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,8 Carpenter, 5 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-

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sion 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 “Tektronix” 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 stereotactically with a “Labtronics” instrument, Model C-4. It was found, as reported by Poirier,\textsuperscript{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).\textsuperscript{14} At frequent intervals, the animals were observed and examined neurologically, with documentation of arrest of tremor by tremograms and movies.

Biochemical studies followed several