acid concentrations

An alternative approach to therapy is to inhibit kynureninase or kynurenine hydroxylase activity, an action which should block the synthesis of quinolinic acid and divert kynurenine metabolism towards kynurenic acid. The practicality of this was demonstrated by the development of nicotinylalanine (Fig. 11) as an inhibitor of these enzymes (Connick et al., 1992; Russi et al., 1992). Nicotinylalanine was administered with L-kynurenine and probenecid (to slow the loss of kynurenic acid from the brain via the acidic transporters) and was shown to increase the brain content of kynurenic acid and to prevent the induction of seizures. These studies were the first to raise the possibility that nicotinylalanine or a related inhibitor of kynurenine metabolism might be of therapeutic interest in reducing states of cerebral hyperexcitability including excitotoxic damage. The results have been replicated and extended by Harris et al. (1998) with the finding that nicotinylalanine protects against NMDA or quinolinic acid-induced damage in the rat striatum. Nicotinylalanine raises the levels of brain kynurenate by up to five-fold, produces sedation in animals, and suppresses seizures (Connick et al., 1992; Carpenedo et al., 1994).

The ability of nicotinylalanine (still administered together with L-kynurenine and probenecid) to protect nigrostriatal neurons against damage caused by the local injection of quinolinic acid or NMDA has been

shown by Miranda et al. (1997, 1999). A surprising feature of these studies, however, is that the levels of cerebral kynurenic acid were raised no more than 3.3-fold. At first sight, this seems insufficient to account for neuronal protection, but the recent demonstration that endogenously generated kynurenic acid is more effective at inhibiting NMDA receptor activation than exogenously added compound (presumably because it is generated focally at physiologically relevant sites) (Scharfman et al., 1999) presents a possible explanation of the findings. Certainly the small increase of kynurenic acid resulting from the perfusion of brain slices with the precursor L-kynurenine is sufficient to prevent the generation of epileptiform bursting activity (Scharfman and Ofer, 1997).

A series of alanine derivatives has also been studied. Meta-nitrobenzoylalanine (Fig. 11) preferentially inhibits kynurenine-3-hydroxylase exhibits an IC_{50} of 0.9 mM as an inhibitor of kynurenine-3-hydroxylase but only 100 μM against kynureninase, while the related compound *ortho*-methoxybenzoylalanine preferentially inhibits kynureninase (Pellicciari et al., 1994; Natalini et al., 1995). Meta-nitrobenzoylalanine is the more potent at increasing kynurenine and kynurenic acid levels in the brain, blood, liver and kidney. Meta-nitrobenzoylalanine and *ortho*-methoxybenzoylalanine are able to increase the amount of kynurenic acid in the hippocampus in vivo, an effect which is associated with a decrease of locomotion and a suppression of seizures in strains of mice sensitive to audiogenic seizures (Chiarugi et al., 1995), and which is also associated with protection against ischaemic neuronal damage in gerbils (Cozzi et al., 1999).

A systemic kynurenine-3-hydroxylase inhibitor, 3,4-dichlorobenzoylalanine (Fig. 11) (PNU156561; formerly known as FCE28833A), has been developed which increases the levels of kynurenine and kynurenic acid in rat brain. In hippocampal dialysates, peak increases of 10- and 80-fold the resting levels respectively were obtained after a single dose. Kynurenic acid remained elevated for 22 h (Speciale et al., 1996). The evidence to date indicates that this agent is more effective than meta-nitrobenzoylalanine (Speciale et al., 1996).

As noted earlier, Behan and Stone (2000) have recently demonstrated that *m*-nitrobenzoylalanine could reduce the hippocampal damage produced by kainate. This strongly supports the concept that it is quinolinic acid, produced by macrophages and microglia in response to neuronal injury, which is partly responsible for the neuronal loss which follows excitotoxin administration and, by implication, ischaemia.

L-kynurenine is metabolised primarily by hydroxylation in the brain and hydrolysis in the periphery. The inhibition of kynurenine hydroxylase by meta-nitrobenzoylalanine causes a decline of 3-hydroxykynurenine levels and an increase of kynurenic acid in brain. In contrast *ortho*-methoxybenzoylalanine, a preferential inhibitor of kynureninase, increases brain 3-hydroxykynurenine but does not reduce the level of brain 3-hydroxyanthranilic acid. The administration of kynurenine hydroxylase inhibitors is, therefore, the most rational way to elevate simultaneously brain levels of kynurenic acid and decrease the amount of 3-hydroxykynurenine and quinolinic acid in the brain (Chiarugi et al. 1996).

The reason for the unexpected ability of *ortho*-methoxybenzoylalanine to leave unchanged the generation of 3-hydroxyanthranilic acid has been explored by Chiarugi and Moroni (1999). They have noted that, while *ortho*-methoxybenzoylalanine does not alter the activity of isolated and purified 3-hydroxyanthranilic acid oxygenase, it does inhibit the enzyme in vivo. Activity is also depressed by mitochondrial proteins, leading the authors to propose that in vivo the combination of these factors leads to a net decrease of 3-hydroxyanthranilic acid oxygenase to a level which compensates for the blockade of kynureninase.

S-aryl-L-cysteine-*S*,*S*-dioxides are inhibitors of kynureninase. The most potent of these have nanomolar activity (Dua et al., 1993). These compounds have been shown to reduce the stimulation of quinolinic acid synthesis induced by interferon-γ in human macrophages (Drysdale and Reinhard, 1998). A different chemical approach has led to a series of *N*-(4-phenylthiazol-2-yl) benzenesulphonamides with high activity as inhibitors of kynurenine-3-hydroxylase. One member of this series, Ro61-8048 (Fig. 11) has a Ki of only 19 nM. The compound is effective after oral administration in gerbils (Rover et al., 1997) and has been shown to be protective against cerebral ischaemia in gerbils following carotid artery occlusion (Cozzi et al., 1999). In light of the comments just made, these inhibitors of kynurenine hydroxylase are likely to prove the more useful agents in practice.

The most recent development in this field has been the synthesis of a series of 4-aryl-2-hydroxy-4-oxobut-2-enoic acids and esters. These have proved to be the most potent kynurenine-3-hydroxylase inhibitors developed to date, with nanmolar potencies (Drysdale et al., 2000). In preliminary functional studies, they have been shown to suppress the formation of quinolinic acid induced by interferon-γ in cultures of human macrophages. It will be important to examine these compounds in whole animal paradigms of neuronal toxicity and damage to support the principle that inhibition of this enzyme can lead to clinically useful therapeutic, neuroprotective agents.

2.1.3. Modulators of quinolinic acid concentrations

An alternative means to prevent the synthesis of quinolinic acid is to inhibit 3-hydroxyanthranilic acid

oxygenase. 4-halo-3-hydroxyanthranilic acids have been shown to inhibit this enzyme leading to a reduction of quinolinic acid formation (Heyes et al., 1988; Melikian et al., 1990; Walsh et al. 1991, 1994). This compound, as well as norharmane and 6-chlorotryptophan attenuate quinolinic acid synthesis with activity in the low micromolar range, and are effective in several cell lines including peripheral monocytes (Saito et al. 1994).

Most recently, the analogue 4,6-dibromo-3-hydroxyanthranilic acid (NCR-631) has been developed by AstraZeneca. This compound inhibits 3-hydroxyanthranilic acid oxygenase and reduces the loss of hippocampal cells produced by anoxia, bacterial lipopolysaccharide or injurious cytokines such as interleukin-1b (Luthman et al., 1998).

3. Conclusion

It is apparent that from two basic discoveries of the neurobiological activity of quinolinic acid and kynurenic acid there has arisen a flood of scientific, clinical and chemical work which has not only shed light on the possible mechanisms underlying major neurological diseases, but has also led to the development of potentially powerful new therapeutic agents for their treatment. The new approaches to drug development offered by the kynurenine pathway will hopefully generate compounds with different or complementary actions to other drug series, and help towards effective treatments for some of the most distressing, and therapeutically frustrating, disorders of mankind.

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