PROTEIN INTAKE AND TREATMENT OF PARKINSON'S DISEASE WITH LEVODOPA

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Abstract We studied the influence of protein ingestion on the therapeutic efficacy and metabolic effects of levodopa in Parkinson's disease. Among eight patients, differing in symptomatic control, neurologic scores (normal 0, maximal 100) on 2 g of protein per kilogram of body weight were, at 8 a.m., 27.8 ± 2.1 (mean ± S.E.M.) and at 3 p.m., 46.7 ± 2.6 ($p < 0.001$). On 10 g of protein per day scores were 24.6 ± 2.1 at 8 a.m. and 24.1 ± 2.7 at 3 p.m. In seven patients maintained on 0.5 g of protein per kilogram of body weight per day for two months to one year, levodopa requirements diminished progressively. Measurement of growth hormone in five patients off levodopa showed low constant levels without the normal fluctuations. Near normal patterns were found in six patients on levodopa, but tended to flatten out in six patients also taking a high protein diet. Although growth hormone affects calcium metabolism, hormone levels and total body calcium showed no correlation in 15 patients taking levodopa. Our findings suggest that a low protein diet benefits patients with Parkinson's disease and with moderate neurologic instability. (N Engl J Med 292:181-184, 1975)

IN some patients treatment of Parkinson's disease with levodopa can have at least two types of late side effects.[1] A direct cerebral effect of the drug is the emergence of involuntary movements,[2] whereas the episodic loss of symptomatic control ("off-on" phenomenon) may be due to diminished entrance of levodopa into the brain. Responsiveness of the brain is preserved during the "off-on" phenomenon, which can be aborted by injection of apomorphine, a centrally active amine.[3,4]

The present study was started because in some of our patients consumption of a high protein meal was reported to provoke the "off-on" phenomenon.[5] This reaction appeared compatible with interception of the amino acid levodopa in peripheral tissues, perhaps owing to competition with alimentary amino acids. The possibility of this explanation was strengthened when the "off-on" phenomenon was diminished by restriction of protein intake in some patients receiving levodopa.*

Late metabolic effects of levodopa treatment but not as yet linked to the control of Parkinson's disease are those attributed to the release of growth hormone.[6] In fasting normal subjects or patients with Parkinson's disease, Boyd et al. found that levodopa raised the serum growth hormone level through hypothalamic mechanisms.[7] It seemed pertinent for us to study this cerebral effect in nonfasting patients, for we had found[8] that pharmacologic doses of this hormone injected into mice promoted, potentiated, and prolonged all cerebral effects of levodopa, suggesting that the hormone released during treatment might have similar effects.[9] Serum growth hormone levels were therefore investigated during dietary modification of symptomatic control.

Finally, Sirtori et al. had warned that levodopa might eventually induce acromegaly because of excessive growth hormone release.[6] Although this prediction has been challenged,[10-12] growth hormone can increase bone calcium, a point of interest because Parkinson's disease is often associated with osteoporosis. The relation of total body calcium and of serum growth hormone levels, therefore, was also studied.

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*The effects of protein restriction were demonstrated by Rosemary Gellene, M.D., while she was at Brookhaven.

MATERIALS AND METHODS

Patients

Four groups of patients were studied.

Group 1 consisted of eight patients with idiopathic Parkinson's disease who had been treated with levodopa continuously for at least 30 months under our supervision and who participated in both phases of the evaluation of the five different diets discussed below. Their neurologic status varied between stability and almost total instability of symptomatic control. All were studied as inpatients in a metabolic ward, with toxicity monitored periodically,[1,2] body weight recorded daily, and total plasma protein measured weekly.

Group 2 consisted of seven patients, five of whom were also members of Group 1, who were kept on a restricted protein diet (0.5 g per kilogram of body weight) for two months to one year. Four were inpatients during two months, and three outpatients during one year.

Group 3 consisted of 17 patients in whom serum levels of growth hormone were followed for eight to 24 hours. Five were studied for 24 hours after being off levodopa for seven days (eight tests), and six for 24 hours while on optimal amounts of levodopa. Another six patients on optimal amounts of levodopa were studied for eight hours (8 a.m. to 4 p.m.) on the third day of having received protein intakes of either 1 or 2 g per kilogram per day.

Group 4 consisted of 15 patients on levodopa in whom total-body calcium was determined as ^{49}Ca after total-body neutron activation.[13] As a correction for lean total-body mass, total body potassium was determined by total-body counting of ^{40}K.[13] On the same day, serum growth hormone levels were measured for eight hours.

Dietary Regimens

The composition of the five diets given to the patients in Group 1 and their acceptance are detailed elsewhere.[14] All five diets had an identical content of total calories and fat. The actual intake of total calories, protein, fat and carbohydrate was assessed from tables[14] by weighing of each meal before and after the patient ate. The protein content is presented in Table 1.

Drugs

Group 1 received levodopa (Nutritional Biochemicals Corporation) administered either in six identical doses by itself (1.8 to 8.0 g per day), or, in a separate phase, with MK-486 (α-methyldopa hydrazine, Merck Sharp and Dohme) (150 mg per day),[15]

Table 1. Periods of Administration of the Different Diets Tested.*

Daily Protein Intake†	Period of Administration (Days)			
	Group 1	Group 2	Group 3	Group 4
1 g/kg	10	—	10	1
1 g/kg (8)‡	6	—	—	—
10 g	4	—	—	—
2 g/kg	4	—	3	—
0.5 g/kg (8)	7	—	—	—
0.5 g/kg (3)§	—	¶	—	—

*All tests on Group 1 were conducted on both levodopa given alone & MK-486 + levodopa; Group 4 received regular hospital diets at time of neutron-activation analysis.

†All isocaloric meals in a given dietary regimen contained consistent proportions of protein, carbohydrate & fat.

‡Figures in parentheses represent no. of meals.

§3 g of protein at breakfast, 3 g at lunch & rest at dinner.

¶2 mo - 1 yr.

and with pyridoxine (300 mg per day).* Six of seven patients in Group 2 received levodopa with MK-486.

Neurologic Evaluation

The symptoms of Parkinson's disease were scored every day[16] one hour after levodopa during maximal and minimal symptomatic control (8 a.m. and 3 p.m.) in Group 1, daily in the inpatients and at each visit of the outpatients of Group 2, and one hour after levodopa in Group 3. The means and standard errors of the neurologic scores were computed separately for each morning and afternoon in each patient for each dietary phase. The statistical significance of the differences among phases was determined by Student's t-test, for all permutations of the dietary regimens, by a program (code word HIER) in a CDC 6600 computer. The statistical similarities of scores obtained early versus late during restricted protein intake were shown by use of the F-test.[17]

Chemical Analyses

The 24-hour urinary outputs of dopa, dopamine and homovanillic acid were measured on the third day of each dietary regimen for each patient in Group 1.[18,19] The mean and standard error of the percentage of levodopa excreted as dopa, dopamine and homovanillic acid was computed for all patients, and the statistical significance of the differences among the phases of the study was calculated for each patient by Student's t-test.

Measurements of Growth Hormone

During the test period, patients on the regimens indicated above remained in their rooms, and 3 ml of blood was drawn from a venous catheter every 30 minutes either for 24 hours or for eight hours (8 a.m. to 4 p.m.). During the night a slow intravenous drip was attached, and the blood was sampled through a three-way stopcock to avoid waking the patients. Electroencephalographic and myographic tracings indicative of sleep could not be obtained, but general appearance, respiratory rate and snoring were closely observed. The blood was immediately refrigerated. After separation of the cells, the serum was frozen in liquid nitrogen and stored at −30°C until analyzed. The hormone was analyzed by radioimmunoassay (Abbott Laboratories), and the results, expressed as nanograms per milliliter, were plotted against time. Each plot was examined visually (Fig. 1 and 2). Then, the mean concentration of hormone was computed in all plots per eight hours both before and after subtraction of the basal value; similar calculations were used for the 24-hour tests. These computations yielded the mean total concentration of the hormone and the mean rise in its concentration. The basal value was the mean of the 10 lowest values in each 24-hour period and of the lowest values in each eight-hour period.

*The dietary regimens in Group 1 were repeated as indicated in Table 1, but with the patients receiving MK-486 plus levodopa, thus diminishing the optimal dose of levodopa by approximately 75%. The data obtained during this second phase were omitted for brevity's sake but are available on request.

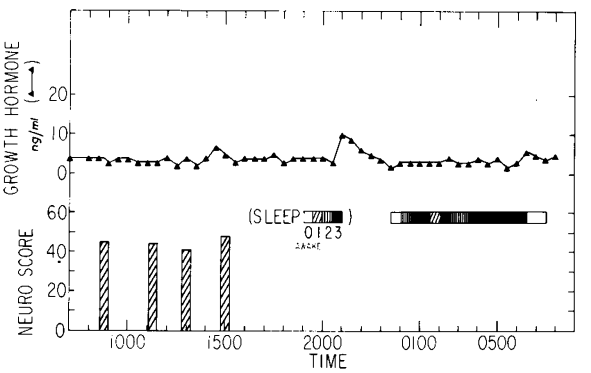

Figure 1. Twenty-four-Hour Serum Levels of Growth Hormone in an Untreated Patient with Parkinson's Disease.

Growth hormone levels are low, with minimal rises, mostly in the evening. Sleep is scored as 0 = awake, and 3 = deep sleep. Neuroscores weigh symptoms and signs of Parkinson's disease (maximal disability = 100, and normality status = 0).

Analysis for growth hormone of 140 duplicate samples from the period from 8 a.m. to 4 p.m. was done also by the double-antibody technic.† Comparison of the two methods yielded a coefficient of correlation of 0.85 for all the data ($p < 0.01$), but for the 93 samples containing 3 ng per milliliter or less, the correlation was not significant.

Results

The results obtained for Group 1 are summarized in Table 2. Comparison of the neurologic scores in the morning versus those in the afternoon (mean for all eight patients) showed that the diet supplying the lowest protein intake tended to even out the differences in symptomatic control between morning and afternoon that were present with the "average" protein intake of 1.0 g per kilogram per day, whereas the highest protein intake exaggerated these differences. The diminution of therapeutic control appeared one hour after high protein luncheons and lasted throughout the afternoon. The only result of giving the "average" diet in eight meals a day rather than the usual three was some lowering of the statistical significance of the difference between the morning and the afternoon scores.‡

Analysis of individual records showed that of the five patients with greater neurologic instability, four gained their greatest stability on restricted protein intakes. Although symptomatic instability was reduced in all these patients, the improvement was not impressive in the two patients who vacillated between dyskinesia and almost total loss of symptomatic control. The two patients whose status was stable were refractory to dietary changes, and so was one with minimal instability.

The output of homovanillic acid changed significantly

†We are indebted to Harold E. Lebovitz, M.D., for the analyses of duplicate samples by the double-antibody technic.

‡When the patients in Group 1 received MK-486 plus levodopa, the differences between morning and afternoon were lessened,[15] but a stabilizing effect of protein restriction still remained in evidence.

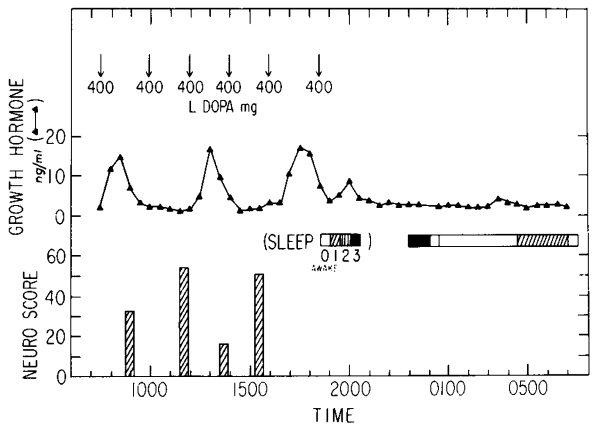

Figure 2. Twenty-four-Hour Serum Levels of Growth Hormone in a Patient with Parkinson's Disease Treated with Levodopa (2.4 G per Day).

Rises in concentration follow three of the six doses. The patient exhibits instability of symptomatic control, as shown by the neurologic scores.

during experiments in Group 1. While the patients were being given protein at the rate of 10 g per day the mean per cent and standard error of administered levodopa recovered as homovanillic acid was 22 ± 2 per cent as opposed to 31.4 ± 3 per cent when they were being given protein at 2.0 g per kilogram per day ($p < 0.03$). Altering the diet did not affect the output of dopa and dopamine. The serum proteins did not change significantly during either the short-term studies or the more extended studies on low protein intake (Group 2) except for one patient whose serum protein levels had a mean and standard error of 6.88 ±0.08 g per 100 ml on 1 g of protein per kilogram per day versus 6.50 ± 0.04 g per 100 ml on 0.5 g of protein per kilogram per day ($p < 0.001$). The albumin-globulin ratio did not change significantly in any of the patients.

Growth Hormone

The patients off levodopa for one week showed almost constant levels of growth hormone with a few minor rises mostly at night (Fig. 1). In the treated patients several of the doses of levodopa were followed 30 to 40 minutes later by 10-fold or higher rises of serum growth hormone lasting between one and 1.5 hours (Fig. 2).

The patients off medications were shown by the Abbott radioimmunoassay (Table 3) to have a lower mean serum concentration of growth hormone during eight hours than those on levodopa. The differences became statistically significant when the double-antibody technic was used. Over 24 hours, mean total growth hormone concentrations measured with the Abbott immunoassay were 4.19 ± 0.54 ng per milliliter in patients off drugs and 4.65 ± 0.52 ng per milliliter in those receiving levodopa ($p > 0.5$). Mean concentrations due to net rises were 1.33 ±0.15 and 2.88 ±0.48 ng per milliliter, respectively ($p < 0.01$).

The six patients who received levodopa in optimal amounts had mean serum concentration of growth hormone significantly higher on the diet containing 1 g per kilogram as opposed to the diet containing 2 g per kilogram per day of protein (Table 4).

Correlations between total-body ^{49}Ca and mean concentrations of growth hormone between 8 a.m. and 4 p.m. were not significant, even after we expressed the total-body calcium "per unit of body surface" or as the ratio of total-body calcium-to-potassium ratio (coefficient of correlation, 0.09).

Since the study had not shown contraindications for long-term reduction of protein intake, five patients with moderate and two with marked neurologic instability were maintained for two months to one year on 0.5 g per kilogram per day of protein in three meals (Table 1), with 3 g of protein given at breakfast, 3 g at lunch, and the remainder at dinner. Improvement of stability was maintained in the five patients with moderate instability as determined by application of the F-test to their neurologic scores.[17] Of those with marked instability, one derived no benefit after two months on this diet, although the levodopa dosage had been reduced by 20 per cent because of increasing dyskinesia. The other was kept for one year on levodopa, and this dietary regimen, although not fully satisfactory, was optimal for her and permitted reduction of the levodopa dosage by 35 per cent. Of the five patients with moderate instability, the three kept on the reduced protein intake for two months required reduction of their levodopa doses by 15 to 42 per cent because of increased dyskinesia. The other two, observed for one year, tolerated the diet well; their neurologic status remained markedly more stable, and they required reduction of levodopa dosage by at most 24 per cent. Moderate weight reduction was observed only in the patient mentioned above as having shown a minor but statistically significant reduction in total plasma protein.

Table 2. Mean and Standard Error of Neurologic Scores in Group I Taken One Hour after Levodopa throughout the Test Period Indicated.*

Daily Protein Intake	8 AM		3 PM	
	Score	P value	Score	P value
1 g/kg	23.4 ± 1.7		33.5 ± 2.7	<0.001¶
1 g/kg†	25.1 ± 1.8	NS‡§	32.9 ± 2.0	<0.05¶ (NS§)
10 g	24.6 ± 2.1	NS	24.1 ± 2.7	<0.05 (NS)
2 g/kg	27.8 ± 2.1	NS	46.7 ± 2.6	<0.001¶ (<0.001§)
0.5 g/kg†	21.8 ± 1.5	NS	30.1 ± 3.4	<0.05¶ (NS§)

*Note significant effect of protein intake on afternoon scores only.
†8 meals. ‡Not significant. §vs 1 g/kg/day protein intake. ¶8 am vs 3 pm.

Table 3. Increase in Serum Growth Hormone Level with Levodopa over Eight Hours.

Status	Total Growth Hormone Concentration*		Net Rise in Growth Hormone Concentration*	
	Radio-immunoassay	Double Antibody	Radio-immunoassay	Double Antibody
	ng/ml			
Untreated†	3.8 ± 0.5	2.2 ± 0.4	1.1 ± 0.3	1.1 ± 0.2
Levodopa‡	5.6 ± 0.6	8.5 ± 0.1	3.4 ± 0.6	6.4 ± 0.1
p value	<0.06	<0.001	<0.007	<0.001

*Mean ± SEM. †8 patients. ‡6 patients.

Discussion

The present study has confirmed that a high protein meal can block the effects of levodopa in some patients with Parkinson's disease since doubling the protein intake usually offered in hospital diets diminished both the therapeutic actions and the cerebral side effects of levodopa in the patients with symptomatic instability. This effect was evident in the long-term (Group 2) as well as the short-term investigations. Stabilization of symptomatic control was brought about rather quickly by restriction of the protein intake. When this restriction, however, was continued for extended periods it potentiated the levodopa effects progressively so that the daily doses of levodopa had to be reduced primarily because of increasing dyskinesia.

Table 4. Effect of Protein-Intake Level on Growth Hormone in Six Patients over Eight Hours.*

	Total Growth Hormone Concentration†	Net Rise in Growth Hormone Concentration†
	ng/ml	
1 g/kg of protein + levodopa	6 ± 0.9	4.5 ± 1.0
2 g/kg of protein + levodopa	3.2 ± 0.7	2.0 ± 0.7
p value	<0.05	<0.1

*Levodopa-treated patients with Parkinson's disease, while they are on a high protein diet, do not exhibit the usual pattern of rises. Growth hormone measured with Abbott radioimmunoassay.

†Mean ± SEM.

Restricted protein intake also diminished the percentage of levodopa excreted as homovanillic acid whereas the high protein diet increased it. Furthermore, peripheral inhibition of decarboxylation of levodopa by MK-486 blocked the "off-on" phenomenon induced by the high protein diet.[15] These findings argue against the assumption that competition between the amino acid levodopa and large amounts of neutral amino acids provided by the diet was the only explanation for the "off-on" phenomenon. They favor the assumption that fluctuating peripheral decarboxylation of levodopa causes fluctuations of the fraction of levodopa entering the brain, thus contributing to the "off-on" phenomenon.[15]

Since growth hormone can increase the incorporation of amino acids into proteins, and its release is promoted by levodopa, the question arises whether this hormone plays a part in the control of Parkinson's disease, especially because we found that pharmacologic doses of growth hormone potentiated the cerebral effects of levodopa in mice.[8] The present work does not answer this question fully because it did not reveal direct correlations between individual rises in serum growth hormone and episodes of either excessive or diminished therapeutic effects. It did show, however, that the abnormally flat patterns and low levels of serum growth hormone in untreated patients became less abnormal while the patients were being treated, provided the protein intake was less than 2.0 g per kilogram per day. This trend toward the normal might in the long run benefit the patients, particularly regarding osteoporosis,[20] despite our failure to show correlations between serum growth hormone levels and total-body calcium at the time of our tests.

The regimen with the most positive effects was one providing levodopa, a peripheral decarboxylase inhibitor, and a protein intake of 0.5 g per kilogram per day. This diet was deemed by others to be more than adequate for patients beyond the childbearing age.[14] Therefore, this combined regimen might be useful in treatment of patients with Parkinson's disease exhibiting moderate instability in their symptomatic control.

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