*THE EFFECTS OF CENTRALLY ACTING DRUGS ON TREMOR IN MONKEYS WITH MESENCEPHALIC LESIONS**

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Abstract.—The effects of centrally acting drugs on tremor were investigated in monkeys with ventromedial tegmental lesions exhibiting hypokinesia or hypokinesia and tremor. In monkeys with resting tremor, the administration of DL-5-HTP (5-hydroxytryptophan) or of DL-DOPA (3,4-dihydroxyphenylalanine) relieves the tremor, but the simultaneous administration of DL-5-HTP or DL-DOPA and atropine results in a much more pronounced relief. These results point to an imbalance between the cholinergic and adrenergic–serotonergic systems in parkinsonism.

In monkeys exhibiting hypokinesia, the administration of harmaline evokes a marked resting tremor of the extremities contralateral to the tegmental lesion. The production of tremor by harmaline is not abolished by lowering the striatal amine levels with specific inhibitors of amine synthesis. Administration of DL-5-HTP protects monkeys from tremors induced by harmaline, which might affect the functions of the central nervous system by interaction with receptors for serotonin. The present results further demonstrate the apparent role of biogenic amines in the extrapyramidal dysfunctions.

Model syndromes of extrapyramidal dysfunction have been produced in monkeys by introduction of unilateral lesions into the ventromedial area of the brain stem, after which the destruction of the pars compacta of the substantia nigra is associated with low concentrations of dopamine and serotonin in the corresponding basal ganglia.[1] Reduction of the biogenic amines in the striatum is concomitant with an impairment in the storage of dopamine and serotonin and with a decrease in the activities of tyrosine hydroxylase and DOPA decarboxylase.[2–4]

To determine further the role of biogenic amines in extrapyramidal dysfunction, we have investigated the effects of centrally acting drugs on tremor in monkeys with mesencephalic lesions.

Methods.—Green monkeys (*Cercopithecus sabaeus*) were used and unilateral radio-frequency lesions were induced in the ventromedial tegmental region of the brain stem as previously described.[1, 2] Hypokinesia of the contralateral extremities appeared immediately afterward. In some monkeys a resting tremor (4 to 6 cycles per sec) developed five to seven days later. The lesions were induced at least one month prior to the beginning of the experiments. Tremograms were obtained by means of a transducer attached to the extremities and recorded on an electroencephalograph. The effects of centrally acting drugs were investigated in monkeys with ventromedial tegmental lesions with a slight spontaneous resting tremor of the contralateral extremities (group I) and in monkeys exhibiting hypokinesia of the contralateral extremities but no resting tremor (group II).

Localization of the lesion in each brain was verified by gross examination and by histological study. The locus and the extent of the lesion were similar to those reported previously.[1] Gross examination revealed that the lesion in the monkeys from group I was

larger, involved more medial structures, and extended to a greater extent into the medial substantia nigra and the dorsomedial peduncle areas than the lesion in group II. A more detailed histological study is in progress.

Results and Discussion.—The effects of various drugs on tremor in monkeys with lesion-induced spontaneous tremor (group I) are summarized in Table 1. The intravenous administration of DL-DOPA at a dose of 30 mg/kg or of DL-5-HTP at 25 mg/kg resulted in disappearance or relief of the tremor, while smaller doses did not produce any marked effects.

Atropine, at an intravenous dose of 0.18 mg/kg, slightly relieved the tremor. Following the combined administration of DL-DOPA or DL-5-HTP with atropine, the tremor disappeared for 30 minutes to two hours, even when the concentration of each of these amino acids was lowered to 15 mg/kg. The simultaneous administration of DL-DOPA (15 mg/kg) and DL-5-HTP (15 mg/kg) also resulted in disappearance of the tremor. Thus, the combined administration of these drugs has a much more pronounced effect on the relief of the tremor than the administration of each drug alone.

TABLE 1. *Effect of separate and combined treatment with* DL-*DOPA*, DL-*5-HTP, and atropine on postural tremor in monkeys with mesencephalic lesions.*

Drug* (dose in mg/kg)	Pharmacological responses on the activities of the contralateral limbs†
None	Sustained hypokinesia and postural tremor
DL-DOPA, (30) or DL-5-HTP (25)	Tremor diminished or completely absent for 30 min–2 hr
DL-DOPA (15) or DL-5-HTP (15)	No effect
Atropine (0.18)	Slightly diminished tremor
DL-DOPA (15) + atropine (0.18)	Tremor absent for 30 min–2 hr
DL-5-HTP (15) + atropine (0.18)	Tremor absent for 30 min–2 hr

* Each drug was administered intravenously to two monkeys. The drugs were tested in each monkey three times.

† The tremor is described as diminished when the amplitude of the tremor was decreased and the tremor was absent for short periods of time (5–10 min).

In monkeys exhibiting hypokinesia but no resting tremor (group II), the administration of harmaline evoked a marked resting tremor of the extremities contralateral to the tegmental lesion (Table 2). The frequency was 4 to 6 cycles per seconds, and it resembled the tremor which spontaneously develops after a ventromedial tegmental lesion.

We investigated the effects of specific inhibitors of amine synthesis on tremor production in group II. As shown in Table 2, administration of α-methyl-*p*-tyrosine, a known inhibitor of tyrosine hydroxylase,[5] had no tremogenic effect. When *p*-chlorophenylalanine, an inhibitor of serotonin synthesis,[6] was administered for 11 days, a very fine resting tremor of low amplitude and 4 to 6 cycles per second appeared on the eighth day in the extremities contralateral to the tegmental lesion. It seems unlikely that the resting tremor developed spontaneously, since the administration of *p*-chlorophenylalanine was started six months after the lesion was placed.

To determine whether the action of harmaline is mediated by striatal amines, harmaline was given to a monkey pretreated with both inhibitors of amine synthesis. Production of tremor by harmaline was not abolished by lowering the amine levels with *p*-chlorophenylalanine and α-methyl-*p*-tyrosine (Table 2).

TABLE 2. *Effects of centrally acting drugs on harmaline-induced tremor in monkeys with mesencephalic lesions.*

Drug*	Pharmacological responses on the activities of the contralateral limbs
None	Sustained hypokinesia
Harmaline	Coarse tremor
MT	No effect
PCPA	Slight tremor (low amplitude)
Harmaline + MT + PCPA	Coarse tremor
5-HTP + harmaline	No tremor or markedly diminished tremor (tremor of the ipsilateral extremities occasionally observed)

Harmaline (5 mg/kg), DL-5-HTP (25 mg/kg), and MT (80 mg/kg) were injected intravenously. PCPA (80 mg/kg) was administered orally every day for a period of 11 days. DL-5-HTP was given 20 min prior to the administration of harmaline.

* MT, α-methyl-*p*-tyrosine; PCPA, *p*-chlorophenylalanine.

Thus, the action of harmaline does not appear to be mediated by striatal amines, but could be due to direct action on the receptors.

We also investigated whether the increase in brain serotonin levels affects tremor production by harmaline. As shown in Table 2, administration of 5-hydroxytryptophan protects the monkeys from tremors induced by harmaline. Since harmaline and serotonin are both indoles, it is conceivable that harmaline affects the functions of the central nervous system by interaction with serotonin receptors.

One possible explanation for the tremogenic action of harmaline in monkeys with mesencephalic lesions might be related to its property of a short-acting inhibitor of monoamine oxidase. However, other long-acting monoamine oxidase inhibitors did not produce this effect,[7] and the present data do not indicate that harmaline exhibits its tremogenic action via the biogenic amines. Possibly the storage of harmaline in the serotonergic neurons is impaired in the ipsilateral striatum in monkeys with mesencephalic lesions. Consequently, the concentration of harmaline might be increased at the receptors on the lesioned side, causing tremogenic action. The observation that DL-5-HTP antagonizes the harmaline-induced tremor indicates that this protective effect is likely to occur at the serotonin receptor sites. Thus, these results also demonstrate the role of serotonin in harmaline-induced tremor.

The results in monkeys are directly comparable to the neuropathological and neurochemical findings in human parkinsonism. The most consistent neuropathological finding in both instances is the degeneration of the melanin-containing nerve cells of the pars compacta of the substantia nigra. The extrapyramidal symptomatology of human parkinsonism is dominated by rigidity, akinesia, and tremor, while in monkeys with ventromedial lesions, hypokinesia and tremor (but not rigidity) develop on the extremities contralateral to the lesion side. The neurochemical findings obtained from postmortem Parkinson's patients have shown a depletion of dopamine and serotonin in the striatum,[8] and monkeys with mesencephalic lesions have also shown a depletion of striatal dopamine and serotonin.[1] Thus, in many aspects the extrapyramidal defects in these animals resemble the syndrome in patients first described by James Parkinson in 1817 and generally known as Parkinson's disease. The present findings

illustrate, at least in one primate species, an apparent role of a deficit of serotonin and dopamine in experimental parkinsonism. The synergistic effects of atropine and DOPA or atropine and 5-HTP on relief of tremor point to an imbalance between the cholinergic and adrenergic–serotonergic systems in parkinsonism. In view of the present treatment of Parkinson's patients with DOPA,[9, 10] the observed effects of the combined administration of DOPA or 5-HTP and atropine on tremor might be of considerable clinical significance. If the results obtained from the monkey could be extrapolated to humans, the combined treatment with DOPA and anticholinergic drugs should be more effective than the administration of each of these drugs alone.

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