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Review

Inhibitors of the kynurenine pathway

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Abstract – Strokes (intracranial thomboses or haemorrhaging) cause death and disability, but effective treatments are lacking. The metabolism of tryptophan leads to the generation of quinolinic acid, an agonist potentially neurotoxic at glutamate receptors, and kynurenic acid, an antagonist at the same population of receptors. The commercial development of the kynurenine pathway has included the use of analogues of kynurenic acid as antagonists at glutamate receptors. A second has been to use prodrugs of kynurenic acid or its analogues. Alternatively, it is proving possible to interfere directly with the kynurenine pathway to block the synthesis of quinolinic acid and promote the formation of kynurenic acid. This change yields neuroprotectant and anticonvulsant compounds. © 2000 Éditions scientifiques et médicales Elsevier SAS

kynurenines / quinolinic acid / kynurenic acid / glutamate / NMDA / N-methyl-D-aspartate / neuroprotection / stroke / neurodegeneration

1. The rationale for studying inhibitors of the kynurenine pathway

1.1. Neurodegeneration

Much of the brain damage following a cerebrovascular accident, or stroke, is not due to hypoxia per se, but to the fact that hypoxia triggers a massive release of the neurotransmitter glutamate from neurones into the extracellular space. Glutamate activates a variety of receptors, including those which induce the opening of ion channels (ionotropic receptors) and those which produce changes in intracellular transduction systems such as adenylate cyclase (metabotropic receptors). The ionotropic receptors are of three major subtypes responding to, respectively, N-methyl-D-aspartate (NMDA), kainic acid and α-amino-3-hydroxy-5-methyl-4-isoxazole (AMPA). The activation of NMDA receptors in particular increases calcium influx into neurones, leading to the activation of destructive enzymes and increasing the formation of reactive oxygen species. A therapeutic objective in the pharmaceutical industry therefore, is to develop agents which block the activation of glutamate receptors.

1.2. The kynurenine pathway

Although most of the pharmacological interest in tryptophan has centred on its conversion to 5-hydroxytryptamine (5-HT), the major portion of tryptophan is metabolised along a completely different route, via kynurenine (*figure 1*). This so-called 'kynurenine pathway' is the source of much of the nicotinic acid required physiologically for the synthesis of nicotinamide and the essential enzymic co-factors such as nicotinamide adenine dinucleotide (NAD).

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Abbreviations: ACEA 1021: 5-nitro-6,7-dichloroquinoxaline-2,3-dione; L689,560: 2-carboxy-5,7-dichloro-4-[[(N-phenylamino)-carbonyl]amino]-1,2,3,4-tetrahydroquinoline; Ro-61-8048: 3,4-dimethoxy-N-[4-(3-nitrophenyl)thiazol-2-yl]benzenesulphonamide; AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazole; SC49648: 6-chloro-2-carboxyindole-3-acetic acid; MDL 100,748: 4-[(carboxy-methyl)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; RPR 104632: 6,8-dichloro-[2-(2H)-[(3-bromophenyl)methyl]-1,2,4-benzothiadiazine-1,1-dioxide-3-carboxylic acid; FCE28833A: 3,4-dichlorobenzoylalanine; GV 150526A: 3-[2-[(phenylamino)carbonyl]ethenyl]-4,6-dichloroindole-2-carboxylic acid; ACEA 1416: 7-chloro-6-methyl-5-nitro-1,4-dihydro-2,3-quinoxalinedione; L695,902: 4-hydroxy-3-(carboxymethyl)-quinoline-2(1H)-one; L701,324: 4-hydroxy-7-chloro-3-(3-phenyloxy)phenyl-quinoline-2(1H)-one; L701,252: 4-hydroxy-3-(cyclopropylcarbonyl)-7-chloroquinoline-2(1H)-one.

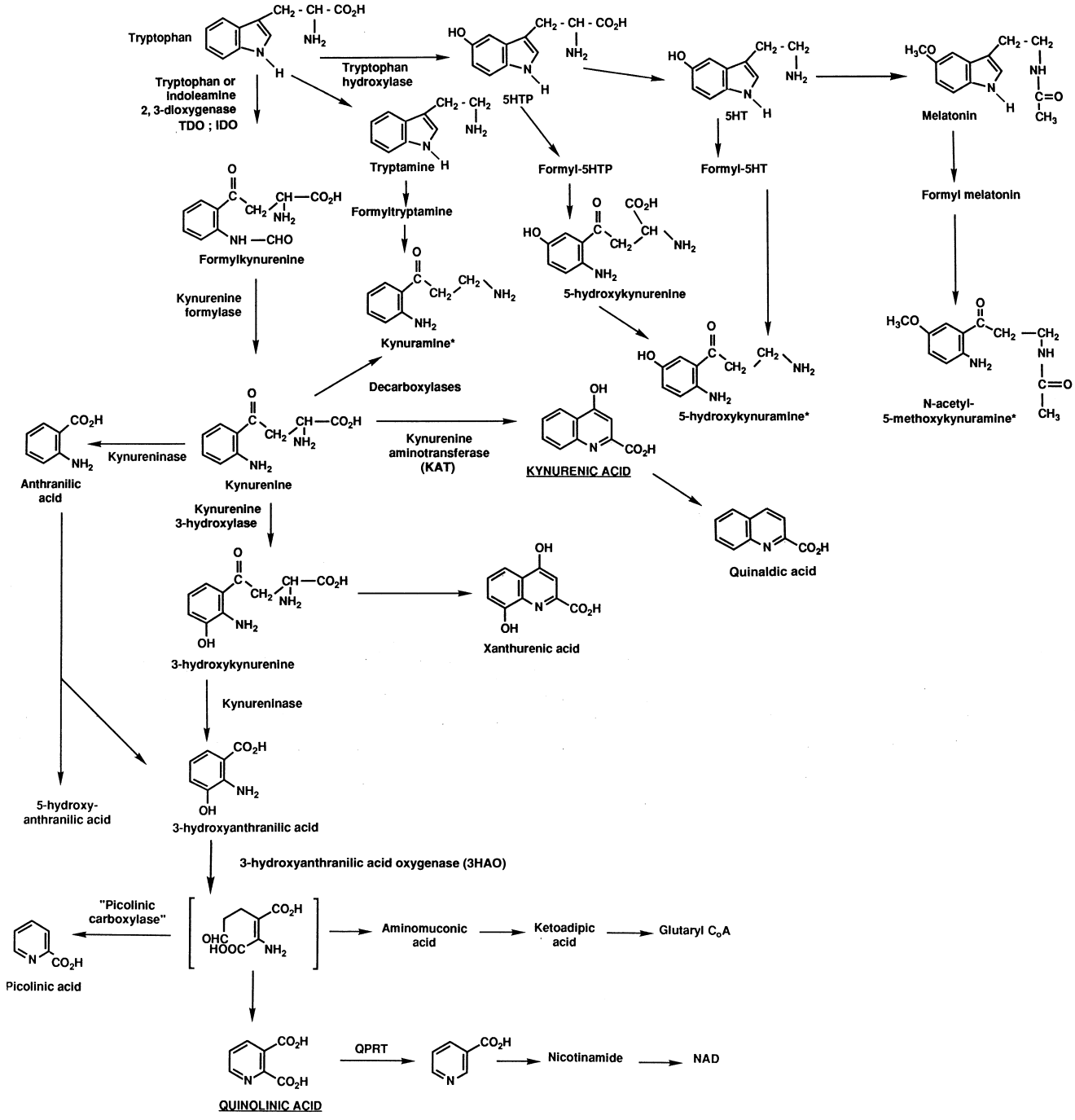

Figure 1. The kynurenine pathway for the metabolism of tryptophan.

1.2.1. Neuroactive kynurenines

Until 1981 interest in kynurenines was limited to this role as precursors of nicotinic acid. In 1981 my laboratory was testing the activity of compounds with structures resembling rigid forms of NMDA. It was discovered that one such compound, quinolinic acid was an effective

agonist at NMDA receptors, producing excitation of neurones in the cerebral cortex [1–6]. An examination of the potential neuronal activity of other members of the pathway then led to the discovery of kynurenic acid by Perkins and Stone [7], who discovered that kynurenic acid could block receptors for glutamate on cortical neurones. Quinolinic acid and kynurenic acid remain the only two endogenous compounds able to activate and block, respectively, the NMDA receptor selectively [8, 9]. The discovery of kynurenic acid opened the way to the development of analogues which would block glutamate receptors and act as neuroprotectants and anticonvulsants.

Kynurenic acid is an antagonist at all three varieties of ionotropic glutamate receptors, and is now frequently used as a test for the involvement of glutamate in synaptic transmission. However, NMDA receptors are often considered to be the most important in neuronal damage, and the detailed investigation of these sites eventually led to the realisation that the receptor is a complex entity at which several co-agonists, acting at linked, allosteric sites, are essential for optimum receptor activation. One of these is glycine [10], acting at a site at which strychnine is not an antagonist and which is therefore quite distinct from the inhibitory, strychnine-sensitive glycine receptor found mainly in the spinal cord. It soon became apparent that kynurenic acid was one of the few compounds which could block the NMDA/glycine binding site with greater potency than it blocked non-NMDA receptors [11].

Kynurenic acid is able to antagonise glutamate receptor activation in rodents [7] and primates [12] and may distinguish subpopulations of kainate receptors [13]. In addition, there is evidence from two independent sources that the potency of kynurenic acid in suppressing NMDA receptor-dependent spontaneous neuronal discharges in the hippocampus does not correlate with its activity as an NMDA antagonist [14, 15]. This observation would suggest an additional novel site of action of kynurenic acid. Kynurenic acid can pass across the blood–brain barrier [16] and is itself able to prevent brain damage following anoxia [17] and ischaemia [18].

1.2.2. Kynurenic acid derivatives as glutamate antagonists

The kynurenic acid structure **1** has been used to model features of the NMDA/glycine site as a prelude to the development of more active agents. The structural requirements required for NMDA receptor blockade have been discussed by several groups [19–27]. In addition, a range of structurally related compounds have been produced [28–34]. Halogen substitution onto the nucleus yielded the potent analogue 5,7-dichlorokynurenic acid **2** [30] which has an IC_{50} of 80 nM against strychnine-resistant glycine binding. The 7-chloro- or 5,7-dichloro-formula has been retained in many of the analogues developed subsequently. Potency could be further enhanced by replacement of the 4-hydroxy group of kynurenic acid with acetic acid or similar substituents (**3**) [25], and this change led naturally to amido- and thio-substituents in the 4-position, with potent analogues such as **4** (MDL 100,748) [20, 31], (**5**) (L689,560) [21–23] and (**6**) [29]. Compound **4** was a marked anticonvulsant agent, while L689,560 (**5**) has become a standard compound, with the displacement of [^{3}H]L689,560 being employed as an assay for the strychnine-resistant (NMDA-linked) glycine binding site.

Kynurenate analogues with a 3-phenyl substituent retained potent activity at the NMDA/glycine site but were more lipid soluble and were orally active [35–38]. One of the compounds produced was MDL 104,653 (**7**). The retention of a keto grouping at position 3 yielded quinones such as **8** (L701,252) which has an IC_{50} of 420 nM against L689,560 binding and an ED_{50} against seizures in DBA/2 mice of 4.1 mg/kg. A group of 2-quinolone sulphonamide analogues of kynurenic acid (**9**) are also active [39]. Of several 3,4-dihydroquinolones and tetrahydroquinolines, those with a 3-nitro-substituent were active as NMDA antagonists if they also included a bulky grouping at position 4 [26, 40]. The compound with no 4-substituent (**10**) proved to be one of the most effective broad spectrum antagonists of NMDA and AMPA receptors known at the time.

1.2.3. Indole analogues

A significant advance was made with the realisation that the quinoline nucleus could be replaced by a five-membered indole nucleus [31, 41–48]. Modifications of the indole nucleus were found generally to parallel those of the kynurenate nucleus [42, 44]. The simplest product was SC49648 (**11**) [47], but the most effective is MDL29,951 (**12**) [31, 41], an agent with an IC_{50} of 140 nM against glycine binding. Oral bioavailability is limited, however. Expansions of the 3-substituent led to compounds such as **13** [46] and **14** (GV150526A) [49]. For the structures of **1**–**14** see *figure 2*.

1.2.4. Other analogues

Although not directly related to kynurenic acid, analogues based on the quinoxaline nucleus have less activity at the NMDA receptor but remain active at the kainate and AMPA receptors [50–52]. Substitution produces a 1 000-fold increased activity at the NMDA/glycine site relative to the AMPA receptors, as in ACEA1021 (**15**).

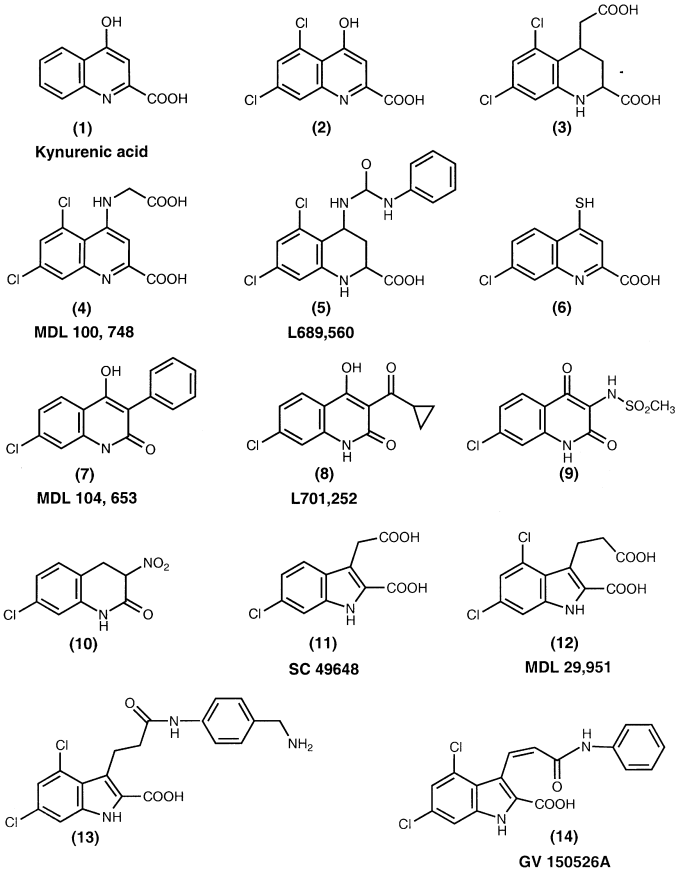

Figure 2. Structures of kynurenic acid analogues.

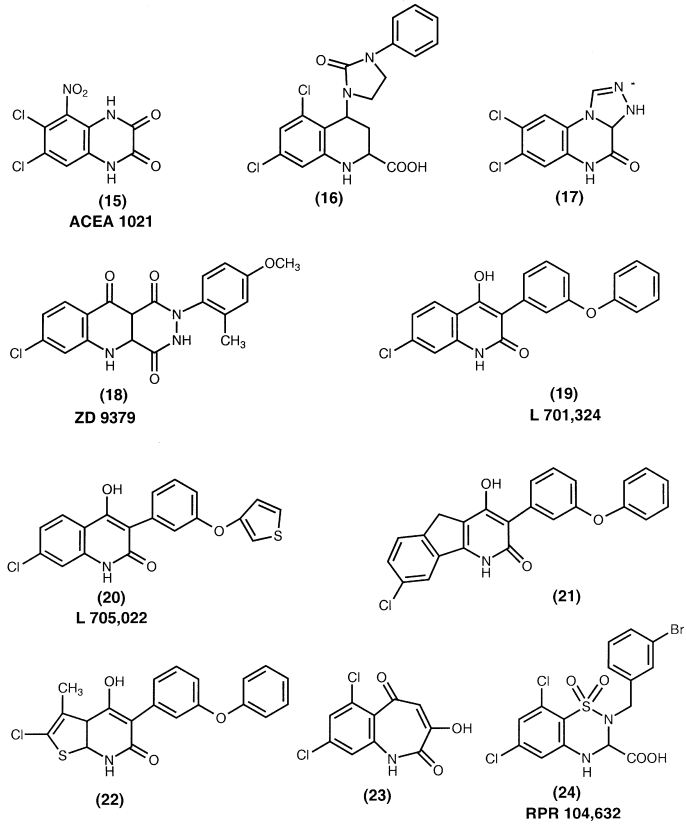

Figure 3. Structures of kynurenic acid analogues.

Heterocyclic substitutions into side chains [23] (**16**) or attached to a quinoxaline nucleus [35] (**17**) are active, while cyclisation of the 2- and 3- substituents has yielded a range of compounds including **18** (ZD9379) [53].

Lipid solubility and blood–brain barrier penetration have been enhanced [40, 54–56] by including more complex lipophilic substituents in the 3-position of the kynurenate nucleus (**19**; L701,324) [57] or indole analogues [58–60]. The two compounds L701,324 (**19**) and the sulphur-containing analogue L705,022 (**20**) have high activity at the glycine site in vitro, and comparable activity in vivo after either systemic or oral administration.

Changing the B ring of the kynurenate nucleus to a substituted 5-membered ring (**21** and **22**) [61, 62] or replacing the nitrogenous ring by a seven-membered ring has produced benzazepinedione compounds **23** with activity at NMDA receptors. Compound **23** displaces strychnine-resistant glycine binding with an IC_{50} of 30 nM and blocks amino acid receptors in vivo after systemic administration of 600 μg/kg i.v. [63]. In addition, this derivative protects against ischaemic brain damage. The insertion of sulphur into the 4-position of the kynurenate nucleus yields benzothiadazine-1,1-dioxide structures such as RPR104632 (**24**) [64]. For the structures of **15**–**24** see *figure 3*.

1.2.5. Prodrugs

Limitations of blood–brain barrier permeability can be circumvented partly by the use of prodrugs to deliver kynurenic acid itself into the brain. The ester compound **25** penetrates the CNS more readily than kynurenic acid itself, but is converted to kynurenic acid within the brain [65]. Compound **26** is hydrolysed within the CNS to an active 4-amino analogue of kynurenic acid [66]. L-4-chloro-kynurenine is transported actively into the brain and converted into the potent kynurenic acid analogue, 7-chlorokynurenic acid. Similarly 4,6-dichloro-kynurenine (**27**) is converted into 5,7-dichlorokynurenic acid (**2**) [67]. Rao et al. [47] developed a series of

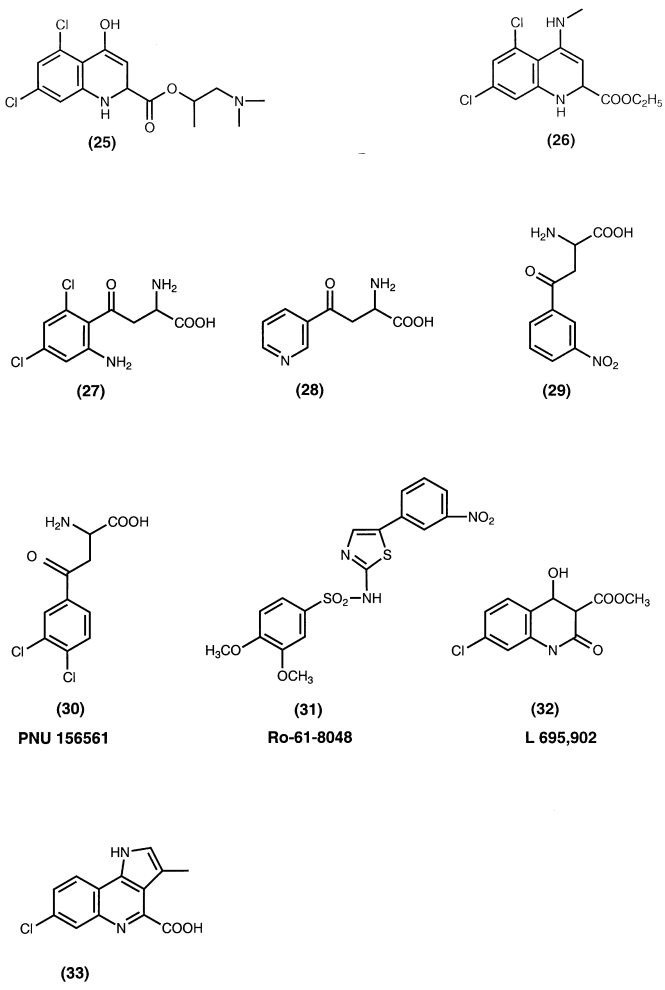

Figure 4. Structures of kynurenic acid analogues.

analogues which are active as amino acid antagonists after systemic (i.p.) injection in rats. These and similar compounds penetrate easily into the brain where they are hydrolysed to the active substance SC49468 (**11**). For the structures of **25**–**27** see *figure 4*.

1.2.6. Advantages of kynurenate analogues

The major advantage of the glycine site antagonists is that they do not exhibit the neurotoxic and psychological side effects, such as neuronal vacuolisation and disturbing psychotomimetic effects, which have proven to be a feature of the non-competitive NMDA channel blockers such as dizocilpine [68] and selfotel [69]. Of the glycine antagonists, kynurenic acid analogues penetrate the blood–brain barrier much more readily than most of the quinoxaline-based compounds. GV150526A and ZD9379 were both entered into Phase I and II trials in 1996 and the results should be available in the near future. Data on the nosology and safety of GV150526 in 66 patients indicate that this drug produces no significant nervous or cardiovascular adverse effects up to doses of 800 mg/kg with subsequent infusions to maintain potentially neuroprotective levels [70].

1.3. Modulators of kynurenic acid concentrations

While the above paragraphs relate to compounds derived from kynurenic acid and which have direct antagonist activity at glutamate receptors, it may also be possible to develop a therapeutic approach to the treatment of neuronal hyperexcitability and ischaemic damage by manipulating the kynurenine pathway. The feasability of this approach was demonstrated by the development of nicotinylalanine (**28**) as an inhibitor of kynureninase and kynurenine hydroxylase [71–73] (*figure 1*). Inhibition of kynurenine hydroxylase results in a decrease in the levels of endogenous quinolinic acid and drives tryptophan metabolism towards 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 and epilepsy [74, 75]. Nicotinylalanine was administered with L-kynurenine and probenecid and was shown both to increase the brain content of kynurenic acid and to prevent seizures. This study was 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 [76].

A number of alanine derivatives have now been synthesised in an attempt to increase the potency and selectivity of nicotinylalanine. L-kynurenine is metabolised primarily by hydroxylation in the brain and hydrolysis in the periphery. *Meta*-nitrobenzoylalanine (**29**) preferentially inhibits kynurenine-3-hydroxylase with an IC_{50} of 900 nM, while *ortho*-methoxybenzoylalanine preferentially inhibits kynureninase [77]. *Meta*-nitrobenzoylalanine is 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 [78]. The inhibition of kynurenine hydroxylase by *meta*-nitrobenzoylalanine causes a decline of 3-hydroxykynurenine levels and an increase of kynurenic acid in the brain. In contrast, *ortho*-methoxybenzoylalanine prefer-

entially inhibits kynureninase, leading to an increase of brain 3-hydroxykynurenine without reducing the level of brain 3-hydroxyanthranilic acid. The administration of kynurenine hydroxylase inhibitors is, therefore, the most rational way to simultaneously elevate brain levels of kynurenic acid and decrease the amount of 3-hydroxykynurenine and quinolinic acid in the brain [79].

PNU156561 (**30**) (formerly known as FCE28833A) is a systemically active inhibitor of kynurenine-3-hydroxylase which is more potent than *meta*-nitrobenzoylalanine [80] and is able to increase kynurenine and kynurenic acid in the rat brain. By measuring the levels of these compounds in microdialysates of rat hippocampus, increases of 10- and 80-fold the resting levels, respectively, were obtained after a single systemic injection, with kynurenic acid remaining elevated for almost 24 h [80].

A series of N-(4-phenylthiazol-2-yl) benzenesulphonamides has been proven to exhibit potent inhibition of kynurenine-3-hydroxylase, with one such compound, Ro61-8048 (**31**) having an IC_{50} of only 37 nM. It is also active after oral administration in gerbils [81], raising kynurenic acid levels in the extracellular fluid of gerbil brain with an ED_{50} of approximately 4 μmol/kg. Systemic administration at the higher dose of 100 μmol/kg still raised brain kynurenic acid levels 7.5-fold. For the structures of **28**–**31** see *figure 4*.

1.3.1. Modulators of quinolinic acid concentrations

The role of endogenous quinolinic acid in the brain remains obscure and controversial, but there is increasing evidence that glia can synthesise and release relatively high concentrations of quinolinic acid after activation by insults to the brain or inflammatory stimuli such as bacterial infection. The increase of quinolinic acid could produce or enhance the amount of neuronal damage produced by the primary brain insult. The reduction of quinolinic acid synthesis could, therefore, limit the amount of brain damage. In addition to the enzyme inhibitors described above, an alternative approach to preventing the synthesis of quinolinic acid is to inhibit 3-hydroxyanthranilic acid 3,4-dioxygenase. 4-Halo-3-hydroxyanthranilic acids can inhibit this enzyme and reduce quinolinic acid formation [82–85].

1.4. Therapeutic indications and trials of kynurenic acid analogues

Many of the agents just described have now been patented for the treatment of CNS disorders involving abnormalities in glutamate receptor function such as head injury, strokes, schizophrenia and epilepsy. Systemically active compounds are of special interest and may be useful in the prevention or slowing of neurodegenerative disorders [52, 86–92]. There are several disorders in which NMDA receptors have been implicated, including the dementia associated with AIDS [93].

1.4.1. Cerebral ischaemia

Neuroprotection against brain damage due to ischaemia, hypoxia or traumatic brain injury remains one of the greatest challenges to neuropharmacology. Kynurenic acid itself is able to protect against damage induced by transient forebrain ischaemia [94] and a number of kynurenic acid analogues have passed into clinical trials in some of these disorders, especially stroke and head injury. These compounds include the simple kynurenic acid analogue L-695,902 (**32**, see *figure 4*), and L-701,324 (**19**) [62], GV150526A (**14**) [49], RPR104632 (**24**) [61] and ZD9379 (**18**) [36]. GV150526A (**14**) reduces neuronal damage following focal cerebral ischaemia in rats [52], producing a 78% reduction in neuronal loss after 30 mg/kg p.o. A reduction of more than 50% of the damage was still seen when the drug was administered 6 h after the insult. GV150526A is one of only a few agents tested, including dizocilpine and ACEA1021 (**15**), able to confer post-ischaemic protection. GV150526A entered Phase II clinical trials in April 1995. The Zeneca compound ZD9379 (**18**) has a half-life of 34 h in rats, a fact which may contribute to its neuroprotective properties. About 50% protection was afforded 24 h after a dose of 10 mg/kg, given 30 min after middle cerebral artery occlusion, followed by a 4-h infusion, in rats [95]. Neither GV150526A (**14**) nor ZD9379 (**18**) have induced neuronal damage and vacuolisation [52].

1.4.2. Neurodegenerative disorders

Part of the cell loss in chronic neurodegenerative disorders, including Parkinson's disease, Alzheimer's disease and Huntington's disease may be due to increased activation of glutamate receptors. One of the neurodegenerative disorders for which there is overwhelming evidence for an involvement of quinolinic acid is that associated with infection by the human immunodeficiency virus (HIV) [93]. The neuro-inflammation which accompanies CNS-AIDS results in a large increase in the level of quinolinic acid in the brain [96, 97]. The resulting neuronal damage gives rise to the AIDS-dementia syndrome which afflicts over 20% of those affected by AIDS. In cases such as these, kynurenic acid analogues with their predilection for NMDA receptors are likely to prove effective, but the strategy of limiting the production of the massively elevated amounts of quinolinic acid and simultaneously increasing kynurenic acid levels by inhibition of the kynurenine pathway enzymes is a promising alternative.

1.4.3. Schizophrenia

There is an increase in the density of glycine binding sites in the post-mortem brains of schizophrenic patients [98–100], consistent with a reduction of glutamatergic function resulting in a compensatory up-regulation. There is also strong evidence for changes in the number and subunit composition of glutamate receptors. A role for glutamate dysfunction is supported by studies of glutamate receptor function, glutamate release and the beneficial effects of glycine-site agonists in some cases [101, 102]. Glycine site antagonists are known to prevent behavioural effects and changes of dopamine metabolism induced by amphetamine in the nucleus accumbens but not the striatum [103]. L701,324 (**19**) reduces amphetamine-induced hyperactivity in animals but has no effect on normal locomotion and does not induce catalepsy. This profile is similar to that of the atypical antipsychotic drugs which reduce schizophrenic symptoms without inducing extrapyramidal signs [57]. The glycine-site agonists may ameliorate schizophrenia by down-regulating the receptors.

2. Summary

The discovery of kynurenic acid as a glutamate antagonist almost 20 years ago, and the subsequent discovery of its potent activity at the strychnine-resistant glycine site has led to a massive chemical and pharmacological interest, leading to kynurenic acid analogues which both act directly at the NMDA/glycine site and are able to disrupt the kynurenine pathway and alter the balance of endogenous kynurenines in the direction of reduced neuronal excitability and neuroprotection. It is likely that, with continued development, a selection of these will soon be suitable for therapeutic intervention in preventing or treating brain damage associated with AIDS dementia, neurodegenerative disorders and strokes, areas which at present remain almost impossible to treat.

References

[1] Stone, T.W., Perkins M.N., Eur. J. Pharmacol. 72 (1981) 411–412.

[2] Perkins M.N., Stone T.W., Brain Res. 259 (1983) 172–176.

[3] Perkins M.N., Stone T.W., J. Pharmacol. Exp. Ther. 226 (1983) 551–557.

[4] Stone T.W., Br. J. Pharmacol. 81 (1984) 175–181.

[5] Stone T.W., Quinolinic Acid and the Kynurenines, CRC Press, Boca Raton, 1989.

[6] Stone T.W., Pharmacol. Rev. 45 (1993) 309–379.

[7] Perkins M.N., Stone T.W., Brain Res. 247 (1982) 184–187.

[8] Stone T.W., Connick J.H., Neuroscience 15 (1985) 597–617.

[9] Stone T.W., Burton N.R., Prog. Neurobiol. 30 (1988) 333–368.

[10] Johnson J.W., Ascher P., Nature 325 (1987) 529–531.

[11] Birch P.J., Grossman C.J., Hayes A.G., Eur. J. Pharmacol. 154 (1988) 85–87.

[12] Stone T.W., Perkins M.N., Neurosci. Lett. 52 (1984) 335–340.

[13] Stone T.W., Br. J. Pharmacol. 101 (1990) 847–852.

[14] Brady R.J., Swann J.W., Epilepsy Res. 2 (1988) 232–238.

[15] Stone T.W., Neurosci. Lett. 84 (1988) 234–238.

[16] Scharfman H.E., Goodman J.H., Neuroscience 86 (1998) 751–764.

[17] Simon R.P., Young R.S.K., Stout S., Cheng J., Neurosci. Lett. 71 (1986) 361–364.

[18] Germano I.M., Pitts L.H., Meldrum B.S., Bartkowski H.M., Simon R.P., Ann. Neurol. 22 (1987) 730–734.

[19] Manallack D.T., Wong M.G., O'Shea R.D., Beart P.M., Neuropharmacology 1 (1990) 7–15.

[20] Harrison B.L., Baron B.M., Cousino D.M., McDonald I.A., J. Med. Chem. 33 (1990) 3130–3132.

[21] Leeson P.D., Carling R.W., Smith J.D., Baker R., Foster A.C., Kemp J.A., Med. Chem. Res. 1 (1991) 64–73.

[22] Leeson P.D., Baker R., Carling R.W., Curtis N.R., Moore K.W., Williams B.J. et al., J. Med. Chem. 34 (1991) 1243–1252.

[23] Leeson P.D., Carling R.W., Moore K.W., Moseley A.M., Smith J.D., Stevenson G. et al., J. Med. Chem. 35 (1992) 1954–1968.

[24] Leeson P.D., Baker R., Carling R.W., Kulagowski J.J., Mawer I.M., Ridgill M.P. et al., Bioorg. Med. Chem. Lett. 3 (1993) 299–304.

[25] Carling R.W., Leeson P.D., Moseley A.M., Baker R., Foster A.C., Grimwood S., Kemp J.A., Marshall G.R., J. Med. Chem. 35 (1992) 1942–1953.

[26] Carling, R.W., Leeson P.D., Moore K.W., Smith J.D., Moyes C.R., Mawer I.M. et al., J. Med. Chem. 36 (1993) 3397–3408.

[27] Bigge C.F., Biochem. Pharmacol. 45 (1993) 1547–1561.

[28] Frey P., Berney D., Herrling P.L., Mueller W., Urwyler S., Neurosci. Lett. 91 (1988) 194–198.

[29] Moroni F., Alesiani N., Galli A., Mori F., Pecorari R., Carla V., Cherici G., Pellicciari R., Eur. J. Pharmacol. 199 (1991) 227–232.

[30] Baron B.M., Harrison B.L., Miller F.P., McDonald I.A., Salituro F.G., Schmidt C.J. et al., Mol. Pharmacol. 38 (1990) 554–561.

[31] Baron B.M., Harrison B.L., McDonald I.A., Meldrum B.S., Palfreyman M.G., Salituro F.G. et al., J. Pharmacol. Exp. Ther. 262 (1992) 947–956.

[32] Foster A.C., Kemp J.A., Leeson P.D., Grimwood S., Donald A.E., Marshall G.R. et al., Mol. Pharmacol. 41 (1992) 914–922.

[33] Foster A.C., Kemp J.A., Tricklebank M.D., Leeson P.D., Carling R.W., Williams B.J. et al., Mol. Neuropharmacol. 2 (1992) 97–102.

[34] Smith E.C.R., McQuaid L.A., Calligaro D.O., O'Malley P.J., Bioorg. Med. Chem. Lett. 3 (1993) 81–84.

[35] McQuaid L.A., Smith E.C.R., South K.K., Mitch C.H., Schoepp D.D., True R.A. et al., J. Med. Chem. 35 (1992) 3319–3324; 3423–3425.

[36] Chapman A.G., Durmuller N., Harrison B.L., Baron B.M., Parvez N., Meldrum B.S., Eur. J. Pharmacol. 274 (1995) 1–3.

[37] Carling R.W., Leeson P.D., Moore K.W., Moyes C.R., Duncton M., Hudson M.L. et al., J. Med. Chem. 40 (1997) 754–765.

[38] Kulagowski J.J., Baker R., Curtis N.R., Leeson P.D., Mawer I.M., Moseley A.M. et al., J. Med. Chem. 37 (1994) 1402–1405.

[39] Sandoz Ltd. (1995) WO9519346.

[40] Cai S.X., Zhou Z.L., Huang J.C., Whittemore E.R., Egbuwoku Z.O., Hawkinson J.E., Woodward R.M., Weber E., Keana J.F.W., J. Med. Chem. 39 (1996) 4682–4686.

[41] Salituro F.G., Harrison B.L., Baron B.B., Nyce P.L., Stewart K.T., McDonald I.A., J. Med. Chem. 33 (1990) 2944–2946.

[42] Salituro F.G., Tomlinson R.C., Baron B.B., Demeter D.A., Weintraub H.J.R., McDonald I.A., Bioorg. Med. Chem. Lett. 1 (1991) 455–460.

[43] Salituro F.G., Harrison B.L., Baron B.B., Nyce P.L., Stewart K.T., Kehne J.H., White H.S., McDonald I.A., J. Med. Chem. 35 (1992) 1791–1799.

[44] Gray N.M., Dappen M.S., Cheng B.K., Cordi A.A., Biesterfeldt J.P., Hood W.F., Monahan J.B., J. Med. Chem. 34 (1991) 1283–1292.

[45] Hood W.F., Gray N.M., Dappen M.S., Watson G.B., Compton R.P., Cordi A.A., Lanthorn T.H., Monahan J.B., J. Pharmacol. Exp. Ther. 262 (1992) 654–660.

[46] Rowley M., Leeson P.D., Grimwood S., Foster A., Saywell K., Bioorg. Med. Chem. Lett. 2 (1992) 1627–1630.

[47] Rao T.S., Gray N.M., Dappen M.S., Cler J.A., Mick S.J., Emmett M.R. et al., Neuropharmacology 32 (1993) 139–147.

[48] Noe C.R., Knollmuller M., Schodl C., Berger M.L., Sci. Pharm. 64 (1996) 577–590.

[49] Glaxo spa. (1993) Patent 2266091.

[50] Birch P.J., Grossman C.J., Hayes A.G., Eur. J. Pharmacol. 163 (1989) 127–131.

[51] Leeson P.D., Iversen L.L., J. Med. Chem. 37 (1994) 4053–4067.

[52] Kulagowski J.J., Expert Opin. Therap. Pat. 6 (1996) 1069–1079.

[53] Zeneca Limited (1995) Patent WO9511244.

[54] Jimonet P., Audiau F., Aloup J.C., Barreau M., Blanchard J.C., Bohme A. et al., Bioorg. Med. Chem. Lett. 4 (1994) 2735–2740.

[55] Cai S.X., Zhou Z.L., Huang J.C., Whittemore E.R., Egbuwoku Z.O., Lu Y., J. Med. Chem. 39 (1996) 3248–3255.

[56] Keana J.F.W., Kher S.M., Cai S.X., Dinsmore C.M., Glenn A.G., Guastella J., J. Med. Chem. 38 (1995) 4367–4379.

[57] Bristow L.J., Flatman K.L., Hutson P.H., Kulagowski J.J., Leeson P.D., Young L., Tricklebank M.D., J. Pharmacol. Exp. Ther. 277 (1996) 578–585.

[58] Siegel B.W., Sreekrishna K., Baron B.M., Eur. J. Pharmacol. 312 (1996) 357–365.

[59] Merrell Pharmaceuticals (1996) Patent US5519048.

[60] Hoechst Marion Roussel (1996) Patent WO9613501.

[61] Rhone-Poulenc Rorer (1996) Patent WO9602536.

[62] Merck GmbH (1996) Patent EP717044.

[63] Jackson P.F., Davenport T.W., Garcia L., McKinney J.A., Melville M.G., Harris G.G. et al., Bioorg. Med. Chem. Lett. 5 (1995) 3097–3100.

[64] Boireau A., Malgouris C., Burgevin M.C., Eur. J. Pharmacol. 300 (1996) 237–246.

[65] Moore L.W., Leeson P.D., Carling R.W., Trickebank M.D., Singh L., Bioorg. Med. Chem. Lett. 3 (1993) 61–64.

[66] Nichols A.C., Yielding K.L., Mol. Chem. Neuropharm. 19 (1993) 269–282.

[67] Hokari M., Wu H.Q., Schwarcz R., Smith Q.R., Neuroreport 8 (1996) 15–18.

[68] Wood P.L., Hawkinson J.E., Expert Opin. Invest. Drugs. 6 (1997) 389–397.

[69] Lees K.R., Neurology 49 (1997) S66–S69

[70] Dyker A.G., Lees K.R., Stroke 30 (1999) 986–992.

[71] Connick J.H., Heywood G.C., Sills G.J., Thompson G.G., Brodie M.J., Stone T.W., Gen. Pharmacol. 23 (1992) 235–239.

[72] Russi P., Alesiani M., Lombardi G., Davolio P., Pellicciari R., Moroni F., J. Neurochem. 59 (1992) 2076–2080.

[73] Moroni F., Russi P., Gallo-Mezo M.A., Moneti G., Pellicciari R.J., Neurochem. 57 (1991) 1630–1635.

[74] Pellicciari R., Natalini B., Costantino G., Mahmoud M.R., Mattoli L., Sadeghpour B.M., J. Med. Chem. 37 (1994) 647–655.

[75] Varasi M., Della Torre A., Heidempergher F., Pevarello P., Speciale C., Guidetti P., Wells D.R., Schwarcz R., Eur. J. Med. Chem. 31 (1996) 11–21.

[76] Harris C.A., Miranda A.F., Tanguay J.J., Boegman R.J., Beninger R.J., Jhamandas K., Br. J. Pharmacol. 124 (1998) 391–399.

[77] Natalini B., Mattoli L., Pellicciari R., Carpenedo R., Chiarugi A., Moroni F., Bioorg. Med. Chem. Lett. 5 (1995) 1451–1454.

[78] Chiarugi A., Carpenedo R., Molina M.T., Mattoli L., Pellicciari R., Moroni F., J. Neurochem. 65 (1995) 1176–1183.

[79] Chiarugi A., Carpenedo R., Moroni F.J., Neurochem. 67 (1996) 692–698.

[80] Speciale C., Wu H.Q., Cini M., Marconi M., Varasi M., Schwarcz R., Eur. J. Pharmacol. 315 (1996) 263–267.

[81] Rover S., Cesura A.M., Hugenin P., Kettler R., Szente A., J. Med. Chem. 40 (1997) 4378–4385.

[82] Walsh J.L., Todd W.P., Carpenter B.K., Schwarcz R., Biochem. Pharmacol. 42 (1991) 985–990.

[83] Heyes M.P., Hutto B., Markey S.P., Neurochem. Int. 13 (1988) 405–408.

[84] Walsh J.L., Wu H.Q., Ungerstedt U., Schwarcz R., Brain Res. Bull. 33 (1994) 513–516.

[85] Naritsin D.B., Saito K., Markey S.P., Heyes M.P., J. Neurochem. 65 (1995) 2217–2226.

[86] Kulagowski B.D., Leeson P.D., Expert Opin. Therap. Pat. 5 (1995) 1061–1075.

[87] Warner D.S., Martin H., Ludwig P., McAllister A., Keana J.F.W., Weber E., J. Cereb. Blood Flow Metab. 15 (1995) 188–196.

[88] Priestley T., Laughton P., Macaulay A.J., Hill R.G., Kemp J.A., Neuropharmacology 35 (1996) 1573–1581.

[89] Ilyin V.I., Whittemore E.R., Tran M., Shen K.Z., Cai S.X., Kher S.M. et al., Eur. J. Pharmacol. 310 (1996) 107–114.

[90] Kretschmer B.D., Kratzer U., Breithecker K., Koch M., Eur. J. Pharmacol. 331 (1997) 109–116.

[91] Wood P.L., Hawkinson J.E., Expert Opin. Invest. Drugs 6 (1997) 389–397.

[92] Hawkinson J.E., Huber K.R., Sahota P.S., Hsu H.H., Weber E., Whitehouse M.J., Brain Res. 744 (1997) 227–234.

[93] Lipton S.A., Annu. Rev. Pharmacol. Toxicol. 38 (1998) 159–177.

[94] Wood E.R., Bussey T.J., Phillips A.G., Neurosci. Lett. 145 (1992) 10–14.

[95] Takano K., Tatlisumak M.T., Formato J.E., Carano R.A.D., Bergmann A.G., Pullan L.M., Stroke 28 (1997) 1255–1263.

[96] Heyes M.P., Rubinow D., Lane C., Markey S.P., Ann. Neurol. 26 (1989) 275–277.

[97] Heyes M.P., Mefford I.N., Quearry B.J., Dedhia M., Lackner A., Ann. Neurol. 27 (1990) 666–675.

[98] Ishimaru M., Kurumaji A., Ross C.A., Pearlson G.D., Biol. Psychiatry 32 (1992) 379–380.

[99] Ishimaru M., Kurumaji A., Toru M., Life Sci. 55 (1994) 1683–1699.

[100] Ishimaru M., Kurumaji A., Toru M., Ross C.A., Pearlson G.D., Trends Neurosci. 19 (1996) 416–417.

[101] Tamminga C.A., Crit. Rev. Neurobiol. 12 (1998) 21–36.

[102] Costa J., Khaled E., Sramek J., Bunney W.E., Potkin S., Clin. Psychopharmacol. 10 (1990) 71–72.

[103] Hutson P.H., Bristow L.J., Thorn L., Tricklebank M.D., Br. J. Pharmacol. 103 (1991) 2037–2044.