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Significance of Central Noradrenergic System on Harmaline Induced Tremor[1]

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YAMAZAKI, M., C. TANAKA AND S. TAKAORI. *Significance of central noradrenergic system on harmaline induced tremor.* PHARMAC. BIOCHEM. BEHAV. **10**(3) 421–427, 1979.—Since there is degeneration of substantia nigra concomitant with that of locus coeruleus (LC) in patients with Parkinson's disease, the study was performed to determine the role of central norepinephrine (NE) on harmaline induced tremor. The duration of harmaline (10 mg/kg IP) induced tremor was significantly reduced by intraventricular administration of L-threo-3,4-dihydroxyphenylserine (200 μg/rat) and 1-NE (50 μg/rat) which increased NE levels in the cerebral cortex, striatum, diencephalon, cerebellum and brain stem. Electrical stimulation of bilateral LC suppressed harmaline-induced 10–12/sec EMG activities in the neck muscle. Bilateral LC lesion upon electrocoagulation and 6-hydroxydopamine treatment resulted in a significant prolongation of the duration of harmaline induced tremor, reducing NE levels in the brain. These data suggest that central NE originating in the LC neurons has an inhibitory effect on the development of the tremor induced by harmaline.

Harmaline Tremor L-threo-3,4-dihydroxyphenylserine Norepinephrine Locus coeruleus 6-Hydroxydopamine

IT HAS been well documented that a decrease of dopamine in the striatum as a result of degeneration of the substantia nigra is responsible for the occurrence of Parkinson's disease. In this disease, however, the simultaneous degeneration of the locus coeruleus (LC) which is composed of norepinephrine (NE)-containing cells has been reported by Greenfield and Bosanquet [10]. A reduction in the level of NE in the subcortical areas has also been found in patients with Parkinson's disease [7]. In our previous paper [34], we demonstrated that L-threo-3,4-dihydroxyphenylserine (L-threo-DOPS) significantly suppressed harmaline induced tremor in mice. This amino acid, directly decarboxylated to NE, elevated NE levels without any significant changes in other monoamine levels in the mouse brain [8,34]. Since harmala alkaloids, harmaline and harmine, produced Parkinson-like tremor in intact and brain-lesioned animals [1, 11, 12, 26], our previous results together with other pathological and biochemical findings suggest that NE derived from the LC may play an inhibitory role on tremorogenic mechanisms in Parkinson's disease. Thus, the present study was an attempt to determine the role of LC neurons in the tremorogenic mechanism involved in harmaline induced tremor.

METHOD

Male Wistar rats weighing 250–300 g were housed in separate cages at 22–24°C under a constant day-night rhythm and a standard diet (Japan CLEA Co., CA-1) and tap water for drinking were provided ad lib. The animals were anesthetized with pentobarbital sodium (30 mg/kg IP) and fixed in a stereotaxic instrument. For intraventricular administration of drugs, a stainless steel tube 4 mm in length with a guide wire was implanted into the left lateral ventricle at 2.3 mm lateral from the midline and 0.9 mm posterior from the coronary suture, then fixed with dental cement. Electrolytic lesions of bilateral LC were made by passing a direct current of 1.0 mA for 10 sec through a stainless steel wire electrode (0.5 mm dia.), which was coated except for 0.1 mm at the tip. The location of LC was determined according to the topographic map of Palkovits and Jacobowitz [24]: 1.8 mm posterior from interaural line, 1.2 mm lateral from midline and 7.0 mm ventral from the surface of the skull. In the sham-operated animals the electrode was inserted 2 mm dorsal to the LC but no current was passed. For chemical lesioning of the bilateral LC, 6-hydroxydopamine (6-OHDA) was locally applied through a glass tube with a 0.2 mm dia. at the tip and this was connected to a 10 μl microsyringe by a polyethylene guide tube. The saline solution of 6-OHDA containing 0.2 mg/ml of ascorbic acid was kept at 0°C until use. Eight μg of 6-OHDA in 2 μl of saline solution were infused at a constant rate of 1 μl per min and the glass tube was left in place for a further 10 min before withdrawal. In experiments when the LC was stimulated, a bipolar stimulating stainless steel electrode of 0.4 mm in dia. and with tip

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separation of 0.1 mm was inserted into the bilateral LC and fixed with dental cement. The stimuli applied to the LC for 2 min were composed of square pulses with 1.0 msec duration and 4.0 V.

Harmaline induced tremor was observed in a sound-attenuated room maintained at a temperature 22 ± 1°C, 7–10 days after the surgical procedure. The animals were placed in observation cages at least 30 min before treatment, to adapt to the new environment. After IP injection of harmaline, intensity of tremor for 1 min was scored every 10 min for 3 hr according to visual assessment as described by Kelly and Naylor [14]. Briefly, score 1 corresponds to mild jaw and head tremor, score 2 severe head tremor without body tremor, score 3 mild whole body tremor and score 4 severe whole body tremor throughout the observation period. The duration of tremor was measured from the beginning of the time of score 1 to the time when the score returned to 1. The effect of LC stimulation of harmaline induced tremor was evaluated by recording electromyogram (EMG) using plate electrodes attached to the dorsal and ventral surfaces of the neck. An ink-writing oscillograph (Nihon Kohden, WI-180-TR) was employed for the EMG recording.

The drugs used were as follows: harmaline HCl, l-norepinephrine (NE) bitartrate and 6-OHDA were from Sigma and L-threo-DOPS was from Kyowa Hakko. NE and L-threo-DOPS were injected into the lateral ventricle 5 and 30 min before harmaline injection, respectively.

At the end of all experiments, the animals were decapitated and the brain was cut just rostral to the superior colliculus. The brain stem was immediately freeze-dried and the location and extent of lesions were examined using routine fluorescent histochemical procedures [6]. The forebrain was also quickly removed and NE content in the cerebral cortex and striatum was assayed fluorometrically by the method of Anton and Sayre [2]. The statistical significance of the data was calculated by Student's *t*-test.

RESULTS

Harmaline induced tremor. When 10 mg/kg of harmaline was injected IP, tremor was apparent within 5–10 min. At first, the tremor occurred during the resting state, and later was also observed during movement of the rat. Fig. 1B shows a typical example of EMG of head tremor produced by harmaline and which consisted of small and occasionally high amplitude burst wave with a frequency of 10–12/sec. Table 1 demonstrates the duration and percentage of occurrence of tremor in the animals treated with harmaline in doses of 5, 7.5, 10 and 12.5 mg/kg. Scoring of the intensity of tremor after administration of 5–12.5 mg/kg of harmaline was increased in a dose-dependent manner, as shown in Fig. 2. The duration of tremor was also increased dose-dependently and tremor occurred in all animals given over 10 mg/kg of the drug. The duration of tremor after 10 mg/kg of harmaline was relatively consistent and ranged from 90–130 min with the mean being 108.3 ± 16.8 (SE, n=10) min. In all following experiments, therefore, a dose of 10 mg/kg of harmaline was given.

TABLE 1

TREMOR INDUCED BY HARMALINE IN RATS

Doses (mg/kg)	N	Duration of Tremor (min)	Percentage of Occurrence
5.0	10	16.7 ± 9.2*	50%
7.5	10	61.7 ± 15.4	80%
10.0	10	108.3 ± 16.8	100%
12.5	10	130.0 ± 10.0	100%

Harmaline was administered intraperitoneally.
N=Number of rats.
*Each figure represents Mean ± SE.

Intraventricular administration of L-threo-DOPS and NE. Table 2 represents the effect of intraventricular administration of L-threo-DOPS and NE on harmaline induced tremor. The intensity and duration of tremor was suppressed dose-dependently by pretreatment with L-threo-DOPS and NE. L-threo-DOPS (100 μg/rat) and NE (10 μg/rat) reduced the

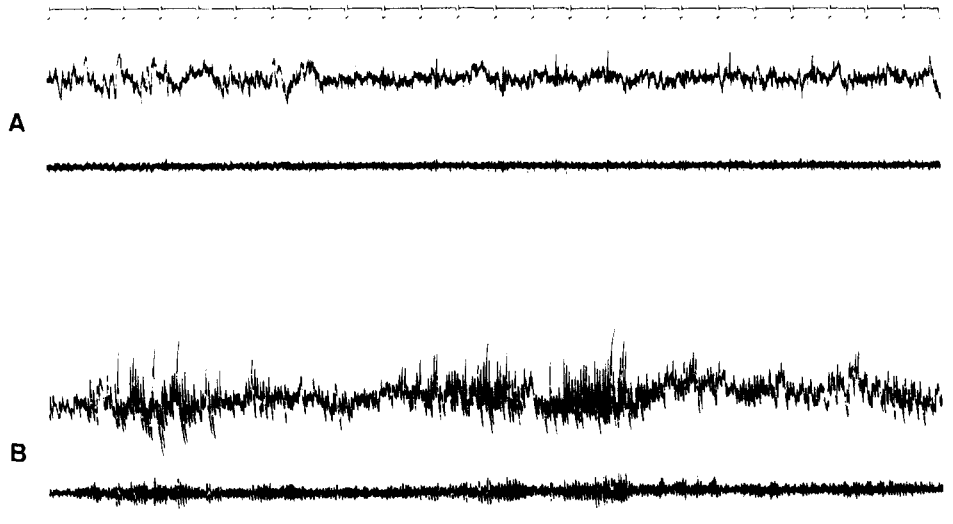

FIG. 1. Electromyogram of the neck muscle in a rat before (A) and after IP injection of 10 mg/kg of harmaline (B). In the each tracing, upper tracing: time constant 0.5 sec, and lower tracing: time constant 0.003 sec. Time scale: 1 sec.

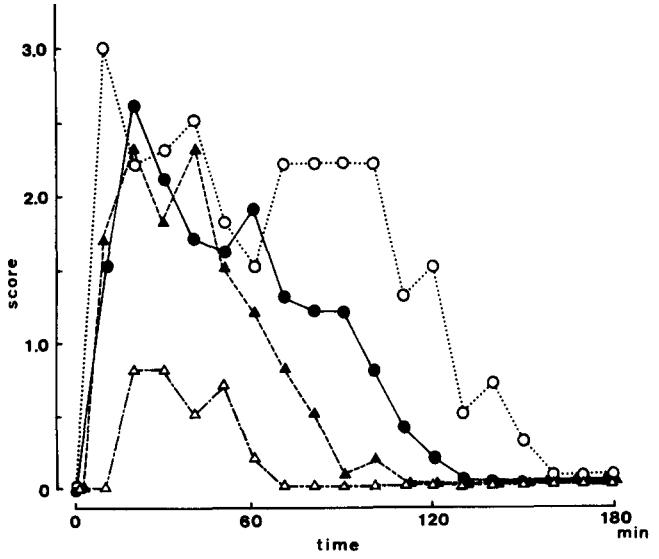

FIG. 2. Time course of intensity of tremor induced by harmaline in doses of 5 (△-·-·-△), 7.5 (▲---▲), 10 (●——●) and 12.5 (○·····○) mg/kg. Each point is the mean score of the intensity of tremor from 10 rats at each observation period.

TABLE 2

EFFECT OF L-THREO-DOPS AND l-NOREPINEPHRINE ON HARMALINE INDUCED TREMOR

Drugs	Doses (μg/rat)	N	Duration of Tremor (min)	% Change
L-Threo-DOPS	0	11	112.7 ± 13.3*	
	100	10	77.0 ± 14.1	-32%
	200	10	63.0 ± 18.6†	-44%
l-Norepinephrine	0	17	116.5 ± 15.1	
	10	14	84.3 ± 11.3	-28%
	50	14	70.0 ± 12.8†	-40%

L-Threo-DOPS and l-norepinephrine were administered intraventricularly, 30 min and 5 min respectively before harmaline 10 mg/kg IP.

N=Number of rats.

*Each figure represents Mean ± SE.

†$p<0.05$, significant as compared with each control.

duration of tremor by approximately 30% of respective controls. The duration of tremor was significantly ($p<0.05$) shortened by 44 and 40% of controls after 200 μg/rat of L-threo-DOPS and 50 μg/rat of NE, respectively.

The regional NE contents were examined when L-threo-DOPS (200 μg/rat) was applied into the lateral ventricle 90 min before sacrifice (Table 3). A significant increase in NE levels was noted in the cerebral cortex, striatum, diencephalon, cerebellum and brain stem.

Stimulation of LC. The effect of activation of LC neurons on harmaline induced tremor was examined by simultaneously stimulating for 2 min the bilateral LC through chronically implanted electrodes. The placement of the electrode was checked histologically after the experiment. This stimulation

TABLE 3

REGIONAL BRAIN NOREPINEPHRINE CONTENTS AFTER INTRAVENTRICULAR INJECTION OF L-THREO-DOPS IN RATS

	N	Norepinephrine (μg/g) Saline	L-threo-DOPS
Cerebral cortex	10	0.18 ± 0.02*	0.38 ± 0.02†
Striatum	10	0.24 ± 0.02	0.55 ± 0.06†
Diencephalon	10	0.48 ± 0.02	1.45 ± 0.12†
Cerebellum	10	0.07 ± 0.01	0.33 ± 0.04†
Brain stem	10	0.36 ± 0.03	0.63 ± 0.01†

L-threo-DOPS 200 μg/rat was injected intraventricularly 90 min before sacrifice.

N=Number of rats sacrificed.

*Each figure represents Mean ± SE.

†$p<0.05$, significant as compared with each control.

produced no apparent alterations of EMG activities of the animals untreated with harmaline (compare B with A in Fig. 3). Harmaline induced tremor characterized by 10–12/sec EMG activities, however, was blocked during the LC stimulation (Fig. 3C and D). Attenuation of intensity of harmaline induced tremor was also visually observed during stimulation of the LC. Under EMG observation, complete blockade of harmaline induced tremor was seen in 6 out of 14 animals in which stimulating electrodes were properly located in the bilateral LC regions. In the remaining 8 animals, the LC stimulation produced partial diminution in the harmaline induced tremor. In contrast, when the stimulating electrode was positioned outside the LC, the tremor remained unchanged during LC stimulation.

Destruction of LC. According to the fluorescent histochemical examination, the animals with electrolytic and 6-OHDA induced lesions in the bilateral LC regions were classified into two groups (Fig. 4): complete and incomplete lesioned animals. The former showed a complete disappearance of NE containing cell bodies in the bilateral LC and an accumulation of fluorescence in nerve terminals in the dorsal tegmental bundle and medial part in the superior cerebellar peduncle (Fig. 5). However, the damage did not extend to the trigeminal mesencephalic nucleus, superior cerebellar peduncle and subcoeruleus area (Fig. 4Aa and Ba). In the latter, there was unilateral destruction of the LC or a considerable residue of NE containing cell bodies in the LC, as the lesion was small (Fig. 4Ab and Bb). The complete lesion of LC was obtained in 8 out of 20 animals with electrolytic procedure and in 6 out of 10 animals with 6-OHDA injection. The remaining animals treated with electrolysis and 6-OHDA belonged to the incomplete lesioned group. As most of animals with a complete lesion of bilateral LC had a haematuria in the first 2 to 5 days, harmaline was injected 7 to 10 days after the operation.

Approximately 60% prolongation of the duration and marked increase in intensity of tremor were produced by harmaline in both groups of the completely lesioned animals treated with electrolysis and 6-OHDA injection (Fig. 4 and Table 4). The mean duration of tremor in rats with complete lesion of the LC was significantly ($p<0.01$). increased as compared with respective sham-operated animals. However, the duration of harmaline induced tremor in the animals with

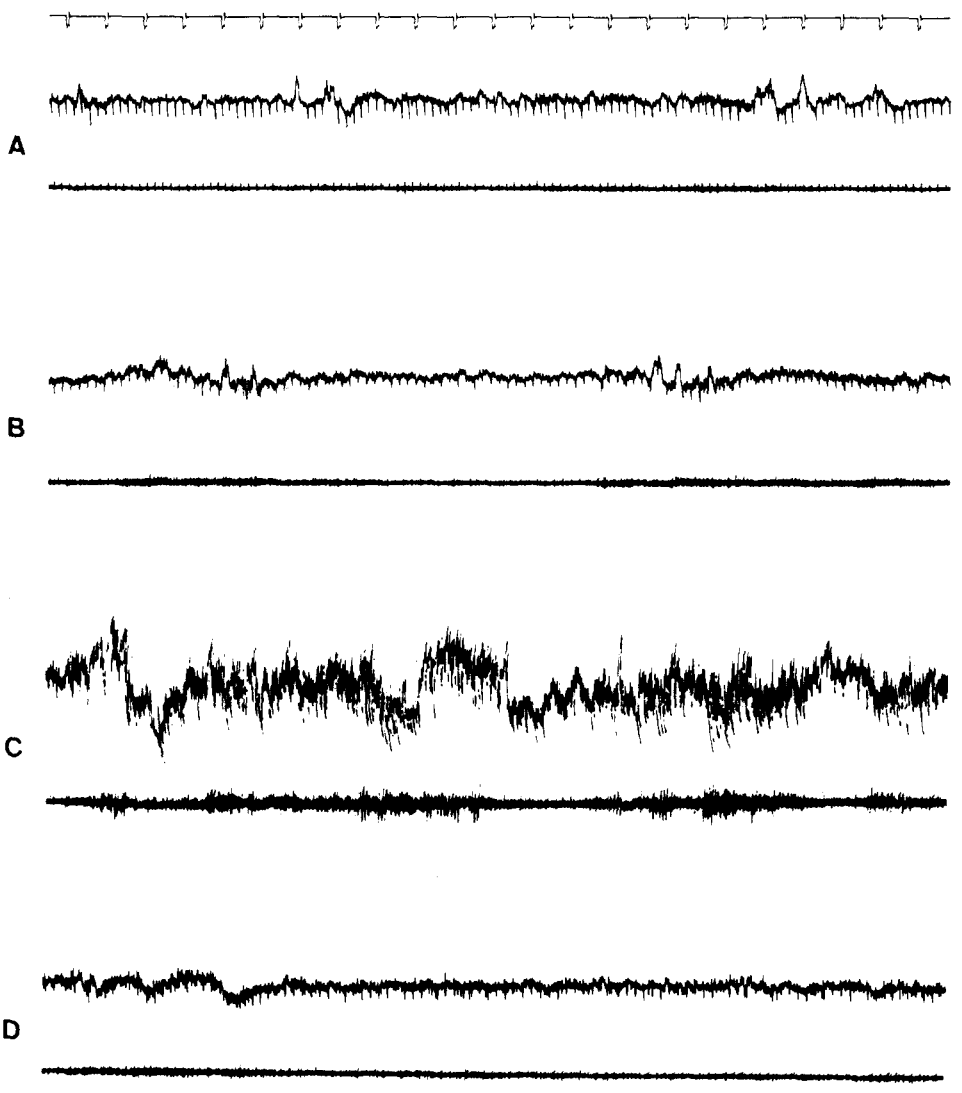

FIG. 3. Electromyogram of the neck muscle. A: non-treated. B: during stimulation of bilateral locus coeruleus (LC) without harmaline. C: 30 min after harmaline (10 mg/kg IP). D: during LC stimulation after harmaline. In each tracing, upper tracing: time constant 0.5 sec, and lower tracing: time constant 0.003 sec. Time scale: 1 sec.

incomplete lesion was not significantly different from that in sham-operated controls.

In cases of rats with total LC-lesioning, NE contents in the cerebral cortex and striatum were significantly ($p<0.01$) reduced regardless of the methods of destruction (Table 5).

DISCUSSION

The duration of tremor produced by IP injection of 10 mg/kg of harmaline in rats was relatively consistent, and under visual assessment ranged from 90 to 130 min. This duration was much the same as that reported by others [16,35]. Furthermore, the tremor recorded on EMG was similar to that reported by Fuentes and Longo [9] and Lamarre and Mercier [19].

We found that elevation of NE levels in the brain after intraventricular administration of NE and its precursor, L-threo-DOPS, reduced the duration of harmaline induced tremor dose-dependently. Since L-threo-DOPS is converted to NE directly, these results suggest that central NE inhibits harmaline induced tremor. In addition, stimulation of the LC resulted in an inhibition of harmaline induced tremor. It has been reported that LC stimulation produces a release of NE and an increase of its metabolites as well as turn over from the regions innervated by LC neurons, such as the cerebral cortex [17, 31, 33]. Therefore, NE released from the terminals of LC neurons may inhibit harmaline induced tremor.

On the contrary, decrease in levels of brain NE as the result of the destruction of bilateral LC prolonged the duration of harmaline induced tremor. In contrast to our results, a reduction in harmine induced tremor was observed in rats pretreated with diethyldithiocarbamate, an inhibitor of

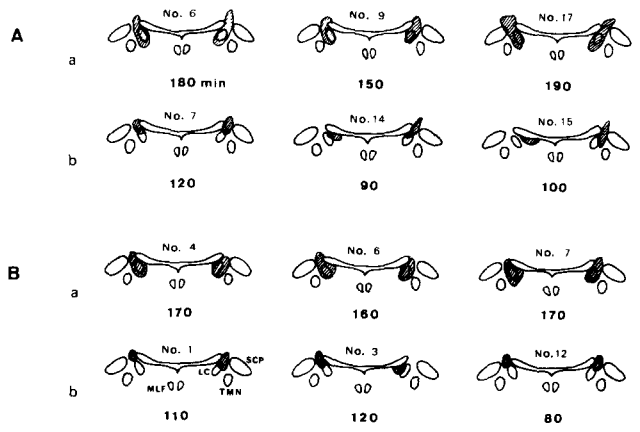

FIG. 4. The placement and size of lesion (shaded area) in the locus coeruleus region. Schematic drawing of frontal plane was situated 1.8 mm posterior from the interaural line. Number over each diagram indicates the number of the particular animal. The duration of tremor induced by harmaline (10 mg/kg IP) is shown below each diagram. A: electrolytic lesion, and B: 6-hydroxydopamine induced lesion. Aa and Ba: complete lesion, and Ab and Bb: incomplete lesion. LC: locus coeruleus, MLF: medial longitudinal fascicle, SCP: superior cerebellar peduncle, TMN: trigeminal mesencephalic nucleus.

dopamine-β-oxidase, thus suggesting that NE is important for the facilitatory effect on harmine induced tremor [4]. This facilitatory action of diethyldithiocarbamate is, however, not likely due to a decrease of NE alone, but to a concomitant increase in the levels of dopamine [3]. It has been reported that electrolytic lesion of the bilateral LC produced a reduction in the levels of forebrain NE with no changes in the levels of dopamine and serotonin [18]. In addition, it has been well documented that 6-OHDA locally injected into the LC results in a degeneration of noradrenergic neurons and a decrease in NE contents in the regions innervated by the LC neurons [5, 28, 32]. Thus, the enhancement of harmaline induced tremor can be attributed to a decrease of NE derived from the LC.

It has been proposed that the tremorogenic mechanism of harmaline and harmine involves an imbalance in the ratio among dopamine, serotonin and acetylcholine in the brain [14, 16, 26]. Recently, Kelly and Naylor [15] reported that harmine induced tremor was reduced by intrastriatal and intrapallidal injection of NE to a greater extent than by dopamine and its agonists, and they suggested that central NE was effective in antagonizing the tremor by stimulating an unspecified dopamine mechanism. Furthermore, the site of action of harmala alkaloids has been discussed in relation

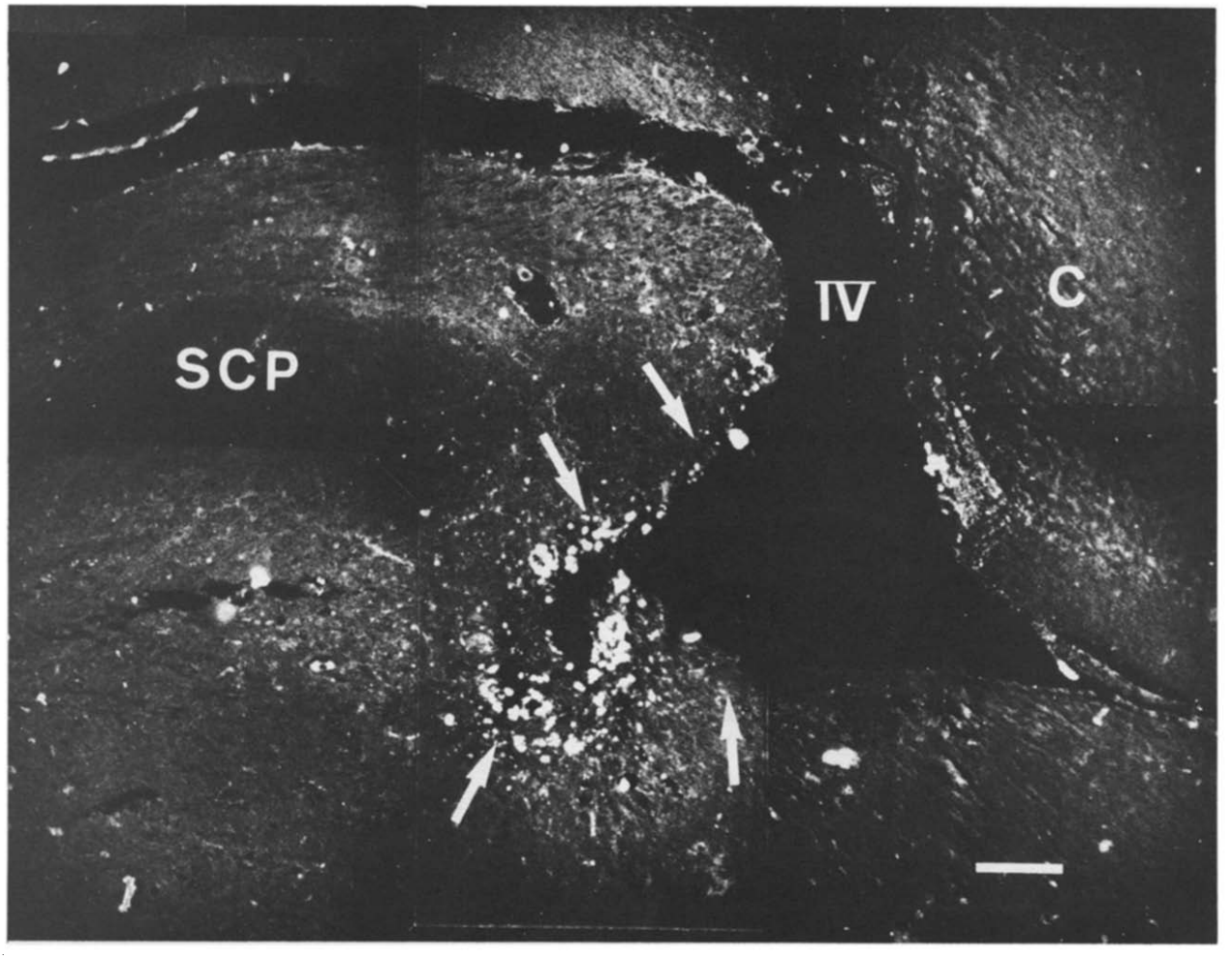

FIG. 5. Fluorescent histochemical section through the complete electrolytic lesion of locus coeruleus (LC). Arrows indicate the lesion of LC C: cerebellum, SCP: superior cerebellar peduncle, IV: fourth ventricle. Calibration mark: 0.2 mm.

TABLE 4

EFFECT OF DESTRUCTION OF LOCUS COERULEUS ON HARMALINE INDUCED TREMOR

	Experimental Group	N	Duration of Tremor (min)	% Change
Electrolytic lesion	Sham operation	15	106.6 ± 11.4*	
	Incomplete	12	113.3 ± 17.3	+ 6%
	Complete	8	168.8 ± 9.7†	+ 58%
6-OHDA induced lesion	Sham operation	11	101.8 ± 12.8	
	Incomplete	4	122.5 ± 4.8	+ 20%
	Complete	6	161.7 ± 4.8†	+ 59%

N=Number of rats.
*Each figure represents Mean ± SE.
†$p<0.01$, significant as compared with each control.

TABLE 5

NOREPINEPHRINE CONTENTS IN THE CEREBRAL CORTEX AND STRIATUM FOLLOWING COMPLETE DESTRUCTION OF LOCUS COERULEUS

Lesion	N	Norepinephrine (μg/g) Cerebral Cortex	% Change	Striatum	% Change
Sham operation	6	0.20 ± 0.02*		0.23 ± 0.03	
Electrolytic lesion	4	0.09 ± 0.01†	−55%	0.10 ± 0.02†	−57%
6-OHDA induced lesion	4	0.10 ± 0.03†	−50%	0.09 ± 0.01†	−61%

N=Number of rats.
*Each figure represents Mean ± SE.
†$p<0.01$, significant as compared with sham operated rats.

to the function of striopallidal [15, 16, 26, 27] and olivocerebellar systems [20, 22, 27]. In the immunohistological study of Swansson and Hartman [30], dopamine-β-hydroxylase sensitive terminals were rarely found in the striatum, however, the projection of ascending noradrenergic neurons from the LC to the striatum and cerebellum has been demonstrated by the methods using glyoxylic acid and 6-hydroxydopa [13, 21, 23, 29]. As a considerable amount of NE has been biochemically demonstrated in the striatum [25], there is probably a close relationship between the site of action of harmala alkaloids and existence of NE originating in the LC neurons.

Our findings demonstrate that the tremorogenic mechanism of harmaline is inhibited when the central noradrenergic neurons originating in the LC are activated. Thus NE no doubt plays the role of inhibitor in the tremorogenic mechanism in Parkinson's disease.

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