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Kynurenic Acid Protects Against the Neurochemical and Behavioral Effects of Unilateral Quinolinic Acid Injections Into the Nucleus Basalis of Rats

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It has recently been demonstrated that kynurenic acid (KYN), an endogenous tryptophan metabolite, provides almost complete protection against the neurotoxic and mnemonic effects of another tryptophan metabolite quinolinic acid (QUIN) on the cell bodies of the nucleus basalis magnocellularis (nbm). The present study further investigated whether unilateral coinjections of KYN and QUIN into the rat nbm antagonized the effects of QUIN alone. Food-deprived rats were pretrained on an eight-arm radial maze, with four arms baited, until choice accuracy stabilized to ≥87% correct. Postoperatively, rats were tested on the radial maze for 32 consecutive days. Feeding behavior and locomotor activity were also measured to determine if nonassociative factors accounted for any observed behavioral deficits. QUIN lesions resulted in significantly more working and reference memory errors compared with sham-operated and coinjected animals, which did not differ significantly from each other. There were no reliable group differences in amount of food eaten or locomotor activity. The QUIN group had a reliable decrease in cortical choline acetyltransferase, with no significant changes for the sham and coinjected groups. Results confirm that KYN antagonizes the neurotoxic and mnemonic effects of QUIN alone and suggest that the memory deficits induced by nbm lesions cannot be solely attributed to changes in feeding or locomotor activity.

The nucleus basalis magnocellularis (nbm), located in the basal forebrain, provides a major source of cholinergic innervation to the cerebral cortex (Coyle, Price, & DeLong, 1983; Fibiger, 1982; Johnston, McKinney, & Coyle, 1981). In recent studies investigators have demonstrated that microinjections of the endogenous tryptophan metabolite quinolinic acid (QUIN) into the nbm selectively destroyed neuronal perikarya (Schwarcz, Whetsell, & Mangano, 1983) and significantly impaired cortical cholinergic function (El-Defrawy, Boegman, Jhamandas, & Beninger, 1986; El-Defrawy et al., 1985). Furthermore, coadministration of another tryptophan metabolite, kynurenic acid (KYN), with QUIN antagonized the neurotoxic effects of QUIN on basal forebrain cholinergic neurons (Boegman, El-Defrawy, Jhamandas, Beninger, & Ludwin, 1985). Such observations have led to the proposal that an imbalance between these two metabolites may be a pathogenic factor in neurodegenerative disorders involving the loss of nbm cells (Stone, 1984).

In a recent preliminary report, the biochemical and mnemonic effects of injecting QUIN alone, or in combination with KYN, into the nbm of the rat were examined. Beninger, Jhamandas, Boegman, and El-Defrawy (1986) demonstrated that unilateral QUIN lesions of the nbm significantly reduced levels of cortical choline acetyltransferase (CAT) and increased working memory errors (reentries into arms of the baited set) as well as reference memory errors (entries into never baited arms) in an eight-arm radial maze, with four arms baited. In contrast, coinjection of KYN with QUIN afforded complete neurochemical and behavioral protection against the toxic action of QUIN. Because the sample size was relatively small and radial maze behavior was assessed for only 4 days postoperatively, these results must be viewed as preliminary. Nevertheless, the results of the QUIN-alone group were in good agreement with the growing body of evidence that has demonstrated that following electrolytic, kainate, or ibotenate lesions of the rat nbm, there is a reduction in cortical CAT and impairment of memory as assessed by passive avoidance, T-maze, and radial maze tasks (e.g., Altman, Crosland, Jenden, & Berman, 1985; Bartus, Pontecorvo, Flicker, Dean, & Figueiredo, 1986; Beninger, Jhamandas, Boegman, & El-Defrawy, 1986; Beninger, Wirsching, Jhamandas, Boegman, & El-Defrawy, 1986; Flicker, Dean, Watkins, Fisher, & Bartus, 1983; Friedman, Lerer, & Kuster, 1983; Hepler, Olton, Wenk, & Coyle, 1985; Murray & Fibiger, 1983; Salamone, Beart, Alpert, & Iverson, 1984).

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Salamone (1986) has recently suggested that nbm cells may play a role in noncognitive processes that may affect performance on memory tasks. For example, lesion-induced changes in motivation, shock sensitivity, feeding and/or locomotor activity may account for the behavioral deficits. Recently, it has been demonstrated that ibotenic and/or kainic acid nbm lesions do not significantly impair shock sensitivity (Friedman et al., 1983) or amount eaten (Dubois, Mayo, Agid, Le Moal, & Simon, 1985), thereby challenging the hypothesis that these factors are responsible for impaired performance. The results on locomotor activity have been equivocal (Dubois et al., 1985; Hepler & Lerer, 1986), and the effects that QUIN nbm lesions have on nonassociative factors have not been investigated.

The present study was undertaken to further determine the possible effect of KYN on QUIN toxicity by examining the neurotoxic and mnemonic effects of unilateral injections of QUIN alone or in combination with KYN into the nbm of the rat. To provide a more rigorous evaluation of whether behavioral deficits can be attributed to a specific disturbance of memory, feeding, and locomotor activity were also assessed.

Method

Subjects

Forty-nine experimentally naive male albino rats of the Sprague-Dawley strain were individually housed in a climatically controlled room (21 ± 1 °C) on a 12-hr light/dark cycle (0600–1800 hr). Initial free-feeding weights of 300 to 350 g were decreased to 80% (adjusted for growth) by daily feeding with measured rations.

Apparatus

The radial maze, elevated 50 cm above the floor, consisted of an octogonal central platform (30 cm wide) surrounded by eight equally spaced radial arms (65 cm long × 10 cm wide). Food wells, located 1 cm from the end of each arm, were 1.0 cm deep and 1.5 cm in diameter. The maze was located in a room that was painted white and lit by 70-W fluorescent tubes. Several visually distinct cues (e.g., door or electrical wiring) were present in the room and remained in the same position with respect to the apparatus.

Activity was monitored in six identical Plexiglas chambers (41 cm × 50 cm × 37 cm) each housed in a Styrofoam sound-attentuating wooden box. Each chamber was illuminated by a 2.5-W light mounted on the ceiling and ventilated by a small fan that provided constant background noise. Located in each chamber were two sets of seven infrared emitters and detectors, 5 and 15 cm above the wire rod floor. A Cromemco microcomputer recorded beam crossings (for a detailed description see Beninger, Cooper, & Mazurski, 1985).

Preoperative Training

Radial maze. Deprivation began one week before training. During this period, each rat was handled daily for approximately 1 min. On Day 5 of deprivation, animals were fed a small quantity of Froot Loops cereal in their home cage because small pieces subsequently were utilized as food reinforcers.

Pretraining. On Day 8 of deprivation, animals were placed for 10 min in pairs on the central hub of the maze with food scattered on the platform and arms. On Day 10, rats were placed singly on the maze. Again, food was scattered on the platform and along a randomly predetermined subset of only four arms, referred to as the *baited* arms. The baiting pattern remained the same throughout the experiment but varied from rat to rat. During Days 10 to 13, the four arms were rebaited until the rat learned to run to the end and collect the food in 10 min or less. Type of arm entry (baited or unbaited) was recorded. An arm entry was defined as crossing a line 10 cm into each arm. After each trial, the maze was cleaned with a 2.5% cider vinegar solution.

Formal training. Each rat received one session per day, 7 days a week. At the start of each session, the four predetermined arms were baited at their distal end (note that arms were not rebaited within a session). Each rat was placed on the platform and left until all four baits were collected, 14 choices were made or 10 min had elapsed, whichever came first. Training continued until choice accuracy stabilized over 4 days to an average criterion of ≥ 87% correct; thus a score of 100% (four out of four unrepeated baited arm entries within the first 4 choices) on at least 2 of the 4 days was required. Rats were then randomly assigned to QUIN (n = 10), coinjection of QUIN and KYN (n = 7), or sham (n = 16) groups. Because the two treatment groups were trained at different times, the latter sample size represents a combination of two control groups: Sham 1 (n = 9) and Sham 2 (n = 7).

Dependent measures. Type of error and reinforcement receipts were recorded. The first entry into a baited arm regardless of whether or not the bait was collected was scored as a correct choice, and a reentry into that arm was scored as a working memory error. Entries into arms that were never baited were scored as reference memory errors. There was a problem with the scoring system for working memory. Namely, if a rat entered one of the baited arms and did not collect the food, a reentry could be considered correct. Therefore another scoring system for working memory errors was used: reentries into an arm that still contained the bait were scored as correct choices.

Surgery

Rats were anesthetized with halothane (Halocarbon, Malton, Ontario, Canada; 2% halothane, 98% oxygen) and positioned in a Narashighe stereotaxic frame. With the incisor bar set at 3.3 mm below the interaural line, unilateral microinjections were aimed at the right or left nbm with coordinates from bregma being 0.8 mm posterior, 2.6 mm lateral to the midline, and 8.0 mm ventral to the surface of the skull. All rats received 1.0 μl infused over 2.5 min, and the cannula (Hamilton, 0.35 mm outer diameter) was left in place for 3.0 additional min to allow for diffusion. Sham rats received 0.9% saline. QUIN (Sigma) was injected in a dose of 120 nmol titrated to pH 7.4 with 1 N NaOH. Coinjections included 120 nmol of QUIN and 360 nmol of KYN (Sigma), similarly adjusted to pH 7.4.

Postoperative Testing

Radial maze. Following at least 1 week of recovery, animals were tested on the radial maze for 32 consecutive days. The procedure was the same as in preoperative testing.

Feeding behavior. On the first test day, 2 hr after radial maze testing, animals were given 10 g of the reinforcer in their home cages. A tray was placed under the wire mesh floor of the cage to catch food spillage. Amount ingested over a 30-min period was calculated by subtracting the remaining food in the cage and the spillage from the 10-g allowance.

Locomotor activity. Each rat was tested before and after the radial maze task for 4 consecutive days. Testing began, on average, 9 and 54 days postlesion. On each test day, animals were removed from

their home cage and placed in the activity chambers. Horizontal and vertical beam crossings were recorded at 30-min intervals for a 2-hr period.

Histology

At completion of behavioral testing, some animals were anesthetized with sodium pentobarbital (Sigma, 50 mg/kg) and perfused through the ascending aorta with 500 ml 0.9% NaCl, followed by 1,200 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 to 3 hr 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 hr. Transverse sections were cut on a freezing microtome and stained with cresyl violet.

Biochemical Analysis

Animals were killed by decapitation, and their brains rapidly removed and rinsed in ice-cold saline. The brains were then placed, ventral surface up, on moistened filter paper on a chilled Plexiglas plate that was kept on ice. A coronal slab of the whole brain was produced with the use of two parallel stainless steel razor blades held 6.0 mm apart in a Plexiglas holder with the back razor blade placed across the pituitary stalk. The slab was positioned with the caudal surface up, and the fronto-parietal cortex was dissected from each hemisphere. A small piece of each cortical section was removed and reserved for the determination of CAT activity, which as based on a modification of the procedure utilized by Fonnum (1975). The basis of the assay was the rate of conversion of [^{14}C]acetyl-CoA (radioactive labeled acetyl-coenzyme A) and choline to [^{14}C]ACh (radioactive labeled acetylcholine). The tissue was homogenized in 20 volumes (w/v) ethylenediaminetraacetic acid solution containing triton X-100. A quantity of the homogenate was added to the reaction medium, and the reaction was allowed to proceed for 1 hr at 37 °C. The labeled ACh was then isolated by liquid cation exchange and counted using liquid scintillation counting.

Results

Radial Maze

Data from animals that failed to learn the task to criterion ($n = 13$) or did not run postoperatively ($n = 3$) were excluded from statistical analyses. To assess preoperative performance, a one-way analysis of variance (ANOVA) was performed on days to criterion. To assess postoperative performance, a one-way repeated measures ANOVA was conducted on total number of working memory errors; a two-way ANOVA with one repeated measure (blocks) was performed on total number of reference memory errors. Error scores, based on the first four choices, were summed over 4 days, yielding eight 4-day blocks. An examination of the working memory data revealed that there were no instances of reentering arms that still contained the bait. Hence, the analysis of working memory errors represents cases wherein animals reentered arms from which the bait had already been collected.

The two sham groups were compared on each of the three dependent variables. Preoperatively, the mean ($\pm SE$) number of days to criterion was 30.3 (± 5.9) and 28.4 (± 4.6) for Sham 1 and Sham 2, respectively. There was no reliable difference between the groups, $F(1, 14) < 1.0, p > .05$. Postoperatively, neither group made any working memory errors. The reference memory performance of the two groups was also similar, becoming consistently better over time. This was supported by no significant effects of group, $F(1, 14) = 3.05, p > .05$, or Group × Block interaction, $F(7, 98) < 1.0, p > .05$, but a reliable block effect, $F(7, 98) = 23.45, p < .001$. As there were no significant group effects, subsequent analyses utilize the pooled data from both sham groups.

The mean ($\pm SE$) number of days to criterion for the QUIN (32.4 ± 5.4), sham (29.5 ± 3.8), and coinjected (32.5 ± 6.1) groups were not statistically different, $F(2, 30) < 1.0, p > .05$. Thus the groups were similar on the number of days it took to acquire the task before surgery.

The mean ($\pm SE$) total number of working and reference memory errors as a function of postsurgical blocks is depicted in Figures 1 and 2, respectively. It is clear that only the QUIN group made working memory errors, which persisted over blocks, $F(7, 63) = 2.06, p > .05$. Similarly, reference memory errors differed reliably among the groups, $F(2, 30) = 30.74, p < .001$. The effect of blocks was significant, $F(7, 210) = 5.29, p < .001$, as was the interaction, $F(14, 210) = 3.13, p < .001$.

Tests of simple main effects of the interaction revealed that reference memory errors decreased over blocks for both the sham, $F(7, 210) = 12.31, p < .001$, and coinjected, $F(7, 210) = 6.58, p < .001$, groups. The QUIN group, by contrast, did not show a decrease in reference memory errors with repeated testing, $F(7, 210) = 1.34, p > .05$. There were also significant group differences at Blocks 2 to 8 (see Table 1). Newman-Keuls multiple comparisons showed that the QUIN group made reliably more reference memory errors than did the sham group at each of Blocks 2 to 8 ($p < .05$), whereas reliable differences between the QUIN and coinjected groups did not become evident until Block 4. The sham and coinjected animals did not differ reliably at any of the blocks ($p > .05$). Overall, the analyses suggest that unilateral QUIN lesions of the nbm produced an impairment of the working and reference memory components of the radial maze task and that coinjection of KYN prevented this deficit.

Feeding Behavior

The mean ($\pm SE$) number of grams of food consumed on the first test day of the radial maze task is presented in Table 2. The two sham groups did not differ reliably in the amount consumed (5.3 ± 0.16 and 5.2 ± 0.18 g for Sham 1 and Sham 2, respectively), which was supported by a two-way ANOVA, $F(1, 14) < 1.0, p > .05$. Hence, the data were pooled. There were also no reliable differences among the QUIN, sham, and coinjected groups in the amount of food consumed, $F(2, 30) < 1.0, p > .05$.

Locomotor Activity

Vertical and horizontal activity were analyzed separately by a four-way ANOVA with three repeated measures (prepost [the 4 days before and the 4 days after radial maze testing] day, and time). Data from the two sham groups were examined for differences. The two sham groups had similar

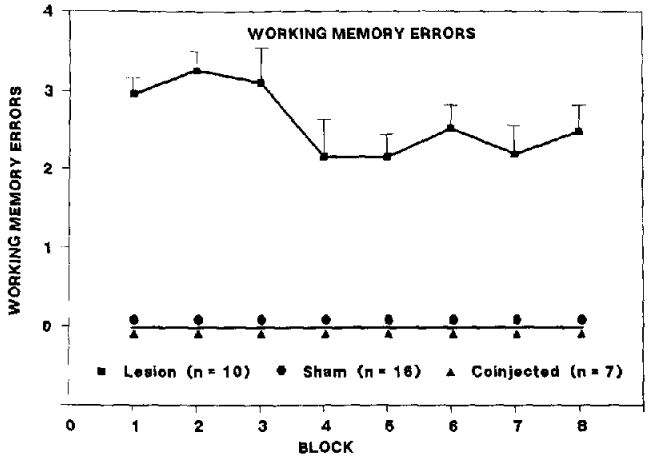

Figure 1. Mean (±*SE*) number of working memory errors within the first four choices summed over 4-day blocks for the quinolinic acid (■——■), sham (●——●), and coinjected (▲——▲) groups.

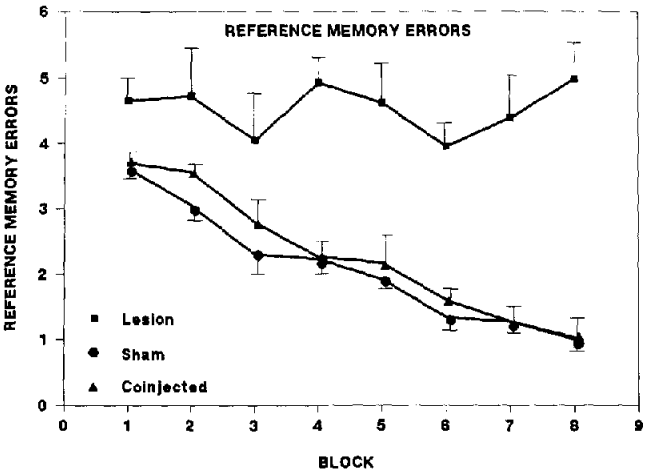

Figure 2. Mean (±*SE*) number of reference memory errors within the first four choices summed into 4-day blocks for the quinolinic acid (■——■), sham (●——●), and coinjected (▲——▲) groups.

vertical activity profiles becoming less active within a session. A significant time effect, $F(3, 42) = 94.52$, $p < .001$, but no significant effects of group, prepost, and day, or interactions among the four variables supports this description of the data.

Horizontal activity decreased significantly both across days, $F(3, 42) = 5.13$, $p < .01$, and over time, $F(3, 42) = 27.29$, $p < .001$, and a significant Group × Prepost × Day interaction emerged, $F(3, 42) = 3.61$, $p < .05$. Separate analyses of the data before and after testing determined that the significant Day × Group interaction occurred during posttesting, $F(3, 42) = 5.19$, $p < .01$. Tests of simple main effects revealed that although activity did not change significantly over days for Sham 1, $F(3, 42) < 1.0$, $p > .05$, it did for Sham 2, $F(3, 42) = 5.68$, $p < .01$. Analysis of the group effect at each day indicated that Sham 2 was significantly less active on Day 3, $F(1, 30) = 4.17$, $p < .05$. Because these differences were likely owing to sampling error, subsequent analyses utilized the pooled data for the two sham groups.

Pre- and postvertical activity scores for the QUIN, sham, and coinjected groups are illustrated in Figure 3. As can be seen, neither the QUIN nor coinjected groups had consistently higher or lower activity scores as compared with the sham controls. This was supported by no significant group differences or significant interaction effects with the group variable. For all groups combined, there was a significant within-session decline in activity, $F(3, 90) = 105.39$, $p < .001$. Significant Day × Time, $F(3, 90) = 3.96$, $p < .01$, and Prepost × Time, $F(3, 90) = 4.86$, $p < .05$, interactions were also observed, but because these effects occurred when groups were combined, they were of little interest.

Pre- and posthorizontal scores for the QUIN, sham, and coinjected groups are shown in Figure 4. There were no reliable group effects or reliable interaction effects with the group variable, again demonstrating the similarity in the activity profiles of the groups. Activity scores for all groups combined changed significantly over days, $F(3, 90) = 5.36$, $p < .05$, and within sessions, $F(3, 90) = 19.36$, $p < .01$. Significant Day × Time, $F(9, 270) = 3.22$, $p < .01$, and Prepost × Day × Time, $F(9, 270) = 1.94$, $p < .05$, interactions also were observed, but these effects did not involve the group variable; therefore they were not analyzed further.

Table 1
Tests of Simple Main Effects of Group at Each of the Different Levels of Block

Comparison	$F(2, 139)$	Significance
Block 1	2.2	*ns*
Block 2	5.4	$p < .05$
Block 3	6.0	$p < .05$
Block 4	15.8	$p < .01$
Block 5	15.2	$p < .01$
Block 6	14.3	$p < .01$
Block 7	21.5	$p < .01$
Block 8	34.8	$p < .01$

Histology

Histological results using procedures identical to those in the present study are presented elsewhere (Boegman et al., 1985). Results from the two reports were comparable. Microscopic examination of animals injected with QUIN re-

Table 2
Mean (±SE) Number of Grams of Froot Loops Consumed in the Home Cage on First Retest Day of the Radial Maze Task

Group	*n*	Grams of Froot Loops
QUIN	10	5.35 ± 0.16
Sham	16	5.28 ± 0.12
Coinjected	7	5.28 ± 0.18

Note. QUIN = quinolinic acid.

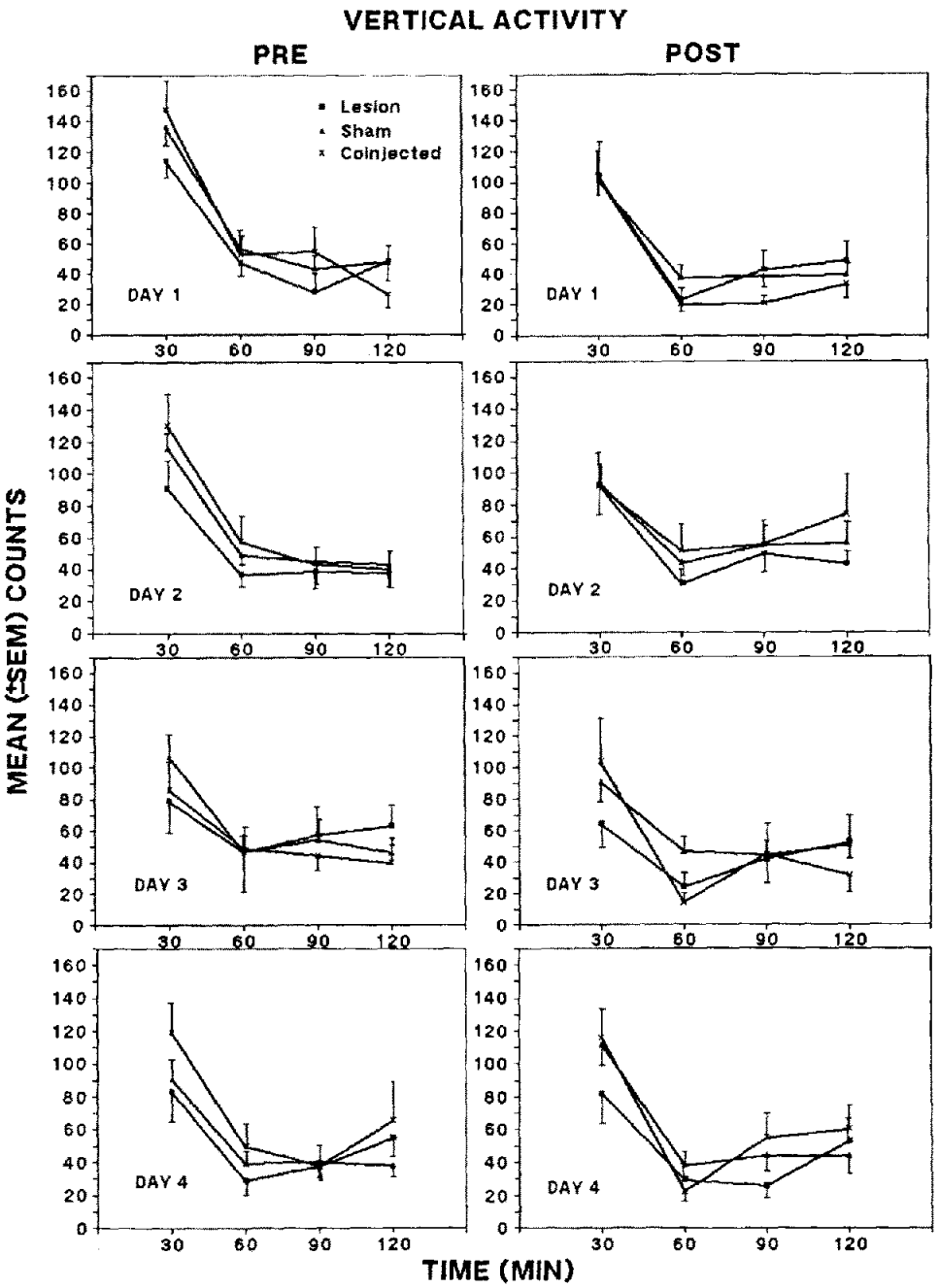

Figure 3. Mean (±*SE*) number of vertical beam crossings for the quinolinic acid (■——■), sham (●——●), and coinjected (×——×) groups. (Panels under the PRE subheading represent the 4 days before postsurgical radial maze testing; those under POST are the 4 days after radial maze testing.)

vealed widespread destruction on the side of the lesion. The destruction seemed to involve a number of nuclei that appeared to depend on the diffusion of QUIN rather than any selective vulnerability. The caudate nucleus, thalamus, nucleus basalis, central amygdaloid nucleus, horizontal limb of the diagonal band, substantia innominata, and the zona incerta were affected. No other anomalies were seen in the rest of the brain. The only abnormality seen in animals coinjected with KYN and QUIN was the presence of the needle tract. This finding was identical to that seen in sham controls: a small needle tract containing hemosiderin-laden macrophages.

Biochemical Analysis

Results from the cortical CAT assays are presented in Table 3. Data were analyzed by a two-way ANOVA with one repeated measure (side). A comparison of the two sham groups

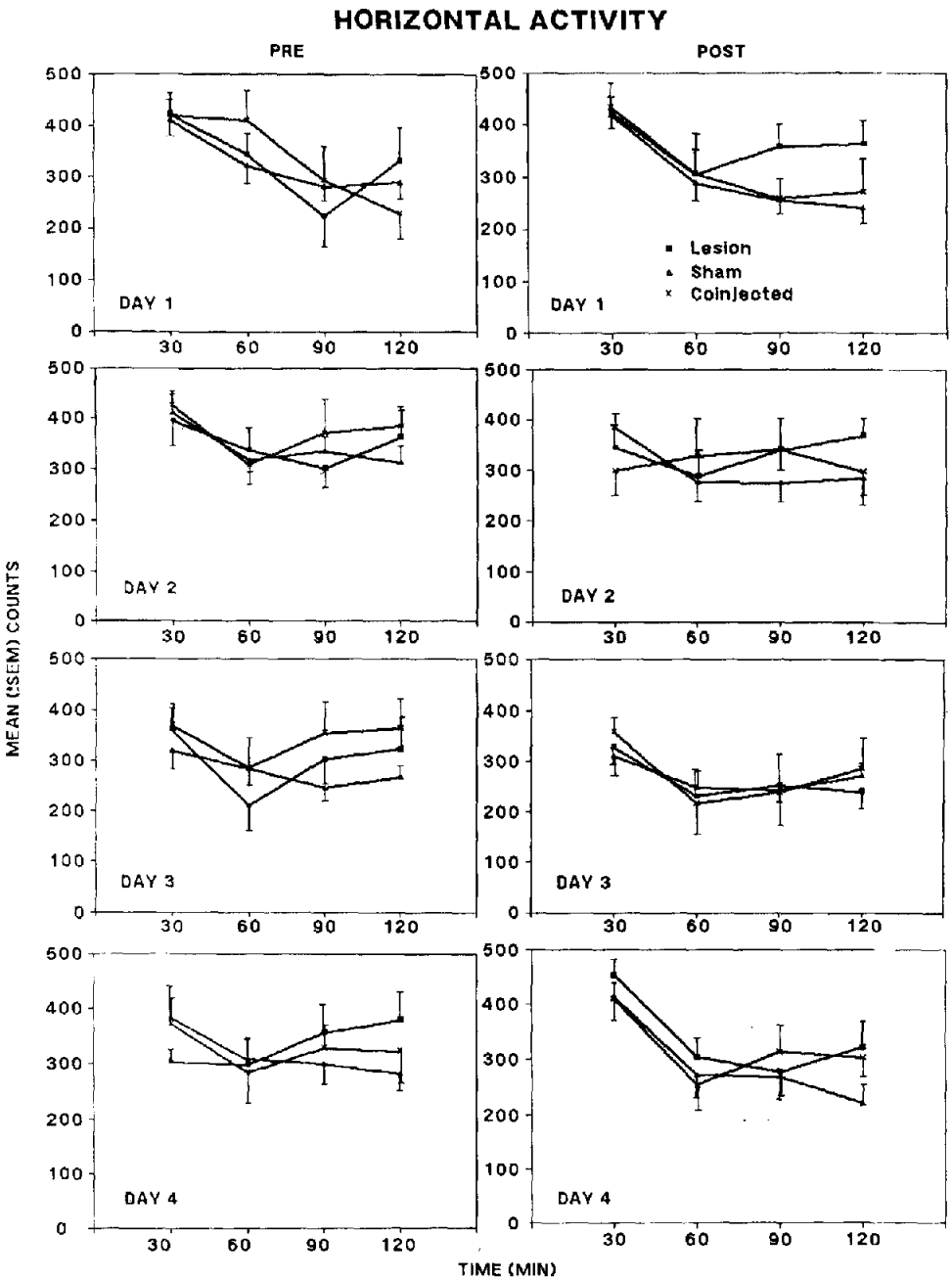

Figure 4. Mean (±*SE*) number of horizontal beam crossings for the quinolinic acid (■——■), sham (●——●), and coinjected (×——×) groups. (Panels under the PRE subheading represent the 4 days before postsurgical radial maze testing; those under POST are the 4 days after radial maze testing.)

revealed a significant group effect, $F(1, 14) = 5.92$, $p < .05$, which was possibly owing to variations in the CAT assay, because each group was tested at a different time. However, within each group, the injected and noninjected sides were always assayed at the same time. The effect of interest, the Group × Side interaction, was not significant for the two sham groups, $F(1, 14) < 1.0$, $p > .05$. On the other hand, the interaction among the three experimental groups was significant, $F(2, 30) = 56.51$, $p < .001$. As expected, tests of simple main effects showed no reliable depletion in CAT activity for sham-operated rats, $F(2, 30) < 1.0$, $p > .05$. QUIN produced a large and reliable depletion in CAT activity on the injected side as compared with the intact side, $F(2, 30) = 145.51$, $p < .001$. In contrast, QUIN coinjected with KYN acid did not produce a reliable decrease in CAT activity, $F(2, 30) < 1.0$, $p > .05$. There was a significant difference among groups on the injected side, $F(2, 40) = 12.41$, $p < .001$, and Newman-Keuls comparisons revealed

Table 3
Mean (±SE) Levels of Cortical Choline Acetyltransferase on the Injected and Noninjected Side

Group	*n*	Injected side	Noninjected side
Sham 1	9	40.7 ± 2.2	39.7 ± 2.7
Sham 2	7	54.0 ± 4.3	52.0 ± 4.5
QUIN	10	22.8 ± 4.1	48.6 ± 5.6
Sham	16	48.1 ± 3.0	46.6 ± 3.1
Coinjected	7	38.5 ± 2.7	37.4 ± 1.7

Note. Nmol acetylcholine formed mg/protein/hr. QUIN = quinolinic acid.

that the QUIN group differed reliably from both the sham and coinjected groups ($p < .05$). There were no reliable differences between the latter two groups ($p > .05$). The group effect on the uninjected side was not statistically significant, $F(2, 40) = 1.78$, $p > .05$.

Discussion

Results confirm the preliminary report that coinjection of KYN with QUIN antagonizes the neurotoxic and behavioral effects of QUIN on the cholinergic neurons of the basal forebrain (Beninger, Jhamandas, Boegman, & El-Defrawy, 1986). This was indicated by a failure to observe a decrease in cortical CAT activity or a performance deficit in the radial maze after KYN plus QUIN injections. It was also observed that QUIN lesions did not significantly affect the amount eaten or locomotor activity, findings that are consistent with Dubois et al. (1985) and Hepler and Lerer (1986), respectively. Locomotor hyperactivity has been reported after larger lesions within the same area (Norton, 1976). However, the possibility that lesion-induced motor deficits accounted indirectly for the performance deficit reported here seems even more unlikely because postural, motor, and tonic anomalies were not observed. A careful study of these behaviors (Flicker et al., 1983) confirms this observation. Although other nonassociative factors (i.e., response inhibition, attention) were not ruled out as possible confounds, data support the growing body of evidence that suggests that the performance deficits observed following nbm lesions are attributable to a specific disturbance of memory.

It should be mentioned that noncholinergic neurons in the nucleus basalis may have been damaged by the QUIN lesion procedure, and thus contributed to the reported behavioral effects. However, this suggestion seems unlikely because damage to other structures that are predominately noncholinergic such as the amygdala and the caudate nucleus have been shown not to affect maze performance (Becker, Walker, & Olton, 1980).

The observation of a significant impairment of memory in the radial maze in rats following unilateral QUIN nbm lesions is in good agreement with numerous previous studies, which demonstrate that unilateral QUIN or kainic acid (Beninger, Jhamandas, Boegman, & El-Defrawy, 1986; Beninger, Wirsching, Jhamandas, Boegman, & El-Defrawy, 1986), unilateral electrolytic (Casamenti, Bracco, Bartolini, & Pepeu, 1985), or bilateral electrolytic, kainic or ibotenic acid lesions of the nbm (e.g., Altman et al., 1985; Bartus et al., 1985, 1986; Dubois et al., 1985; Flicker et al., 1983; Murray & Fibiger, 1983) lead to memory deficits in various tasks. However, the present and previous studies are inconsistent as to the type of memory deficit. Bartus et al. (1986), for example, showed that bilateral ibotenate nbm lesions impaired working but not reference memory. Murray and Fibiger (1983), in contrast, found that bilateral ibotenate nbm lesions increased both working and reference errors. Similarly, in the present and previous study from this laboratory (Beninger, Jhamandas, Boegman, & El-Defrawy, 1986), unilateral QUIN nbm lesions produced an increase in both types of errors.

It may be possible to reconcile these apparently contradictory data by considering the level of training. Murray and Fibiger (1983) examined the effects of nbm lesions on the acquisition of a 16-arm radial maze task with 9 arms baited. In the present and other reports (Bartus et al., 1986; Beninger, Jhamandas, Boegman, & El-Defrawy, 1986), nbm lesion effects were examined in previously trained animals in an eight-arm maze, with animals in the Bartus et al. (1986) study receiving a more rigorous and longer pretraining period. Possibly, rats with extensive pretraining are less susceptible to the memory disrupting effects of nbm lesions and as such do not exhibit impaired performance on both the trial unique (i.e., working memory) and unchanging reinforcement contingency (i.e., reference memory) aspects of the radial maze task. This proposal gains some support from the observation that the spatial memory of overtrained rats is relatively resistant to the impairing effects of high doses of anticholinergics (Buresova & Bures, 1982; Deutsch, 1971). Thus the level of pretraining may be an important factor in determining the type of memory impairment that will be observed following lesions of the basal forebrain.

In conclusion, coinjection of KYN with QUIN provided complete protection against the neurochemical and memory-impairing effects of QUIN alone on the cholinergic neurons of the basal forebrain. This finding provides further support for the hypothesis that an imbalance between KYN and QUIN acid may be a factor in neurodegenerative disorders involving the loss of nbm cells. Moreover, the impaired radial maze performance observed following QUIN injections alone appeared to have been due to a specific disturbance of memory processes rather than lesion-induced changes in feeding and/or locomotor activity.

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