Abnormal regulation of prolactin release in idiopathic Parkinson's disease

N F LAWTON AND J MACDERMOT

From the University Department of Clinical Neurology and the Department of Clinical Pathology, The National Hospital for Nervous Diseases, Queen Square, London

SUMMARY Levodopa with carbidopa suppressed prolactin release induced by thyrotrophin releasing hormone less effectively in patients with idiopathic Parkinson's disease than in normal subjects. This finding supports the view that the biochemical defect in idiopathic Parkinson's disease extends to the hypothalamus and is not confined to the basal ganglia. Aetiological considerations in Parkinson's disease should encompass a widespread disorder of neurotransmission whose extent merits further investigation.

The therapeutic response to levodopa in Parkinson's disease is associated with dopamine deficiency in the nigro-striatal system.¹ A separate dopaminergic system with neurones in the hypothalamus but axons terminating in the median eminence² is closely concerned in the regulation of prolactin release. The purpose of this study was to determine whether the disorder of neurotransmission in idiopathic Parkinson's disease extends to this hypothalamic system or is confined to the basal ganglia. We now report evidence of hypothalamic involvement in untreated patients, shown by the following technique.

Dopamine is a potent inhibitor of prolactin release. Plasma levels are reduced by levodopa and by dopamine agonist drugs in both normal subjects and patients with hyperprolactinaemia.³⁻⁵ In contrast, the thyrotrophin releasing hormone (TRH) stimulates prolactin release and Refetoff *et al*⁶ have shown that this response also can be inhibited by pretreatment with levodopa. We therefore stimulated the release of prolactin by TRH in Parkinsonian patients and normal subjects, and have examined the effect of pretreatment with levodopa upon this response. By combining levodopa with a peripheral

decarboxylase inhibitor we have ensured that inhibition of prolactin release involved intracerebral decarboxylation of levodopa to dopamine.

Patients and methods

Seven patients with idiopathic Parkinson's disease and seven normal subjects were investigated with their informed consent. Each group comprised four males and three females, ages ranging from 32 to 72 years in the control group (mean 49.4 years) and from 37 to 68 years in the patients (mean 55.7 years). None of the patients had been treated with dopaminergic or anticholinergic drugs. The optimum pre-treatment dose of levodopa combined with a peripheral decarboxylase inhibitor (Sinemet, Hoechst) was determined by measuring the dose-response effect of Sinemet on TRH-induced prolactin release. Figure 1 shows the inhibitory effect of pretreatment with single doses on prolactin release induced by TRH 200 µg intravenously in a normal subject. The dose of levodopa 62.5 mg with carbidopa 6.25 mg was chosen in order to achieve partial suppression of the normal response. This preliminary study also refuted the report by Woolf *et al*⁷ that levodopa is incapable of inhibiting prolactin release when combined with a peripheral decarboxylase inhibitor.

Each patient and normal subject received TRH 200 µg intravenously on two occasions with an interval of at least three days. In experiment 1 serum prolactin was measured before and 20 minutes after TRH to determine the normal response. In experiment 2 the procedure was repeated following oral

Address for reprint requests: Dr NF Lawton, Wessex Neurological Centre, Southampton University Hospitals, Southampton SO9 4XY.

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Fig 1 Inhibition of the prolactin response to TRH in a normal subject by graded doses of Sinemet given orally 90 min prior to TRH injection.

Sinemet given 90 minutes prior to TRH injections. Stress reactions, such as vomiting, did not occur. Prolactin radioimmunoassay was carried out in a single batch by the method of Sinha *et al*⁸, normal basal values being 2.9–12.4 ng/ml in males and 6.1–19.5 ng/ml in females. The unpaired Student's *t* test was used for statistical analysis.

Results

The results of prolactin assay are detailed in the table. Basal levels did not differ significantly in controls and patients in either experiment. Pretreatment with Sinemet consistently lowered basal prolactin by 0.5 to 4.6 ng/ml with no significant differ between controls and patients in experiment prolactin response to TRH injection showed the expected variation in magnitude between individuals, but the increment (Δ Prl) did not differ between controls and patients in experiment 1 (no pretreatment with Sinemet). In order to measure the degree of inhibition achieved by this pretreatment, the ratio of prolactin increments Δ 1 and Δ 2 Prl) in the two experiments has been expressed as a percentage for each individual (fig 2). The mean prolactin increment after TRH was reduced by $69.7 \pm 20.8\%$ (SD) in controls and by only $26.5 \pm 11.43\%$ (SD) in the patients. This difference is highly significant (*t* test, $p < 0.005$).

Discussion

The present findings demonstrate the inability of levodopa combined with a peripheral decarboxylase inhibitor to achieve normal suppression of TRH-induced prolactin release in idiopathic Parkinson's disease. If this observation is to be interpreted as a reflection of altered dopaminergic

CONTROLS			T R H			SINEMET + T R H			
No.	Age	Sex	0'	+20'	Δ_1	-90'	0'	+20'	Δ_2
1	32	M	8.0	23.7	15.7	4.7	3.7	5.6	1.9
2	34	M	3.5	11.5	8.0	3.4	2.8	3.8	1.0
3	72	F	12.1	47.6	35.5	—	3.4	8.6	5.2
4	65	F	18.1	54.5	36.4	—	8.1	20.0	11.9
5	32	M	6.0	30.0	24.0	5.5	3.3	11.5	8.2
6	63	M	10.9	34.0	23.1	6.8	5.6	18.0	12.4
7	48	F	7.5	31.0	23.5	7.5	5.2	20.0	14.8
PATIENTS			9.4 ± 4.8			7.9 ± 5.4			
1	71	F	6.6	33.5	26.9	5.2	3.7	19.7	16.0
2	40	M	6.0	14.0	8.0	4.5	3.4	8.7	5.3
3	54	M	8.2	27.0	18.8	6.3	5.6	18.5	12.9
4	62	F	17.0	35.5	18.5	4.3	3.8	17.0	13.2
5	68	M	10.0	19.5	9.5	9.6	6.5	13.7	7.2
6	37	F	8.8	44.0	35.2	9.8	5.2	32.5	27.3
7	58	M	5.1	16.2	11.1	9.6	5.4	16.0	10.6
			8.8 ± 4.0			13.2 ± 7.2			

Table Basal and TRH induced serum prolactin (ng/ml). Δ_1 and Δ_2 represent increments in prolactin induced by TRH in experiments 1 and 2. Mean levels $\pm$ 1 S.D.

Fig 2 Inhibition of the prolactin response to TRH by pretreatment with Sinemet.

transmission in hypothalamic-hypophyseal pathways, it is pertinent to consider the mechanism by which Sinemet inhibits prolactin release.

Dopamine has a direct effect on the pituitary^{9 10} but inhibition of prolactin release could be caused either by intracerebral or extracerebral conversion of levodopa to dopamine. If extracerebral decarboxylation were inhibited, dopamine generated by intracerebral decarboxylase could reach the pituitary via the hypophyseal-portal system which is the physiological pathway for dopamine in its role as a prolactin inhibiting factor. We have previously reported potentiation of levodopa inhibition of prolactin release by a peripheral decarboxylase inhibitor in normal subjects with the dose of Sinemet used in this study.¹¹ This observation led us to suggest that intracerebral decarboxylation of levodopa to dopamine played an important part in the mechanism of the response. The opposite conclusion, implicating extracerebral decarboxylase, was drawn by Brown *et al*¹² who reported a small rise in basal prolactin after administration of a peripheral decarboxylase inhibitor to normal subjects. The authors attributed this effect to the presence of dopaminergic terminals in the median eminence which lies outside the blood brain barrier. However, the reported effect of peripheral decarboxylase inhibition occurred only after a week of treatment and may have pharmacological rather than

physiological significance. It is also known that dopamine is present within the hypothalamus and thus within the blood brain barrier where decarboxylation would depend upon intracerebral enzyme.² The doses of levodopa and peripheral decarboxylase inhibitor which we chose are small but certainly affect intracerebral pathways. For example, one patient in the study developed transient involuntary movements and could not tolerate long-term treatment with Sinemet. Indeed clinical experience of patients sensitive to levodopa with a peripheral decarboxylase inhibitor has led to the introduction of a comparable therapeutic dose (Madopar 62.5 mg Roche).

The question of intracerebral versus extracerebral decarboxylation of levodopa to dopamine may only be finally resolved by a reliable method for plasma dopamine assay. On the available evidence, however, we suggest that impaired inhibition of prolactin release results from inadequate intracerebral decarboxylation of levodopa. This interpretation is supported by the post-mortem findings of Lloyd and Hornykiewicz¹³ who reported diminished activity of dopa decarboxylase in the hypothalamus of patients with Parkinson's disease. The decrease was less pronounced than in the putamen and caudate nuclei, but these authors predicted that the striatum was not the only site of the pharmacological effects of levodopa. This view is supported by Rinne *et al*¹⁴ who noted post-mortem deficiencies of dopamine and homovanillic acid in the hypothalamus of Parkinsonian patients.

The clinical effects of striatal dopamine deficiency clearly overshadow the importance of hypothalamic involvement in Parkinson's disease. Ultimately, however, a deficiency of hypothalamic dopamine would cause hyperprolactinaemia accompanied by impotence in males and by amenorrhoea in females.¹⁵ Our patients did not have advanced Parkinson's disease, but early reports of therapy with levodopa noted an alteration in sexual function. Rinne¹⁶ noted a transient increase of libido in 20% of patients, and the occurrence of post-menopausal bleeding in seven females. In patients with advanced Parkinson's disease a raised serum prolactin might forewarn of such side effects prior to treatment with levodopa.

Finally, it should be remembered that altered dopaminergic transmission outside the striatum does not necessarily imply a primary metabolic cause for idiopathic Parkinson's disease. Hypothalamic disturbances are common in post-encephalitic disease, presumably due to wide-

spread viral damage. Further work is necessary to determine the extent of impaired dopamine metabolism in idiopathic Parkinson's disease.

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