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Neurotoxicity of Tryptophan Metabolites[a]

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INTRODUCTION

The excitotoxins, a group of molecules that are structurally related to glutamic or aspartic acid, have made an important contribution to the field of neurobiology.[1-3] Under appropriate conditions these compounds are capable of producing neuronal degeneration while sparing axons of passage. This property has been put to use in neuroanatomical and neurochemical studies and in producing animal models of neurodegenerative disease. The resemblance between experimental lesions and human neuropathology seen in certain neurodegenerative disorders has led to the hypothesis that endogenous neurotoxic compounds with a structure similar to that of the excitotoxins exist and are responsible for the development of neural degeneration *in vivo*.[1-3] One of these excitotoxins is the tryptophan metabolite quinolinic acid.

Quinolinic acid (pyridine-2, 3-dicarboxylic acid), a metabolite of tryptophan, is an intermediate in the kynurenine pathway (FIG. 1). It is a rigid analogue of *N*-methyl-D-aspartate (NMDA) and exerts its effect on neurons by activating NMDA receptors.[4,5] In the mammalian brain the concentration of quinolinic acid is approximately one micromolar,[6] and its presence has also been demonstrated in human cerebrospinal fluid.[7] The enzyme responsible for the synthesis of quinolinic acid, 3-hydroxyanthranilic acid oxygenase, shows a regional distribution in rat brain,[8,9] while the enzyme that converts quinolinic acid to nicotinic acid mononucleotide has also been detected in rat and human brain.[10] The activity of both enzymes in the brain is, however, two to three orders of magnitude lower than that in liver or kidney. In addition these enzymes are preferentially localized in glia rather than neurons. On the basis of kinetic experiments, the brain has a greater ability to synthesize quinolinic acid than to degrade it, suggesting that under normal conditions this pathway is rigidly controlled. The kynurenine pathway serves as the precursor for quinolinic acid. However, kynurenine may also be converted to a number of other intermediates (FIG. 1) some of which have been reported to antagonize both the neuroexcitant and neurotoxic properties of quinolinic acid.[11-13]

Microinjections of quinolinic acid into the central nervous system have been found to have behavioral effects. Thus, Lapin *et al.*[14] have shown that injections of this

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compound into the cerebral ventricles of rats produced generalized tonic-clonic seizures. In addition rats receiving bilateral intrastriatal injections of quinolinic acid were spontaneously hyperactive, adipsic, and aphagic[15] and failed to show the usual cataleptic response to dopamine receptor antagonists.[16] Barone *et al.*[17] reported that rats with unilateral quinolinate-induced lesions of the striatum turned ipsilateral to the side of the lesion, following the injection of dopamine agonists. We have found that rats receiving unilateral injections of quinolinic acid into the nucleus basalis magnocellularis (nbM) were unimpaired in their ability to eat and did not show a change in locomotor activity measured in photocell cages[18]; however, animals with these lesions showed memory impairments in T-maze alternation[19] and radial maze tasks.[18,20]

In the studies described below using neurochemical, morophological, and behav-

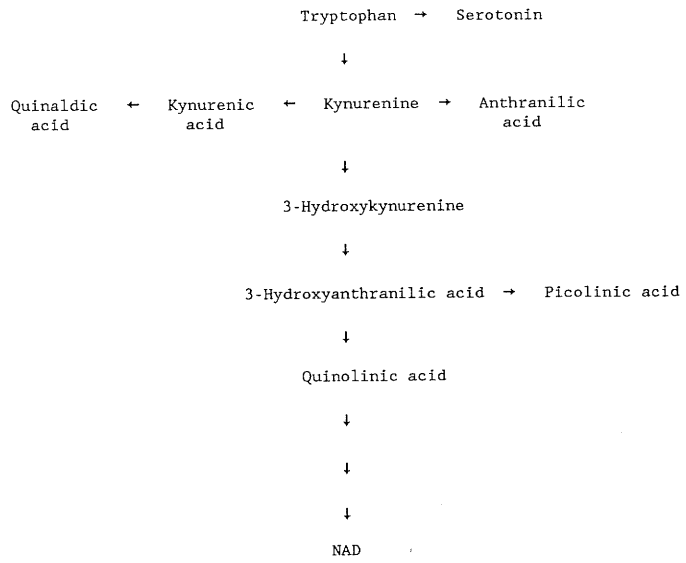

FIGURE 1. Tryptophan metabolic pathway indicating some of the major kynurenic acid metabolites.

ioral criteria, we have evaluated the neurotoxicity of quinolinic acid in the nucleus basalis magnocellularis and the striatum. The ability of kynurenine metabolites to act as NMDA agonists or antagonists was also studied.

MATERIALS AND METHODS

Surgery

Experiments were performed on male Sprague–Dawley rats weighing between 250 and 300 g. Under halothane anesthesia a single unilateral injection of the compound under study was made into the nbM (coordinates from bregma 0.8 mm posterior, 2.6 mm lateral to the midline, and 8.0 mm ventral to the surface of the skull) or striatum

(0.12 mm anterior, 3.2 mm lateral, and 4.0 mm ventral).[21] Solutions were infused over a period of 2.5 min and the cannula was left in place for three additional minutes to allow for diffusion.[12,22] Sham-injected rats received 0.9% saline alone.

Neurochemical Analysis

A coronal slab of the whole brain was prepared using two parallel razor blades held 6.00 mm apart in a Plexiglass holder with the caudal razor blade across the pituitary stalk. A small piece of each cortex was removed for the determination of choline acetyltransferase (ChAT) activity.[22,23]

A modification of the procedure described by Lehmann and Scatton[24] was used to study the release of [^{3}H]acetylcholine ([^{3}H]ACh) from slices of the frontoparietal cortex. Dispersed brain slices (0.3 mm thick) were incubated in a physiological solution containing [^{3}H]choline chloride before being transferred to a superfusion chamber where they were superfused with Krebs–Henselite buffer. The release of radioactivity into the superfusate following inclusion of 35 m*M* K^+ was used as an index of the evoked release of acetylcholine from the tissue.[22,24]

Histology

Animals used for morphological analysis were pretreated with diisopropylfluorophosphate (DFP) six hours before sacrifice in order to facilitate the visualization of acetylcholinesterase (AChE), producing neurons in the nbM and striatum.[25] Under anesthesia rats were perfused transcardially with 0.9% saline followed by 4% paraformaldehyde in 5 m*M* sodium phosphate buffer pH 7.4. Following post-fixation in 30% sucrose, 40-μm sections were cut on a freezing microtome and subsequently stained for AChE and nicotinamide adenine dinucleotide phosphate-diaphorase (NADPH-d) activity.[26,27]

Behavioral Testing

Rats were trained on an eight-arm radial maze until choice accuracy stabilized over four days to an average criterion of greater than 87% correct. Animals were then randomly assigned to sham or drug groups. Following at least one week of post-surgical recovery, animals were tested on the radial maze for 32 consecutive days using the same preoperative testing procedure.

RESULTS

The neurochemical data from experiments in which saline or quinolinic acid were infused into the nbM is shown in FIGURE 2. As has been demonstrated previously, there is a dose-dependent decrease in cortical ChAT activity following a unilateral injection of quinolinic acid into the nbM.[12,28] A maximal decrease of 59.0 ± 6.0% was observed

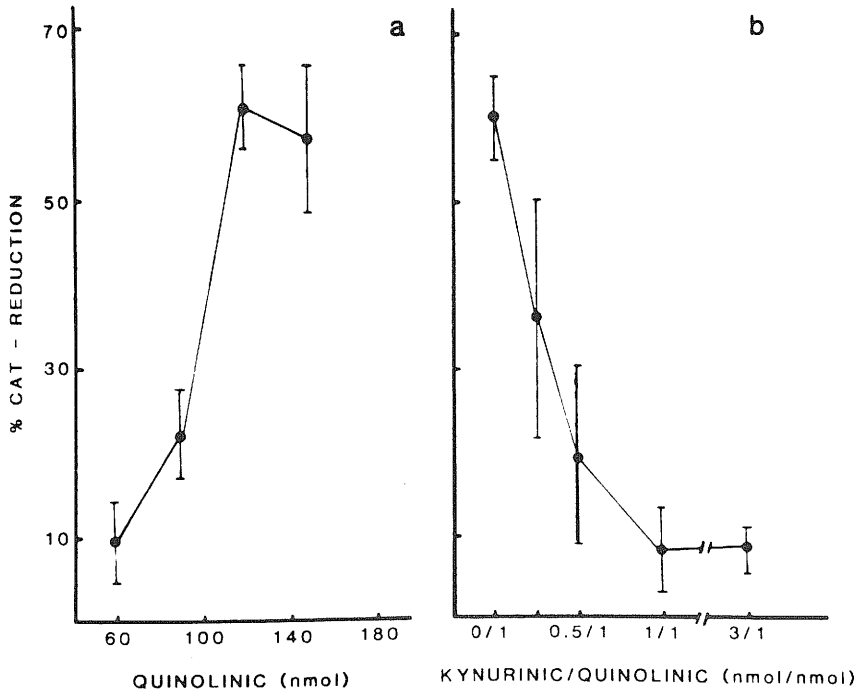

FIGURE 2. The response of cortical ChAT activity following unilateral 1-μl infusions of different doses of quinolinic acid into the nbM (**a**). Coinjections of different molar ratios of kynurenic plus quinolinic acid, with the latter kept constant at 120 nmoles, into the nbM on cortical ChAT activity (**b**).

at a dose of approximately 120 nmole quinolinic acid per μl injected with a steep dose–response curve between 60 and 120 nmoles.

A dose of quinolinic acid that gave a reduction in cortical ChAT activity of 55% was injected into the nbM in combination with different molar ratios of kynurenic acid or picolinic acid two kynurenine metabolites (FIG. 1). A 1:1 ratio of kynurenic acid to quinolinic acid afforded full protection of cholinergic neurons in the nbM to the neurotoxicity produced by quinolinic acid alone (FIG. 2). Picolinic acid, while without significant neurotoxic effects on its own, also protects against the neurotoxicity of quinolinic acid when co-injected with the latter (TABLE 1). We have found that while picolinic acid protects against quinolinic acid toxicity, it does not appear to be as potent as kynurenic acid in antagonizing the neurotoxicity associated with quinolinic acid.

The K^+-evoked release of [^{3}H]ACh from cortical slices ipsilateral to a quinolinic acid lesion in the nbM showed a 41% reduction when compared to the contralateral control cortex. (TABLE 1 and FIG. 3). However, in animals that received a coinjection of quinolinic plus kynureninic acid in a 1:3 molar ratio, there was no significant reduction in cortical [^{3}H]ACh release (FIG. 3). Similar results were obtained following a coinjection of quinolinic acid plus picolinic acid at a 1:3 molar ratio.

The DFP-pharmacohistochemical procedure allows a clear visualization of the large AChE-positive neurons in the nbM (FIG. 4). Injections of quinolinic acid alone produced a dramatic reduction in the number of AChE-positive neurons (FIG. 4). In animals in which kynurenic acid was coinjected with quinolinic acid into the nbM, no significant decrease in the number of AChE-positive neurons was observed, indicating that kynurenic acid antagonizes quinolinic acid's neurotoxicity.

Intrastriatal injections of kynurenic acid or saline did not significantly reduce the number of AChE or NADPH-d-containing neurons (FIG. 5). In contrast, injections of

TABLE 1. The Effect of Lesions Placed in the nbM on Cortical ChAT and [^{3}H]ACh Release[a]

Treatment	ChAT (nmoles ACh formed/mg protein/hr)	[^{3}H]ACh Release (% release over base)
Saline (Sham)		
Uninjected	58.2 ± 2.1	19.5 ± 1.4
Injected	51.1 ± 2.4	17.8 ± 2.0
% Change	12.3[b]	10.0
Quinolinic acid (120 nmoles)		
Uninjected	49.4 ± 6.2	17.9 ± 2.1
Injected	20.2 ± 4.7	10.6 ± 2.1
% Change	60.1[c]	40.7[c]
Kynurenic acid (360 nmoles)		
Uninjected	41.7 ± 1.3	
Injected	37.1 ± 5.2	
% Change	11.0 ± 4.7	
Quinolinic plus kynurenic (120:360 nmoles)		
Uninjected	47.8 ± 3.5	19.9 ± 4.4
Injected	46.5 ± 5.2	17.8 ± 2.1
% Change	2.6	10.5
Picolinic acid (360 nmoles)		
Uninjected	45.4 ± 3.2	
Injected	39.3 ± 4.1	
% Change	13.5 ± 3.2	
Quinolinic plus picolinic acid (120 + 360 nmoles)		
Uninjected	50.0 ± 2.5	
Injected	45.3 ± 3.9	
% Change	9.4 ± 4.5	

[a]Unilateral 1-μl injections of either 0.9% saline, 120 nmoles quinolinic acid, or 120 nmoles quinolinic plus 360 nmoles kynurenic acid or picolinic acid were made into the right nbM of adult rats. Frontoparietal cortical cholinergic markers were measured seven days later in both the injected and contralateral side. Values are mean ± SEM from four to nine animals.

[b]$p < 0.005$.

[c]$p < 0.0005$.

quinolinic acid into the same area resulted in a marked loss of NADPH-d neurons in the injection area (FIG. 5). Coinjections of quinolinic plus kynurenic acid again afforded full protection of the NADPH-d neurons against the neurotoxicity associated with a single intrastriatal injection of quinolinic acid alone.

Intrastriatal injections of quinolinic acid produced a large reduction in the number of striatal AChE-positive neurons (FIG. 5). Coinjections of quinolinic plus kynurenic acid into the striatum did not result in a reduction of AChE-staining neurons.

Animals with quinolinic acid-induced lesions to the nbM showed a greater deficit in the working memory component of the radial maze task than the reference memory

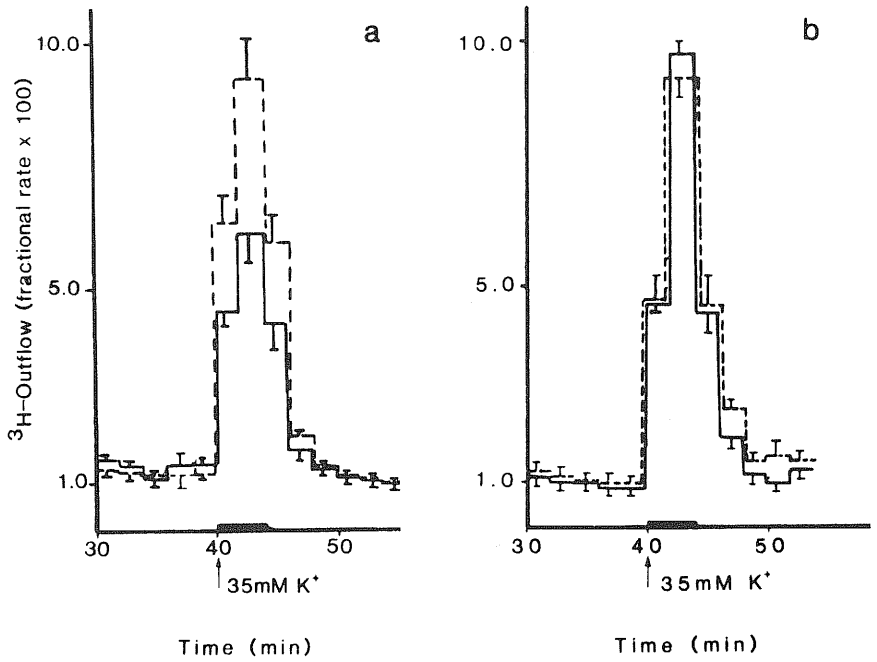

FIGURE 3. K^+-induced release of [^{3}H]acetylcholine from cortical slices obtained from animals in which the nbM was injected seven days previously with saline (----, **a** & **b**) quinolinic acid (___, **a**) or quinolinic plus kynurenic acid in a 1:3 molar ratio (___, **b**).

component.[18] This supports the concept that cholinergic neurons projecting from the nbM to the cortex play a role in memory.

Some endogenous tryptophan metabolites provide protection against the neurotoxic effects of quinolinic acid as assessed by neurochemical techniques; it was therefore of interest to determine if these substances can also protect against behavioral deficits. In one study, Lapin *et al.*[14] showed that coinjection of kynurenic acid with quinolinic acid into the cerebral ventricles of rats dose-dependently decreased the frequency of seizures compared to quinolinic acid alone. In agreement with these findings, we recently reported that the mnemonic deficits seen after quinolinic acid lesions of the nbM were completely prevented in rats which received a coinjection of

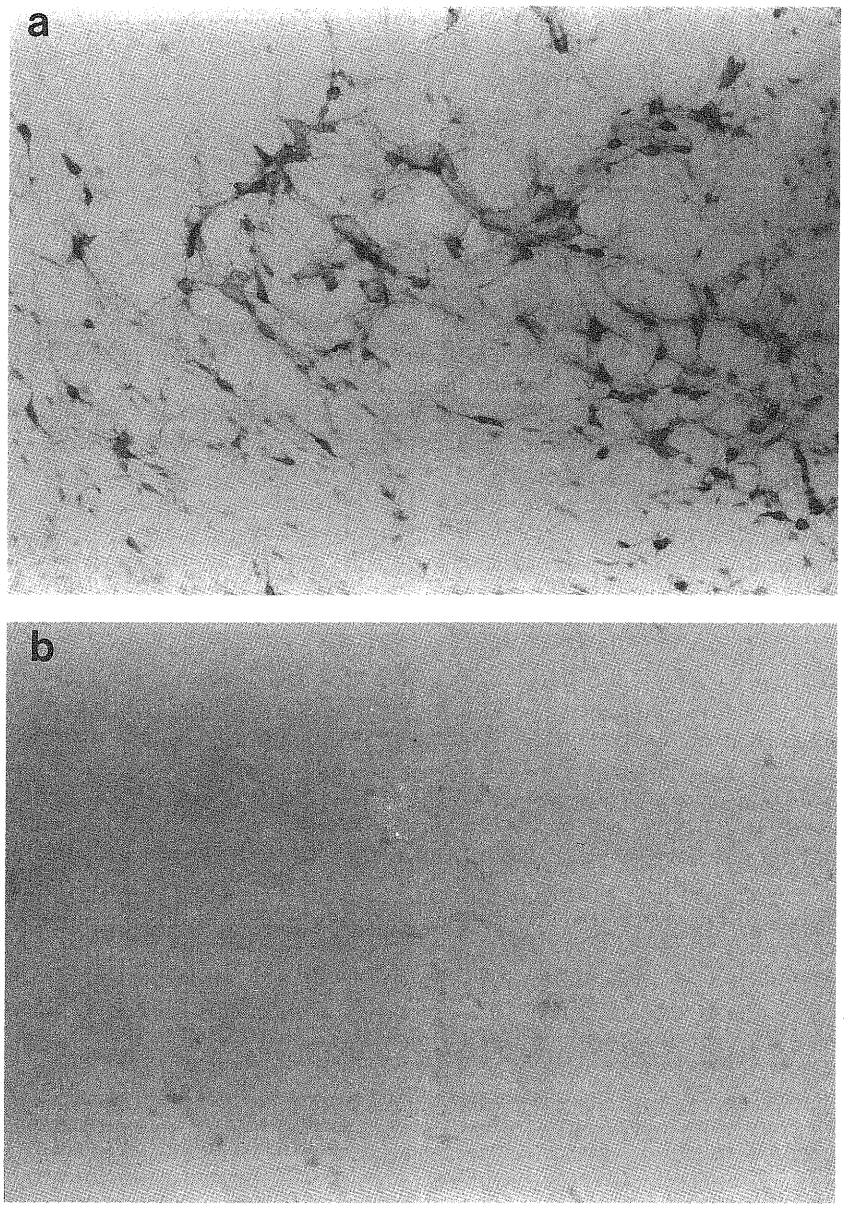

FIGURE 4. Photomicrographs indicating the response of neurons in the nbM containing AChE, 24 hours after a 1-μl infusion of saline (**a**) or quinolinic acid (**b**, 120 nmoles) into the nbM. Original magnification $\times 128$; reduced by 30%.

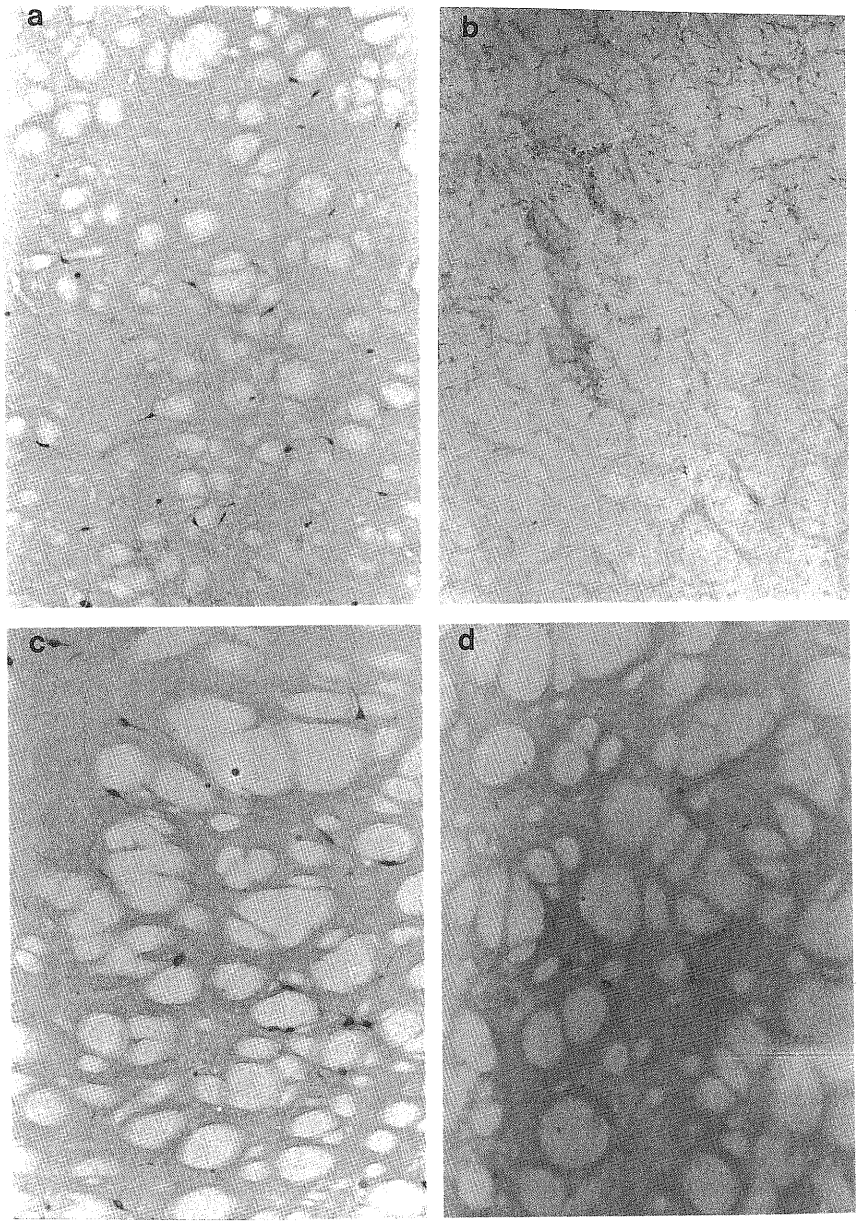

FIGURE 5. Photomicrographs illustrating striatal neurons containing NADPH-d (**a,b**) or AChE (**c,d**) activity following a 1-μl infusion of saline (**a,c**) or quinolinic acid (**b,d** 120 nmoles). Original magnification $\times 128$; reduced by 50%.

the excitotoxin plus kynurenic acid at a 1:3 molar ratio.[18,20] These results confirm that kynurenic acid protects against both the neurochemical and behavioral deficits produced by quinolinic acid.

We have recently assessed the possible protective effects of another tryptophan metabolite, picolinic acid, in rats trained in the four-out-of-eight arm radial maze experiment. This was of particular interest as picolinic acid has been shown to afford only partial protection against the neurotoxic effects of quinolinic acid at equimolar concentrations.[39] Frequently, large neurochemical depletions are required before behavioral deficits are seen. Thus, it was possible that picolinic acid, although providing partial protection against the neurotoxic effects of quinolinate,[39] might provide greater protection against the mnemonic deficits seen after quinolinic acid alone. Rats were trained in the radial maze and then underwent surgery, receiving picolinic acid (360 nmol in 0.5 μl), quinolinic acid (120 nmol in 0.5 μl), or quinolinic acid (120 nmol) plus picolinic acid (360 nmol) injections into the nbM.

TABLE 2. The Effect of Lesions Placed in the nbM on Cortical ChAT (Mean ± SEM) and Behavioral Response (Total Correct Choices ± SEM)[a]

	Picolinic Acid ($n = 6$)	Quinolinic Acid ($n = 13$)	Co-injected ($n = 13$)
ChAT (nmol acetycholine formed/mg protein/hr)			
Injected side	39.5 ± 5.7	17.2 ± 2.3	19.9 ± 5.5
Uninjected side	40.5 ± 5.2	33.0 ± 3.4	26.6 ± 1.4
% Decrease	2.5 ± 8.3	48.3 ± 4.2[b]	24.8 ± 4.6[b]
Total Correct Choices (maximum 16)			
4 days pre-surgery	14.5 ± 0.2	14.2 ± 0.1	14.4 ± 0.2
Days 1–4 post surgery	12.7 ± 0.4	9.4 ± 0.5	10.9 ± 0.5
Days 5–8 post surgery	12.8 ± 0.8	10.4 ± 0.5	11.8 ± 0.6
Days 9–12 post surgery	13.8 ± 0.6	11.5 ± 0.7	12.0 ± 0.7
Days 13–16 post surgery	13.0 ± 0.8	12.9 ± 0.5	12.5 ± 0.4

[a]Unilateral injections of either picolinic acid (360 nmoles), quinolinic acid (120 nmoles), or both in a 3:1 molar ratio were made into the nbM of adult rats. After a recovery period of one week, the behavioral response was tested on the eight-arm radial maze for 16 days after surgery for three groups.

[b]Difference from picolinic acid, ANOVA, $p < 0.005$.

When retested, the picolinic acid alone group showed no significant change in choice accuracy in the radial maze (TABLE 2). Both the quinolinic acid group and the coinjected group showed a significant lesion effect, choice accuracy decreasing on the first post-lesion test block. However, the coinjected group was midway between the other two groups. Both groups improved to the level of the picolinic acid alone group by the end of the 16 days of post-lesion testing. Thus, coinjection of picolinic acid with quinolinic acid provided partial neurochemical and partial behavioral protection. In one other behavioral paper, Lapin *et al.*[14] reported that picolinic acid coinjected with quinolinic acid into the cerebral ventricles of rats failed to protect against the seizure-inducing effects of quinolinate.

While the neurochemical data from the picolinic plus quinolinic acid group indicated that a significant degree of neuronal protection occurred when compared to

ChAT data obtained with quinolinic acid alone, the picolinic plus quinolinic acid group was somewhat variable (compare TABLES 1 and 2). Possible reasons could be that a molar ratio 3:1 for picolinic plus quinolinic acid was just sufficient to antagonize quinolinic acid's toxicity,[39] while with kynurenic acid a molar ratio of one (kynurenic: quinolinic) afforded the same degree of neurochemical protection.[39] Secondly, the ChAT values reported in TABLE 1 were obtained from animals seven days after the lesions, while those in TABLE 2 were from behavioral experiments in which the animals were tested for eight weeks after the lesion before being sacrificed for neurochemical analysis.

DISCUSSION

Data from neurochemical and electrophysiological experiments indicate that one or more dicarboxylic amino acids may act as synaptic transmitters at amino acid receptors in the central nervous system. In the search for selective agonists and antagonists at these receptors, many structure–activity studies have been reported.[4,29–31] The activity of quinolinic acid and the pipiridine dicarboxylic acids at amino acid receptors has been shown to be greatly influenced by steric factors. Thus in the cortex *cis*-2,3-pipiridine dicarboxylic acid acts as an antagonist at excitatory amino acid receptor sites while *cis*-2,4-; 2,5-; or 2,6-dicarboxylic analogues do not.[4] In addition *cis*-2,3-pipiridine dicarboxylic acid also acts as a partial agonist by increasing the firing of cortical neurons. The appearance of neuronal degeneration following intracerebral injection of quinolinic acid or its structural analogues also supports the concept that the receptors activated by quinolinic acid have strict structural requirements for activation. From these studies it has been proposed that all toxic compounds are structurally related to NMDA and possess one positive and two negative changes under physiological conditions: the absence or blockade of one carboxyl group or substitution of the nitrogen atom, resulting in a loss of neurotoxicity.[31] Compounds with two adjacent carboxyl groups are neurotoxic while those without adjacent carboxyl groups on the six-membered ring are inactive. Antagonism of quinolinic acid's neurotoxicity by kynurenic and picolinic acids indicates that these compounds, while not meeting the structural requirements derived from agonists listed above, interact with the receptor in such a manner that quinolinic acid can no longer adequately bind to the receptor surface.

Using microiontophoretic techniques, Perkins and Stone[32] were the first to demonstrate that kynurenic acid antagonized the neuroexcitation produced by quinolinic acid. In the hippocampus kynurenic acid antagonizes both the seizures and neurodegeneration which result from a local injection of quinolinic acid, while in the striatum kynurenic acid protects against quinolinic acid-induced neuronal cell death and loss of striatal choline acetyltransferase activity. We have found that kynurenic acid will also offer complete protection against quinolinic acid-induced cell death in the nbM, resulting in retention of cortical cholinergic markers. That injections of kynurenic acid alone were without effect on cortical cholinergic markers indicates that kynurenic acid acts only as a neurotoxic antagonist and not as a partial agonist. This observation supports the electrophysiological data which shows that kynurenic acid does not alter the spontaneous activity of cortical neurons.[4] Similarly picolinic acid is not neurotoxic

when injected into the brain on its own but affords neurochemical protection against the neurotoxicity of quinolinic acid when coinjected with it.

Striatal neurons containing the enzyme NADPH-d also contain somatostatin and neuropeptide Y.[33] These neurons most likely belong to the category of medium-sized aspiny type I neurons, which represent only a small portion of the total striatal neuronal population.[34] Intrastriatal injections of quinolinic acid produced a loss of both NADPH-d- and AChE-positive neurons in the central injection core area. However, NADPH-d-positive neurons were always much less numerous than AChE neurons indicating that the former were more sensitive to the neurotoxic effect of excitatory amino acid agonists. The large cholinergic neurons located in the ventral pallidum which constitute the nbM also were destroyed by a local injection of quinolinic acid. Coinjections of quinolinic acid with kynurenic acid, which previously was found to afford neurochemical protection, resulted in complete morphological protection against the neurotoxicity associated with injections of quinolinic acid alone. In view of the protection afforded by kynurenic and picolinic acid against the neurotoxicity produced by quinolinic acid alone, neural damage *in vivo* by endogenous neurotoxins may be due to an imbalance between agents that destroy cells and those that protect them.

In recent years it has been discovered that the brains of persons dying of Alzheimer's disease showed a significant loss of cortical cholinergic innervation from the basal forebrain.[35,36] As Alzheimer's disease is characterized by a loss of memory,[37] it was of interest to assess the effects of cortically projecting cholinergic neurons of the nbM on memory. One technique involves the use of the eight-arm radial maze[38] with four arms baited. Working memory errors are said to occur on any particular trial when the rat re-enters an arm of the baited set from which food has already been eaten. Reference memory errors are said to occur when the rat enters an arm of the never-baited set. These two types of errors can be seen to reflect two types of memory. Working memory errors reflect an impairment in recalling recent information that is useful only transiently; it is impairments of this type of memory that are the first clinical sign of Alzheimer's disease.[37] Reference memory errors reflect an impairment in remembering previously learned information that should be well established; this type of memory is relatively intact in the early stages of Alzheimer's disease. Our results have shown that rats well-trained in the radial maze task and undergoing quinolinic acid lesions of the nbM are relatively more impaired on the working memory component of the task.[18] These results support the hypothesis that cholinergic systems in general and the nbM projection to the cortex in particular are involved in the control of memory.

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