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## Quinolate-induced cortical cholinergic damage: modulation by tryptophan metabolites

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Certain products of tryptophan metabolism interact with excitatory amino acid receptors to produce or protect against excitotoxicity. In this study, the action of several tryptophan metabolites, yielded by the kynurenine pathway, on cortical cholinergic toxicity was evaluated following focal injection into the rat nucleus basalis magnocellularis (nbM). Metabolites were injected singly or in combination with a fixed dose of quinolinic acid (QUIN). Cholinergic toxicity, or protection against it, was evaluated by measurements of choline acetyltransferase (ChAT) activity or potassium-evoked release of [<sup>3</sup>H]acetylcholine ([<sup>3</sup>H]ACh) from slices of the frontoparietal cortex, from the injected and uninjected sides. Focal injections of QUIN and 3-hydroxyanthranilic, but not kynurenic, picolinic, quinaldic or anthranilic acid, produced a dose-related decrease in ChAT activity, with QUIN being more potent. Kynurenic, picolinic, quinaldic and anthranilic acid, co-injected into the nbM with QUIN (120 nmol), produced dose-related antagonism of the neurotoxicity associated with QUIN alone. Picolinic acid also prevented the reduction in cortical [<sup>3</sup>H]ACh release induced by injections of QUIN. Kynurenic and picolinic acid produced a complete blockade of QUIN's effect on cortical ChAT activity, while quinaldic and anthranilic acid produced a partial blockade. The order of effectiveness against QUIN was kynurenic > picolinic > quinaldic or anthranilic acid. Evaluation of thin sections following Cresyl violet staining indicated that injections of QUIN produced neuronal loss and glial proliferation, while co-injections of picolinic or quinaldic acid with QUIN protected neurons. These findings show that several tryptophan metabolites have the potential to either produce or antagonize cholinergic toxicity. It is suggested that a balance between tryptophan metabolites producing neurotoxicity and those antagonizing this action may influence neuronal cell survival in disorders associated with neuronal degeneration.

### INTRODUCTION

Tryptophan metabolism via the kynurenine pathway yields certain metabolites which interact with excitatory amino acid receptors in the central nervous system (CNS). One such metabolite, quinolinic acid (QUIN), a pyridine dicarboxylic acid, excites neurons by activation of NMDA receptors, while kynurenic acid (KYA), another metabolite, blocks this excitation<sup>7,13</sup>. Focal injection of QUIN into brain regions innervated by glutamatergic neurons produces excitotoxic action similar to that induced by the exogenous excitotoxins kainic or ibotenic acid. Schwarcz et al.<sup>16</sup> showed that focal injections of QUIN in the rat produce axon sparing lesions in the striatum and other areas of the CNS. Foster et al.<sup>6</sup> reported that KYA blocks the excitotoxic action of QUIN on striatal cholinergic neurons and prevents seizures induced by this agent. We have previously shown that injections of QUIN into the nucleus basalis magnocellularis (nbM) destroy cholinergic cells projecting to the frontoparietal cortex and produce impairments in memory-related tasks<sup>4,18</sup>. It was also shown that co-injection of KYA protects against both biochemical and behavioural manifestations of QUIN-induced damage to the

nbM neurons<sup>1,18</sup>. These and other observations on the action of QUIN have stimulated interest in the possibility that endogenous excitotoxins such as QUIN may play a role in the neuronal degeneration that characterizes certain neurological disorders<sup>15</sup>.

Besides QUIN and KYA, the kynurenine pathway yields a number of other metabolites with structural features in common with QUIN or KYA. In a recent electrophysiological study, some of these tryptophan metabolites were found to inhibit neuronal firing in the hippocampus<sup>14</sup>. However, the extent to which various intermediates share the excitotoxic properties of QUIN or the anti-excitotoxic properties of KYA is largely unknown. The present study addresses this question by evaluating the effects of a single injection into the nbM of these agents, alone or in combination, on the survival of cholinergic neurons projecting to the cerebral cortex. The status of cortical cholinergic neurons was examined by measurement of choline acetyltransferase (ChAT) activity or potassium-evoked release of [<sup>3</sup>H]acetylcholine ([<sup>3</sup>H]ACh) in the frontoparietal cortex. This report demonstrates that tryptophan metabolites have differential effects on cholinergic neurotoxicity. A brief account of this work has recently been presented<sup>8</sup>.

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## MATERIALS AND METHODS

*Stereotaxic injections*

All experiments were performed on male Sprague-Dawley rats (275–350 g) anesthetized with a 2% halothane/98% oxygen mixture. The anesthetized animal was placed in a stereotaxic frame and given a single injection of saline or a tryptophan metabolite into the right nbM. In some experiments, the tryptophan metabolite was co-injected with a fixed dose of QUIN. All injections were delivered in a 0.5  $\mu$ l volume using the coordinates: 0.8 mm posterior to Bregma, 2.6 mm lateral and 8.0 mm ventral to the surface of the skull, with the incisor bar set at  $-3.3$  mm<sup>4</sup>. The injection was made over 2.5 min, and the cannula (Hamilton 0.35 o.d.) was left in place for 3.0 additional minutes to allow for diffusion. All agents tested (all obtained from Sigma Chemical Co., St. Louis, MO), except 3-hydroxyanthranilic acid, were suspended in 0.9% saline and solubilized by adjusting pH to 7.4 by addition of 0.1 N NaOH. In the case of 3-hydroxyanthranilic acid, the pH was adjusted to 9.0, and the corresponding control injection of saline was also adjusted to this pH. The animals were allowed to recover and killed 7 days post-injection for biochemical assessment of cholinergic markers and morphological evaluation of the lesion site.

*Biochemical assessment*

A slab of frontoparietal cortex was dissected from the injected and uninjected hemispheres and immediately homogenized for measurement of ChAT activity. The assay for ChAT was conducted in triplicate using the method of Fonnum<sup>5</sup>. Protein was measured by the method of Lowry et al.<sup>11</sup> with bovine serum albumin as standard. In some experiments, the release of [<sup>3</sup>H]ACh from slices of frontoparietal cortex, removed from the injected and uninjected sides, was also examined using the procedure described in preceding papers<sup>1,4</sup>.

*Histological assessment*

For histological evaluation of lesions, neurotoxin injections were made into a separate group of animals. The animals were anesthe-

tized with sodium pentobarbital (50  $\mu$ g/kg) (Sigma Chemical Co.) and perfused through the ascending aorta with 200 ml 0.9% NaCl, followed by 500 ml 4% paraformaldehyde in 50 mM sodium phosphate buffer (pH 7.4). The brain was dissected out and placed in the same fixative for 2–3 h at 6 °C. This was followed by immersion in 30% sucrose and 0.1 M sodium phosphate buffer (pH 7.4) for at least 12 h. Transverse sections were cut on a freezing microtome and stained with Cresyl violet.

*Statistical analysis*

Statistical analysis of data was performed using a Student's *t*-test for paired comparisons.

## RESULTS

*Single injection experiments*

A unilateral focal injection of QUIN (45–150 nmol) into the nbM resulted in a dose-related reduction in cortical ChAT activity 7 days post-administration (Fig. 1). A maximal decrease of  $52.6 \pm 9.7\%$  ( $n = 6$ ) was observed at a dose of 120 nmol. Similar injections of the tryptophan metabolite, 3-hydroxyanthranilic acid (240–600 nmol), also produced a significant dose-related reduction in cortical ChAT activity ( $P < 0.01$ ), but this metabolite was much less potent than QUIN. At a dose of QUIN which produced a maximal reduction in ChAT activity (120 nmol), 3-hydroxyanthranilic acid produced a  $10.1 \pm 2.5\%$  ( $n = 5$ ) reduction, an effect not significantly different from that produced by an infusion of saline alone ( $13.0 \pm 4.6\%$ ) ( $P > 0.05$ ). However, the maximal reduction in ChAT activity ( $45.0 \pm 4.9\%$ ) produced by

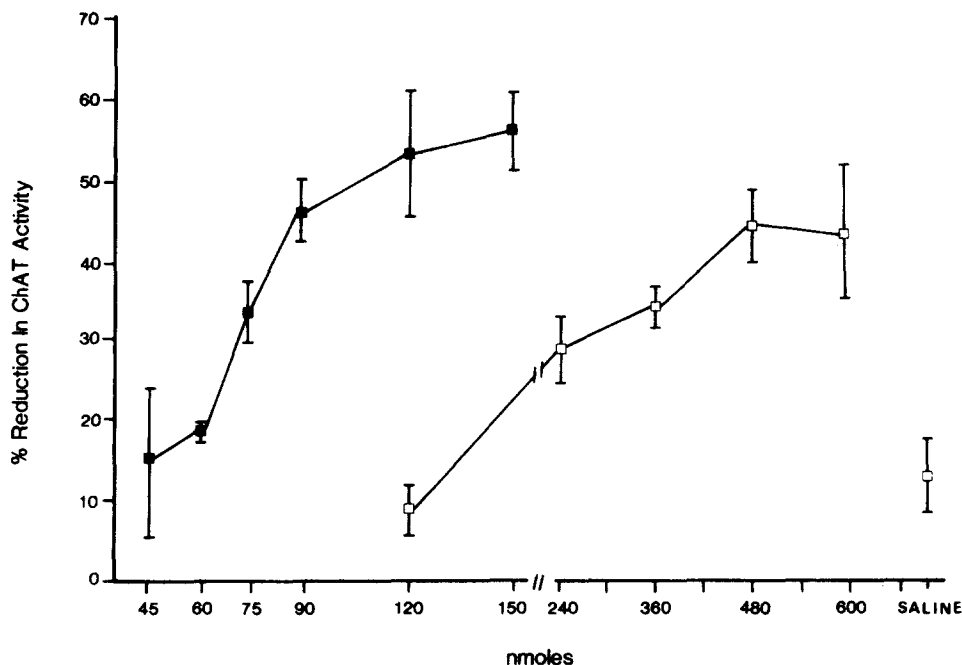


Fig. 1. Comparative effects of quinolinic acid (■) and 3-hydroxyanthranilic acid (□) on cortical ChAT activity after unilateral injection into the rat nbM. ChAT activity was measured 7 days post-injection in the ipsilateral and contralateral frontoparietal cortex. The percent difference between the two values is graphed as a function of drug concentration. The value on the far right corresponding to control ChAT activity ( $32.8 \pm 4.3$  nmol/mg protein/h) after a saline injection into the nbM. Each value is the mean  $\pm$  S.E.M. and is an average of 5–6 experiments.

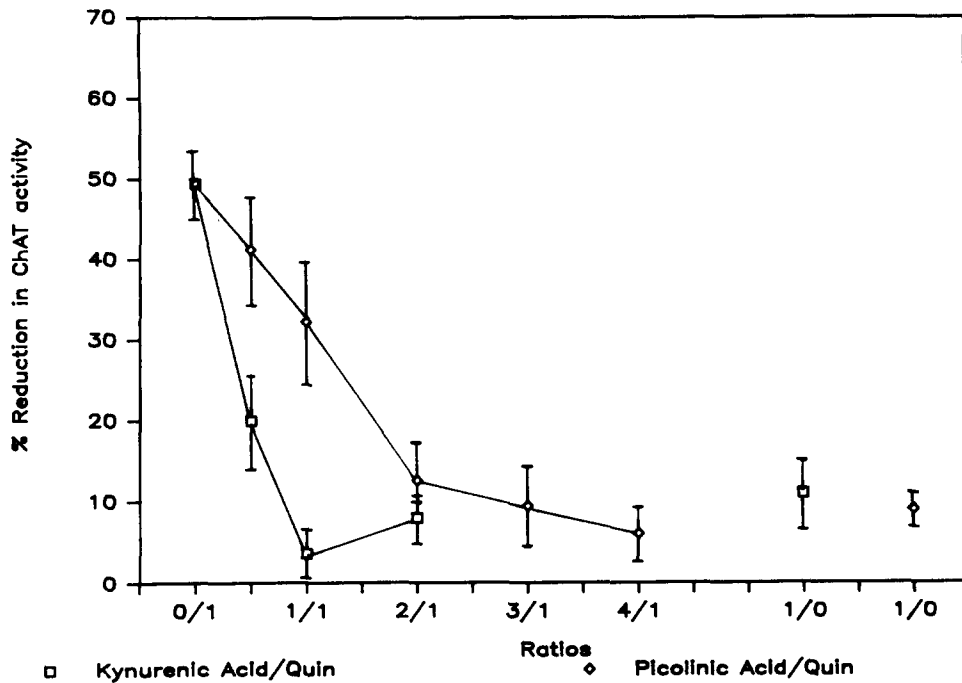


Fig. 2. Cortical ChAT activity after injection of different molar ratios of kynurenic acid plus quinolinic acid (□) and picolinic acid plus quinolinic acid (◇). The dose of quinolinic acid (Quin) was held constant at 120 nmol. Injections were made into the right nbM and cortical ChAT activity in the ipsilateral and contralateral cortex was measured 7 days later. The percent difference between the two values was graphed as a function of molar ratios. The values on the far right represent actions of kynurenic and picolinic acid in the absence of QUIN. Each value is the mean ± S.E.M. from 6 experiments.

480 nmol of 3-hydroxyanthranilic acid was comparable to that elicited by 120–150 nmol of QUIN. Injections of KYA, quinaldic, anthranilic and picolinic acid produced

reductions in ChAT activity that were not significantly different from those produced by a saline injection (data not shown). Thus, of the metabolites tested here, only

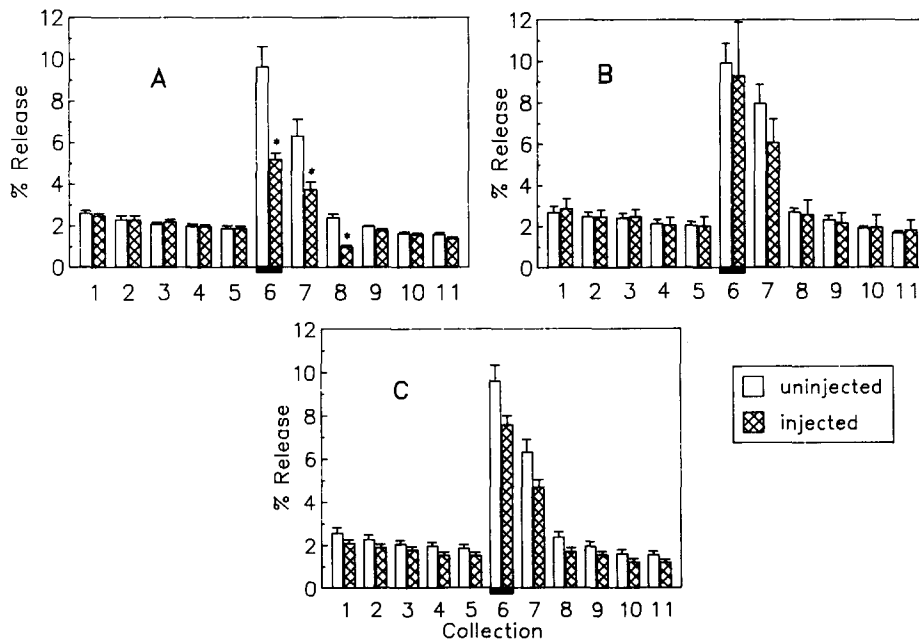


Fig. 3. Potassium-evoked release of [<sup>3</sup>H]ACh from slices of the frontoparietal cortex 7 days after injections of the following into the nbM graphed as mean ± S.E.M.: A, QUIN (120 nmol) (n = 5); B, picolinic acid (360 nmol) (n = 5); and C, picolinic plus quinolinic acid (molar ratio 1:3) (n = 6). The blank bars and hatched bars in each figure represents [<sup>3</sup>H]ACh release from the uninjected side and injected side, respectively. Each collection period represents a 5-min collection. Slices were exposed to a 5-min pulse of potassium (35 mM) at the fifth collection period. \*Significantly different (P < 0.001) from corresponding collection (blank bar).

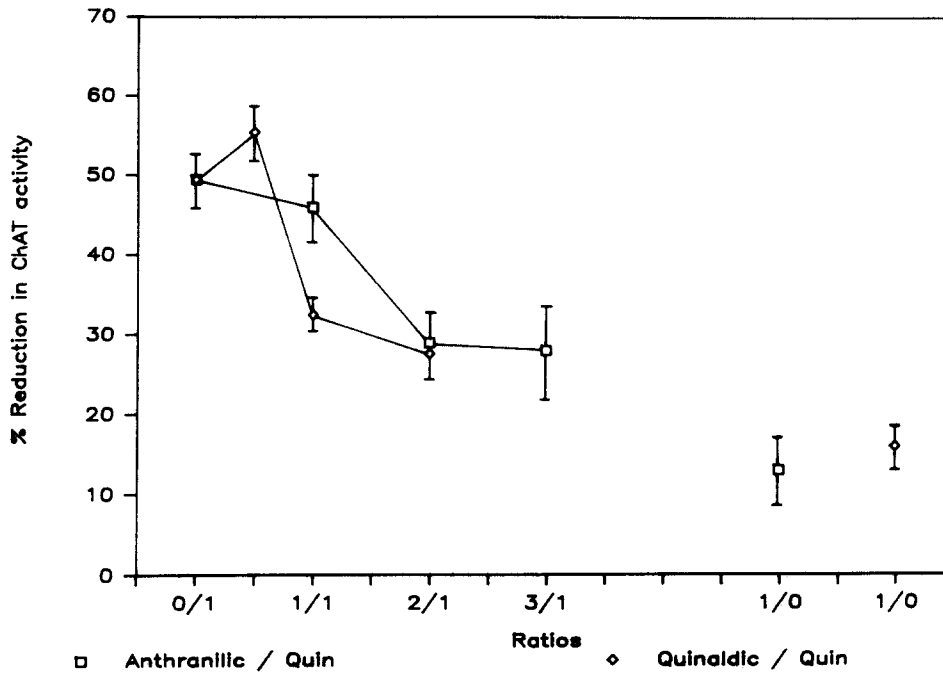


Fig. 4. Cortical ChAT activity after injection of different molar ratios of quinaldic plus quinolinic acid (□) and anthranilic plus quinolinic acid (◇). The dose of quinolinic acid (Quin) was held constant at 120 nmol. Injections were made into the right nbM and cortical ChAT activity in the ipsilateral and contralateral cortex was measured 7 days later. The percent difference between the two values was graphed as a function of molar ratios. The values on the far right represent actions of quinaldic and anthranilic acid in the absence of QUIN. Each value is an average of 6 experiments and represents the mean  $\pm$  S.E.M.

### 3-hydroxyanthranilic acid mimicked the action of QUIN.

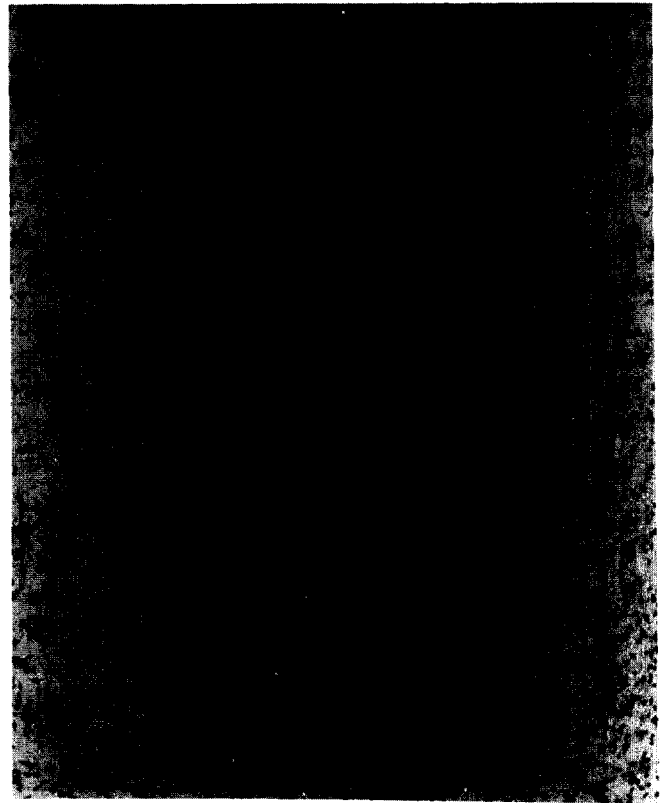
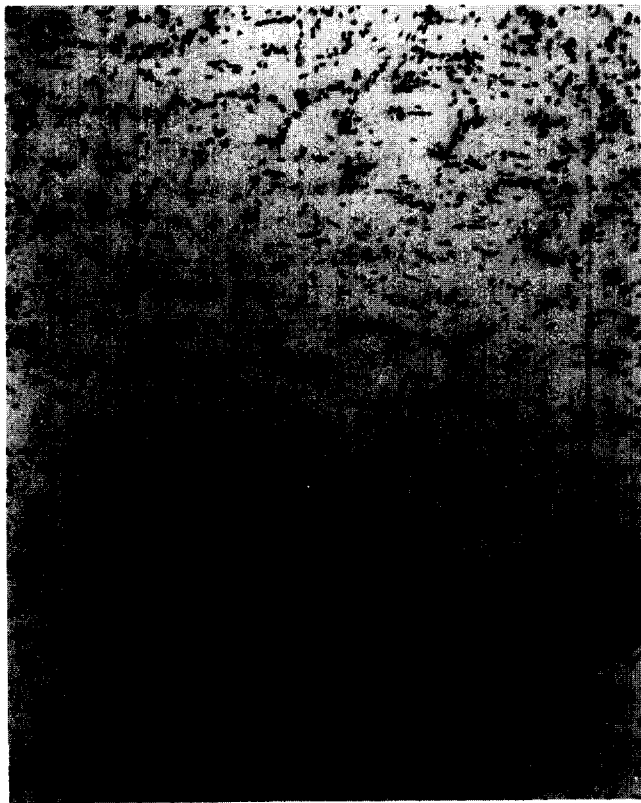
#### Co-injection experiments

**Neurochemistry.** Fig. 2 shows comparative effects of KYA and picolinic acid (a pyridine monocarboxylic acid) on QUIN-induced reduction in cortical ChAT activity. Injection of QUIN (120 nmol) alone produced a  $50.5 \pm 5.9\%$  ( $n = 6$ ) reduction in ChAT activity, while its combination with KYA (molar ratio 1:1) produced a  $3.6 \pm 3.0\%$  reduction in ChAT activity. The latter was not significantly different from that obtained with saline. Kynurenic acid therefore completely prevented the QUIN-induced cholinergic damage. Picolinic acid co-injected with QUIN in a molar ratio of 1:1 reduced ChAT activity by  $32.3 \pm 7.0\%$  ( $n = 6$ ). Thus, at this dose picolinic acid partially antagonized the QUIN effect ( $P < 0.05$ ). However, a higher molar ratio of picolinic-QUIN (4:1) reduced the enzyme activity by  $6.0 \pm 3.5\%$  ( $n = 6$ ). This value was not significantly different from that in saline controls ( $P > 0.05$ ). Thus, at a higher dose picolinic acid afforded full protection against QUIN-induced damage. Comparison of the dose-response relationships for KYA and picolinic acid showed that, while both agents afforded a complete protection against

the neurotoxic effect of QUIN, picolinic acid was clearly less potent than KYA.

Previous work has shown that the protective effect of KYA against QUIN is also reflected in another marker of presynaptic cholinergic function — the potassium-induced release of cortical [ $^3\text{H}$ ]ACh. The reduction in potassium-evoked release of cortical [ $^3\text{H}$ ]ACh following QUIN injection into the nbM<sup>4</sup> is not observed if QUIN is co-injected with KYA<sup>1</sup>. To evaluate if picolinic acid affords protection against the QUIN-induced deficit of presynaptic cholinergic function, the potassium-evoked release of cortical [ $^3\text{H}$ ]ACh was examined after injections of picolinic-QUIN or picolinic-saline combinations into the nbM. As shown in Fig. 3A, the potassium-evoked release of cortical [ $^3\text{H}$ ]ACh was significantly reduced (by approximately 50%) following an injection of QUIN alone ( $P < 0.001$ ). Picolinic acid injection into the nbM did not result in altered release of cortical [ $^3\text{H}$ ]ACh (Fig. 3B). The release of [ $^3\text{H}$ ]ACh was also not significantly affected by the picolinic-QUIN combination (molar ratio 3:1;  $n = 5$ ), although the injected side consistently showed a slightly lower transmitter release (Fig. 3C). Statistical comparison of values (peak release or area under the release curve (Fig. 3C) showed no significant

Fig. 5. Photomicrographs of Cresyl violet stained coronal sections of rat basal forebrain taken at the site of saline (A), QUIN (B), QUIN plus picolinic acid (C), or QUIN plus quinaldic acid (D) infusions into the nbM. Note the presence of large cells in A, C and D indicated by arrows.  $\times 512$ .



difference between the injected and uninjected sides ( $P > 0.05$ ). Thus, picolinic acid afforded significant protection against the presynaptic deficit induced by a single infusion of QUIN into the nbM.

Fig. 4 shows comparative effects of quinaldic and anthranilic acid on QUIN-induced decreases in cortical ChAT activity. A quinaldic-QUIN molar ratio of 1:1 produced a  $32.5 \pm 1.5\%$  ( $n = 6$ ) reduction in enzyme activity, a value significantly lower than that produced by QUIN alone ( $P < 0.01$ ). However, higher molar ratios (2:1) failed to produce a greater protective effect on ChAT activity, indicating that the neuroprotection by quinaldic acid had reached a maximal level. Anthranilic acid co-injected with QUIN produced effects that were comparable in magnitude to those produced by quinaldic acid. The effect of anthranilic acid also peaked at a molar ratio of 2:1 (6 experiments). Thus, in contrast with KYA and picolinic acid, metabolites which demonstrated a potential for complete antagonism of QUIN-induced decreases in cortical ChAT activity (Fig. 2), both quinaldic and anthranilic acid produced a partial blockade of QUIN neurotoxicity when administered under similar conditions.

**Histology.** Examination of thin sections cut through the nucleus basalis at the infusion site indicated that saline alone did not destroy neurons and that there was little glial proliferation (Fig. 5A). In contrast, injections of QUIN resulted in marked glial proliferation and no neurons were observed in the infusion area (Fig. 5B). Co-injection of either picolinic or quinaldic acid with QUIN protected neurons in the injection area and limited glial proliferation to the cannula tract (Fig. 5C,D).

## DISCUSSION

This study investigated the potential of several tryptophan metabolites of the kynurenine pathway to act as neurotoxins or to antagonize the neurotoxic action of QUIN. As was done in a previous study<sup>4</sup>, cholinergic neurotoxicity was assessed by observing changes in two biochemical markers of cortical cholinergic function: ChAT activity and potassium-evoked release of cortical [<sup>3</sup>H]ACh. Previous work has established that QUIN-induced reductions in these presynaptic cholinergic markers are associated with neuron loss in the nbM<sup>1,4</sup> and impairments in memory-related tasks<sup>18</sup>. The results of this study demonstrate that other metabolites of tryptophan have the potential to mimic or to antagonize the neurotoxic action of QUIN on the basocortical cholinergic neurons. This report also identifies significant potency differences among these metabolites.

Of the several metabolites tested here, 3-hydroxy-

anthranilic acid was the only agent that mimicked the neurotoxic action of QUIN. However, the potency of this metabolite was much lower than that of QUIN. In contrast, the maximal neurotoxic effect produced by 3-hydroxyanthranilic acid was comparable in size to that produced by QUIN. The excitatory and neurotoxic effects of QUIN, a pyridine dicarboxylic acid, are thought to involve activation of the NMDA receptor<sup>10,13,16,17</sup>. Since 3-hydroxyanthranilic is not a dicarboxylic acid, it is unlikely to directly interact with the NMDA receptor to produce neurotoxicity. However, it may do this by an indirect mechanism that involves its conversion to QUIN. In the kynurenine pathway, 3-hydroxyanthranilic acid is an immediate precursor of QUIN and it has been reported that, on incubation with brain homogenates, this metabolite can undergo conversion to QUIN<sup>7</sup>. Thus, a conversion of this metabolite to QUIN after a focal injection into the nbM could explain the observed neurotoxicity. However, 3-hydroxyanthranilic acid may also produce neurotoxicity by an NMDA receptor-independent mechanism. Indeed, Dykens et al.<sup>3</sup> have demonstrated that 3-hydroxyanthranilic acid is auto oxidized to several products (superoxide, H<sub>2</sub>O<sub>2</sub>, hydroxyl and anthranil radical) with a potential for toxicity. Regardless of the exact mechanism involved, it appears that a QUIN-like neurotoxic action is also produced by another tryptophan metabolite.

Several other metabolites, while inactive when injected alone, blocked QUIN-induced cholinergic toxicity in the co-injection experiments. These metabolites differed both in the potency and the extent of antagonism against QUIN. Both KYA and picolinic acid, in appropriate molar ratios, afforded complete antagonism of QUIN's neurotoxicity although KYA was 3-fold more potent. In contrast, both quinaldic and anthranilic acid produced a partial blockade of QUIN's effect. The actions of picolinic acid, a pyridine monocarboxylic acid, are of special interest since this agent is not recognized as an excitatory amino acid antagonist. In contrast, dipicolinic acid, 2,6-pyridine dicarboxylic acid, produces excitation<sup>9</sup> but not neurotoxicity<sup>2,9</sup>. The neuroprotective action of picolinic acid observed here was reflected in both markers of presynaptic cholinergic function: ChAT activity and potassium-evoked [<sup>3</sup>H]ACh release. Thus, in the neurotoxicity experiments, picolinic acid exhibited an activity profile resembling that of KYA. However, this observation is inconsistent with its profile in the *in vitro* studies. In the rat hippocampal slice experiments, picolinic acid poorly antagonized the synaptically evoked responses that are blocked by KYA<sup>14</sup>. In separate experiments, we have observed that, unlike KYA, picolinic acid does not effectively block the QUIN-induced release of striatal [<sup>3</sup>H]ACh, an effect that is

mediated by NMDA receptors (unpublished data). Thus, picolinic acid blocks QUIN-induced neurotoxicity without an apparent interaction with excitatory amino acid receptors. Antagonism of QUIN by picolinic acid may involve an unknown interaction with factors that modulate excitotoxicity and are operative *in vivo*<sup>15</sup>. Further studies are required to establish the specificity and the mechanism of picolinic acid's action.

Both quinaldic and anthranilic acid blocked QUIN-induced cholinergic toxicity; however, these agents produced only a partial blockade. The anti-excitotoxic action of quinaldic acid, a metabolite structurally related to KYA, most likely involves blockade of excitatory amino acid receptors, since in the hippocampal slice preparation it blocks synaptically evoked neuronal firing and is less potent than KYA<sup>14</sup>. However, in hippocampal slice experiments, quinaldic acid is more potent than picolinic acid<sup>14</sup>, while in the *in vivo* neurotoxicity experiments, the order is reversed. This suggests that the anti-QUIN action of picolinic acid seen *in vivo* may involve factors other than amino acid receptor blockade (see above). The mechanism by which anthranilic acid affords protection against QUIN is also not clear. Unlike 3-hydrox-

yanthranilic acid, this metabolite was not neurotoxic on its own. Thus, the presence of a hydroxyl group appears to contribute to the neurotoxicity associated with 3-hydroxyanthranilic acid.

The present findings on tryptophan metabolites have implications for the role of endogenous toxins in neuronal cell death. Since QUIN produces axon-sparing lesions that resemble those occurring in neurodegenerative disorders, this endogenous substance has been implicated in the etiology of such diseases<sup>15</sup>. However, measurement of the brain QUIN content in Alzheimer's disease has revealed no significant abnormalities<sup>12</sup>. In view of the findings that certain tryptophan metabolites block QUIN-induced damage, measurements of QUIN and its endogenous antagonists may prove more useful than levels of QUIN alone. A balance between endogenous excitotoxins (e.g. QUIN) and endogenous antagonists (such as KYA or picolinic acid) may influence neuron survival in certain neurodegenerative disorders.

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