Increase in Noradrenaline-synthesizing Enzyme Activity in Medulla Oblongata in Parkinson's Disease*

N. Kopp 1, L. Denoroy 2, M. Tommasi 1, N. Gay 1, G. Chazot 3, and B. Renaud 1

1 Laboratoire d'Anatomie Pathologique et Neuropathologie, Faculté de Médecine Alexis Carrel, Rue Guillaume Paradis, F-69372 Lyon Cédex 2, France
2 ERA CNRS 894 and Laboratoire de Neuropharmacologie, Faculté de Pharmacie, Lyon, France
3 Unité Neurométabolique (Pr. Schott), Hôpital Neurologique, B.P. Lyon Montchat, F-69394 Lyon Cédex 3, France

Summary. Dopamine beta hydroxylase (DBH), the noradrenaline-synthesizing enzyme, and phenylethanolamine-N-methyltransferase (PNMT), the adrenaline-synthesizing enzyme, were assayed in 18 areas of brain stem in eight cases of parkinsonian syndromes and of four age- and postmortem delay-matched controls. Dissection was performed by the “punch” technique and enzyme activities assayed by radiometric methods. No significant change was found for PNMT activity. DBH activity was significantly increased in the A2-C2 area of the medulla oblongata (including the nucleus tractus solitarius) in the cases of Parkinson’s disease.

The A2-C2 area is known to be implicated in the control of blood pressure in rats. These findings are discussed in relation to orthostatic hypotension and the influence of L-dopa therapy.

Key words: Parkinson’s disease — Catecholamine — Enzyme — Medulla — Hypotension

Introduction

Orthostatic hypotension, sleep disorders, and depression are frequently encountered in the course of Parkinson’s disease (PD) and point to noradrenaline and/or adrenaline metabolism disorders, in addition to the degeneration of the nigro-striatal dopaminergic pathway. Indeed, the noradrenaline (NA) concentration has been found diffusely decreased in brains of patients with PD (Farley and Hornykiewicz 1976; Riederer et al. 1977) except in the hypothalamus (Agid 1981, pers. commun.)

Apart from the work of Nagatsu et al. (1977), no detailed study has been undertaken in this syndrome, of the activity of the NA-synthesizing enzyme, dopamine-beta-hydroxylase (DBH), and of the adrenaline-synthesizing enzyme, phenylethanolamine N-methyltransferase (PNMT), which are considered as functional markers of noradrenergic and adrenergic systems, respectively. The activities of DBH and PNMT were assayed, therefore, in brain areas implicated in different patients with parkinsonian syndromes and, particularly in medullary nuclei, considered as cardiovascular centers, and where neuropathologic lesions are a classical finding in PD (Escourolle et al. 1971).

Material and Methods

Human postmortem samples were obtained from (a) eight patients with PD: seven males, one female; mean age (m.a.) = 69.7; postmortem delay (p.m.d.) = 13 h. All had been treated with dopa; (b) two patients with Adams-Van-Bogaert-Van der Eeken's striato-nigral degeneration (SND). Case 1: male, aged 78 with p.m.d. = 5; case 2: female, aged 56 with p.m.d. = 16 h; (c) two female patients with Steele-Richardson-Olszewski's progressive supranuclear palsy (PSP). Case 1: aged 64 with p.m.d. = 9.5; case 2: aged 74 with p.m.d. of less than 10 h; (d) two female patients with Shy-Drager's idiopathic orthostatic hypotension (IOH). Case 1: aged 87 with p.m.d. = 24; case 2: aged 55 with p.m.d. of less than 36 h; and (e) four “control” patients without known neurologic, psychiatric, or blood pressure disorder: two males and two females: m.a. = 68.7; p.m.d. = 17.5 h; causes of death: myocardial infarction, acute heart failure, bronchial carcinoma, and renal insufficiency.

Brain nuclei were dissected from frozen slices as previously reported (Kopp et al. 1979, 1980) using the atlases of Olszewski and Baxter (1954) and of Roberts and Hanaway (1970) as references (Figs. 1, 2).

The samples were homogenized in 40 volumes of 20mM phosphate buffer, pH = 6.0, containing 0.2% Triton × 100 (v/v). After centrifugation (9,000g, 15 min), the supernatants were used for biochemical assays. The DBH activity was measured on 10μl supernatant according to a modification (Kopp et al. 1980) of the method of Molinoff et al. (1971) and in the presence of a final copper concentration of 4 × 10⁻⁵ M. The PNMT activity was measured on...
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DBH Activity. The DBH activity in brain stem areas of the control and parkinsonian brains is shown in Table 1.

The most striking modification in PD brains, as compared to controls, was an elevation of DBH activity in the A2-C2 area of the medulla (including the nuclei of the 12th nerve, dorsal vagus, and tractus solitarius). This significant increase was found at the caudal (+65%) and intermediate level (+86%). No correlation could be established between this increase in DBH activity and the duration of the disease, the level of blood pressure, or the dose of dopa.

In a case of IOH, the DBH activity was also found increased in the A2-C2 area, but, in addition decreased in the rostral part of the lateral reticular nucleus.

PNMT Activity. As shown in Table 2, the PNMT activity was not significantly modified in PD. Nevertheless, in the caudal part of the C2 area, the PNMT activity was moderately decreased in PD, SND, and IOH. In addition, the PNMT activity was slightly increased in the intermediate part of the “A2-C2” area in PD.

In the substantia perforata posterior (part of the tegmento-ventral area), the PNMT was found decreased, though not significantly, in PD. This modification seems to be larger in IOH.

Discussion

Anatomic Distribution of DBH and PNMT Activity

The distribution of DBH activity in discrete areas of the brain stem, and especially in the medulla oblongata, had previously only been studied in infants (Kopp et al. 1980) but not in adults. In the present work, the distribution of DBH activity in the controls is in agreement with earlier reports using a different procedure of dissection (Vogel et al. 1969; Nagatsu et al. 1977; Mackay et al. 1978), showing a low activity in the basal ganglia. The order of magnitude of the difference between area with the highest activity (locus ceruleus) and the area with the lowest activity was about the same as that found by Nagatsu et al. (1977). Nevertheless, we found only traces of DBH activity in the substantia nigra, whereas Nagatsu et al. (1977) found a moderate activity and MacKay et al. (1978) a notable activity; we have no explanation for these discrepancies.

1 The name “A2-C2 area” is used here with reference to our previous work (Kopp et al. 1979); it indicates two adjacent punches. C2, actually, is the dorsal group of adrenergic neurons in the rat according to Hökfelt et al. (1974).