The Effects of Ventrolateral Thalamic Lesions on Tremor and the Biosynthesis of Dopamine in Monkeys with Lesions in the Ventromedial Tegmentum*

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Dopamine, a catecholamine, is synthesized from the amino acid tyrosine by a series of enzymatic reactions, outlined in Fig. 1. Andén, et al.,1 using the fluorescent method, found dopamine in vesicular granules localized to a system of fine nerve fibers which can be traced from the substantia nigra to the caudate nucleus. Dopamine in the caudate is concentrated in nerve fiber terminals which seem to make intimate contact with neurons of the caudate nucleus. The distribution of dopamine in the brain shows an extremely high content in the striata, as compared to other neural structures, while norepinephrine is highest in the hypothalamus.4 The different distribution of dopamine and norepinephrine suggests that dopamine might have another function besides being the precursor of norepinephrine. When Hornykiewicz and his colleagues2,9,13 reported that the endogenous dopamine (3, 4-dihydroxyphenylethylamine) content of the caudate was extremely low or absent in patients with Parkinson's disease, the possibility of finding a chemical basis for the symptoms and signs of this disease became more realistic.

In the Rhesus monkey, Ward, et al., in 1948,20 Peterson, et al.,15 Carrea and Mettler,6 Carpenter,6 and Poirier16 were able to induce a postural tremor in the contralateral extremities by a lesion in the ventromedial tegmental area. Such a tegmental lesion resulting in tremor of the contralateral extremities was found, by Poirier and Sourkes in 1965,17 to be associated with an extremely low endogenous dopamine and a low norepinephrine content in the striatum ipsilateral to the lesion. These findings correlate well with Hornykiewicz's report of the chemical changes in the striata of man with parkinsonism. Poirier and Sourkes also found a marked loss of cells in the compacta layer of the substantia nigra ipsilateral to the tegmental lesions. They proposed that these cells exerted, through their efferent connections, a direct action on the dopamine level in the ipsilateral striatum. However, studies of the endogenous catecholamines in parkinsonian patients and in monkeys with unilateral medial tegmental lesions have not revealed the mechanism by which catecholamines are depleted in the striata.

To elucidate this problem, we have investigated the effect of tegmental lesions on the biosynthesis and storage of dopamine in the striatum. We have shown, in the African green monkeys with unilateral medial tegmental lesions, that the uptake of radioactive labelled dopamine is almost completely impaired in the striatum on the lesion side.10 From the work of Hassler and Reichert in 1954,12 Cooper and Bravo,7 and others, it has been shown that a lesion placed in the ventrolateral thalamic area in patients with parkinsonism can relieve the tremor. The question arises whether or not the dopamine level in the caudate increases, or returns to normal values, following such a tremor-relieving lesion. A relationship between this relief of tremor by a thalamic lesion and the dopamine level in the striatum could be best analyzed in monkeys in which the tremor was relieved by a thalamic lesion. We have, therefore, undertaken in monkeys with tegmental lesions a study in which we have correlated the relief of tremor by a second le-
Thalamic Lesions and Dopamine Biosynthesis

Fig. 1. Transformation of tyrosine to dopamine.

In the ventrolateral thalamic area with dopamine levels in the striatum.

Method

The African green monkey (Cercopithecus sabaeus), a species slightly smaller than the Rhesus, was used throughout our experiments. Prior to the placement of the tegmental lesion, the animal was anesthetized with intravenous alpha-chloralose (80 mg/kg body weight). For the placement of the thalamic lesion and for ventricular perfusion, pentobarbital sodium (20 to 30 mg/kg body weight) was administered intravenously. To determine the site of the tegmental lesion, an array of three electrodes, spaced 1.5 mm between the tips, was mounted parallel to the sagittal plane. Coordinates were 1.5 to 2 mm from the sagittal plane, 8 to 9 mm above the interaural line, and 8 to 7.5 mm anterior to the interaural line. The middle electrode was directed according to the coordinates. Electrical activity was monitored by a "Tektrotron" cathode ray. With Chloralose, it was possible to identify the red nucleus by its characteristic fast electrical activity of low voltage. This electrical recording identified the passage of the electrodes through the red nucleus to its ventral border, and, also, stimulation through these electrodes was carried out. The lesions were placed stereotaxically with a "Labtronics" instrument, Model C-4. It was found, as reported by Poirier,16 that the optimum site for placement of the lesion to produce a tremor of the contralateral extremities was indicated by a response, on electrical stimulation, of ipsilateral pupillary constriction and minimal eye movement.

Several weeks to several months after the appearance of tremor of the contralateral extremities produced by the tegmental lesion, a second lesion was placed, this time in the ventrolateral thalamic area ipsilateral to the tegmental lesion. Average coordinates for the thalamic lesion, H 9, F 10.5, L 6, were determined by modifying measurements from the Olszewski Atlas of the "Macaca Mulatta" (Fig. 2). At frequent intervals, the animals were observed and examined neurologically, with documentation of arrest of tremor by tremograms and movies.

Biochemical studies followed several
weeks to months after the thalamic lesion. The animals were anesthetized with intravenous pentobarbital, and intubated. Needle cannulae were then inserted into the right and left lateral ventricles, using stereotaxic guidance, and 25 μC of dopamine-H3 was injected into each lateral ventricle. Four hours prior to the intraventricular injection, pheniprazine, a monoamine oxidase inhibitor, was injected intraperitoneally (10 mg/kg body weight). The injected dopamine-H3 was allowed to equilibrate for 3 hours. The animal was then given more pentobarbital, and a bilateral craniotomy was performed. The chest was opened, and breathing maintained by a respirator. A large cannula was placed into the aorta or the left ventricle, and the right auricle was opened. Normal saline at 1° to 2°C was injected slowly, to perfuse the brain and to keep its temperature just above freezing. The dura was opened, and the brain removed from the skull. The brain was maintained at or below 0°C, and sectioned. The caudate, putamen, and other subcortical structures were dissected for chemical analysis. The sections through the lesion site were then fixed in 10% formalin for histological verification.

![Diagram of brain structures](image)

Fig. 2. Section modified from the Olzewski Atlas for the Macaca Mulatta (F = 10.5) to indicate the anatomical relations of the ventrolateral thalamic nucleus. AV: nucleus anterior ventralis, Caud: nucleus caudatus, Ci: capsula interna, For: fornix, Pall: nucleus pallidus, Ped: pes pedunculi, R: nucleus reticularis, VLo: nucleus ventralis lateralis oralis.

**Results**

*Observations and Histological Studies.* At 5 to 7 days after radiofrequency lesions were placed in the left medial thalamic areas (Figs. 3 and 4), the monkeys developed postural tremor (4 to 6 cycles/sec) of their contralateral extremities (Fig. 5). This tremor in the upper and lower extremities was intensified by excitement and disappeared on voluntary movement. Alternating contractions of the flexor and extensor muscle groups, in rhythmic manner, were easily discernible in the muscles of the arm and forearm. The tremor was usually more apparent in the distal than in the proximal muscles. There was a hypokinesia associated with the postural tremor. The extremity was usually held and moved in a semi-flexed position from the elbow, indicating that the animal was not unaware of it; that the position was deliberately maintained and that its infrequent use was also deliberate. When in use, the rate of its movement, once initiated, was similar to that of the opposite, normal extremity. In the involved extremity, as compared to the normal, the strength on gross testing was equal; the reflexes were equal or slightly hyporeactive. Additionally, ipsilateral to the thalamic lesion there was dilatation of the pupil and ptosis of the eyelid (Fig. 6), as described by others.16,17

Our histological studies of the lesions and interrupted pathways have been restricted to the lesion site, since other brain structures were removed for biochemical studies. The lesion site (Figs. 3 and 4) did involve the medial substantia nigra, the dorsomedial region of the cerebral peduncle, and an area adjacent to the midline encroaching on the ventral aspect of the red nucleus.

At 3, 4, and 14 months, respectively, after left thalamic lesions, additional lesions were placed in each left ventrolateral thalamic area (Figs. 3 and 4). The resting tremor (Fig. 5) was immediately relieved in the three monkeys, without gross weakness. One monkey exhibited slight weakness which disappeared after several days. The tremor has remained absent in one monkey 20 months after the thalamic lesion. In the other two, tremor had not returned during the respective 2-month and 4-month periods prior to the animals' sacrifice. There was no change in the behaviour of the three monkeys after
undergoing tegmental and thalamic lesions.

The thalamic lesions were in the ventrolateral area and encroached to varying extents on the internal capsule (Figs. 3 and 4). The lesion sites in the ventrolateral thalamic area varied from animal to animal; however, because of their large size, they were still effective in relieving the spontaneous resting tremor produced by the tegmental lesion.

Biochemical Studies: Exogenous and Endogenous Dopamine Concentrations in the Caudate Nuclei. In monkeys with medial tegmental lesions and resting tremor, the concentrations of endogenous dopamine and of the intraventricularly injected radioactive-labelled dopamine were extremely low on the lesion side as compared to the intact side (Table 1).

In monkeys with both tegmental and ventrolateral thalamic lesions, the concentrations of endogenous dopamine and the intraventricularly injected radioactive-labelled
Fig. 4. Monkey No. 94. Top: The left medial tegmental lesion (arrow) which resulted in postural tremor of the contralateral extremities. Luxol fast blue—PAS stain, $\times 5$. Bottom: The lesion in the left ventrolateral thalamic area which relieved the postural tremor. Luxol fast blue—PAS stain, $\times 15$. 
After Lesion in Left Tegmental Area

Right Upper Limb

Left Upper Limb

After Lesion in Left Ventrolateral Thalamic Area

Right Upper Limb

Left Upper Limb 1 Sec.

Fig. 5. Monkey No. 94. Tremogram of the right and left upper extremities. Note the frequency of the postural tremor of the right upper limb at rate of 4 to 6 cycles/sec (after left tectmental lesion). Also, note the relief of the postural tremor of the right upper limb after lesion in the left ventrolateral thalamic area.

dopamine were as low on the lesion side as in the monkeys with only tectmental lesions (Table 1). Thus, the thalamic lesion, although it relieved the tremor, did not alter the endogenous or exogenous dopamine concentration in the caudate on the lesion side.

Discussion

In the African green monkey, the site of the medial tectmental lesion which produces contralateral resting tremor corresponds well with the site reported by Poirier, et al., in the Rhesus monkey. The reports from different laboratories indicate that the duration of postural tremors resulting from medial tectmental lesions in monkeys varies. In the African green monkey, however, intensity and amplitude of tremor have remained unabated for a period of 3 years after the lesion. The tremor which had been produced by a tectmental lesion was immediately relieved, without permanent associated weakness, by a lesion in the ventrolateral thalamic area. Moreover, no overt alteration in behavior was exhibited from the preoperative state, which agrees with the reports of Poirier, et al. in Rhesus monkeys. Schreiner, et al., however, have stated that the Rhesus monkey became quite docile after a medial tectmental lesion, and that the resting tremor was relieved by a lesion placed in the ipsilateral globus pallidus. It is not known in our monkeys if the lesion in the ventrolateral thalamic area will result in permanent relief of tremor; however, there has been no reappearance of tremor 20 months after the placement of the thalamic lesion.

The results of our studies have shown that the relief of tremor in monkeys by a ventrolateral thalamic lesion is not associated with restoration of normal dopamine concentrations in the ipsilateral striatum. It is note-
It is worthy that Bertler\(^3\) found that destruction of the thalamus in the rabbit does not alter the endogenous dopamine in the striatum. The use of monkeys with thalamic lesions as "models" for the investigation of Parkinson symptomatology has been strengthened by the results of the present studies. Parkinson patients and "model monkeys" exhibit similar neurological findings which are associated with reduced dopamine levels in the striata.\(^10,11,13,17\) The relief of the tremor by a lesion in the ventrolateral thalamic area is effective in monkeys as well as in Parkinson patients. The findings in "model monkeys" that dopamine levels of the striata were not restored to normal values after thalamic lesions suggest that in Parkinson patients, following thalamotomy and relief of tremor, the dopamine concentrations of the striata are probably similarly deficient. These results suggest that Dopa might be of therapeutic value in Parkinson patients with persistent symptoms after thalamotomy, and Umbach and Baumann\(^19\) have reported beneficial effects from Dopa administration in such patients.

The part played by dopamine in the etiology of tremor and rigidity in Parkinson patients is still unresolved. It has been reported\(^8\) that patients with Parkinson's disease manifest a decrease of rigidity after large oral doses of Dopa, a precursor of dopamine, but that there is minimal effect, if any, upon the associated tremor unless very large doses are administered. This would seem to indicate that dopamine may be related to the mechanism of rigidity.

It remains to be investigated whether the thalamic lesion affects other biogenic amines, such as serotonin and acetylcholine, and whether a new ratio of the amine concentrations is established by the placement of the thalamic lesion. It may follow that the ratio of various amines in the striatal structures, rather than the depletion of one or another or several, is the important correlation with tremor and rigidity.

**Summary**

To elucidate the association of tremor production and dopamine deficiency in the striatum of monkeys with unilateral ventromedial or thalamic lesions, a second lesion was made in the ventrolateral thalamic area. The thalamic lesion relieved the resting tremor in the contralateral extremities produced by the ventromedial thalamic lesion, but did not restore the dopamine content of the ipsilateral striatum to normal. Thus, the abolition of tremor by the thalamic lesion is not associated with dopamine levels in the ipsilateral striatum.

**References**


