

## A balanced carbohydrate:protein diet in the management of Parkinson's disease

**Article abstract**—Although restricting dietary protein is a proposed adjunct to treating Parkinson's disease (PD), the effect of carbohydrate consumption is unknown. We measured plasma levodopa and large neutral amino acid (LNAA) levels in nine PD patients treated with carbidopa/levodopa and different isocaloric meals containing high protein-low carbohydrate, low protein-high carbohydrate, and balanced 5:1 carbohydrate:protein mixtures. We found that levodopa levels increased significantly regardless of the type of diet, but that plasma LNAA levels varied less and motor performance was superior after the balanced diet than after the other two meals. We conclude that PD patients can consume nutritionally adequate meals and still maintain a stable plasma levodopa:LNAA ratio.

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**Levodopa**, the principal drug used in the treatment of Parkinson's disease (PD), is a large neutral amino acid (LNAA) whose passage across biological membranes depends on the same system that transports other LNAAs—including valine, leucine, isoleucine, tyrosine, tryptophan, and phenylalanine.<sup>1</sup> Although there may be some interaction between levodopa and the LNAAs in absorption across the intestinal mucosa, competition with LNAAs at the blood-brain barrier limits levodopa's entry into the brain because of the low  $K_m$  of this transport system. Two factors determine the amount of levodopa entering the brain: the plasma concentration of levodopa and the summed concentrations of the LNAAs. Clinical experiments confirming the importance of the plasma levodopa:LNAA ratio in PD showed that administration of LNAAs to PD patients worsened motor symptoms that had been stabilized by constant infusions of levodopa.<sup>2,3</sup> Pincus and Barry<sup>4</sup> suggested that plasma levels of LNAAs in PD patients are better predictors of clinical responses to levodopa than levodopa levels alone.

Soon after levodopa was introduced into clinical practice, Mena and Cotzias<sup>5</sup> proposed that dietary manipulations could potentiate drug effects. Subsequently, Pincus and Barry<sup>6</sup> recommended a diet low in protein content for restoring clinical benefit to PD patients who had become unresponsive to levodopa and for minimizing fluctuations in motor activity such as on-off phenomena and end-of-dose loss of efficacy. Whether low-protein diets are efficacious in PD remains controversial<sup>6-8</sup>; they are, however, widely known and publicized. In chronic conditions such as PD, emphasis on protein restriction may be dangerous as it may lead to protein malnutrition. Furthermore, protein restriction may be unnecessary because consumption of carbohydrates, by eliciting insulin secretion, can also lower plasma LNAA levels. We, therefore, undertook a study to determine the effects on plasma levodopa and LNAA levels of giving PD patients test diets that contained carbohydrate and protein in various ratios. Dietary means of maintaining predictable plasma levels of LNAAs should enhance precision in titrating oral doses of levodopa to achieve optimal clinical benefit.

**Methods.** The participants in this study were nine men with PD. All signed an informed consent form approved by the MIT Subcommittee on the Use of Humans as Experimental Subjects. The patients had a mean age (SEM) of 60.6 years (1.9) and weight of 80.3 kg (3.9); their mean duration of illness was 12.4 years (1.4), and the mean Hoehn and Yahr stage was 2.3 (0.2). All patients took a combination of carbidopa/levodopa (Sinemet) with a mean levodopa dose of 1,000 mg/d (range, 600 to 1,750 mg/d) in divided doses. Throughout the study, patients received their usual dose of medication; all took 100 mg of levodopa at 8 AM with breakfast, and four patients also required 100 mg on rising at 6 AM.

All patients were admitted to the MIT Clinical Research Center for 3 consecutive days and each morning consumed breakfasts of different composition but equivalent caloric value (table 1). All patients received the three meals in a random order. Blood samples were collected at 8 AM from an indwelling venous catheter before breakfast and levodopa, and again 1 and 2 hours after ingesting carbidopa/levodopa and the experimental breakfast. Blood was centrifuged, and the plasma separated and frozen at  $-20^{\circ}\text{C}$  until assay. Plasma levodopa and LNAA levels were measured by high-performance liquid chromatography; plasma tryptophan was measured by a spectrofluorometric method.

Three clinical measures were used to monitor the behavioral consequences of levodopa-diet interactions at baseline and 1 and 2 hours after levodopa administration:

(1) *Subjective assessment by the patient.* Subjects rated their motor state on a qualitative scale that extended from hypokinetic and trembling through normal to hyperkinetic and dystonic. One of the investigators (E.M.B.) who did not know the composition of the diet examined each patient during the morning to determine the presence of involuntary movements.

**Table 1. Composition of the three different breakfast meals\***

Diet	Carbohydrate (g)	Protein (g)	Fat (g)	Carbohydrate:protein ratio
High protein	24 (15)†	80 (50)	25 (35)	0.3
High carbohydrate	128 (80)	6 (3)	12 (17)	21.3
Balanced	107 (67)	20 (12)	15 (21)	5.4

\* All meals contained approximately 640 calories.  
† Percent composition in parentheses.

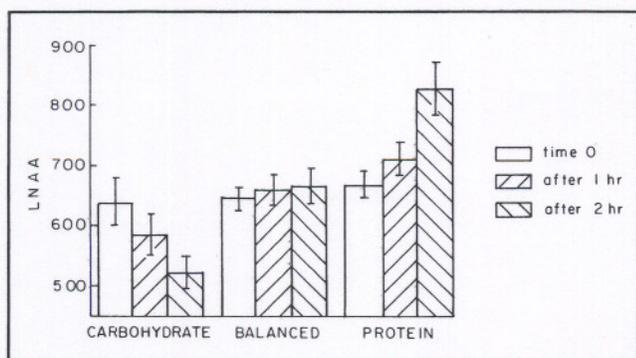


Figure. Plasma LNAA levels (nmol/ml) after high-carbohydrate, high-protein, and balanced carbohydrate:protein meals. Bars indicate SEM. LNAA levels 1 and 2 hours after all three meals were significantly different from each other.

(2) *Purdue Pegboard Test.* The number of pegs placed in the board by the right hand, by the left hand, and then bi-manually were counted during a 30-second period. The three scores were summed; the greater the number of pegs, the better the performance.

(3) *Writing a standard nine-word sentence.* The length of the sentence and the time taken to write it were measured.

The data were analyzed by repeated measures analysis of variance (ANOVA) using the SAS statistical software package (SAS Institute Inc., Cary, NC). Alpha was set at 0.05. Post-hoc testing by the Newman-Keuls test was performed when the ANOVA was significant.

**Results. Plasma amino acid levels.** Fasting levels of LNAAs and levodopa were similar on all 3 days and did not differ significantly across patients. There was a significant difference ( $p < 0.001$ ) in the LNAA levels in response to the different diets (figure). Mean LNAA levels rose 24% after the high-protein meal, fell 18% after the high-carbohydrate meal, and remained the same (<3% change) after the balanced diet. Post-hoc analyses showed that the LNAA levels resulting from all three diets were significantly different from each other at 1 and 2 hours.

**Levodopa levels.** Levels of levodopa increased significantly ( $p < 0.01$ ) after carbidopa/levodopa administration regardless of diet (table 2). There was a significant diet by time interaction in the calculated plasma levodopa:LNAA ratio ( $p = 0.038$ ); the ratio was still rising at 2 hours after a high-carbohydrate meal, steady after the balanced meal, and had returned to baseline value after the high-protein meal.

**Clinical assessment.** According to the subjective scores, all patients felt undermedicated before breakfast and all improved after levodopa/carbidopa treatment regardless of the diet consumed. Nonetheless, five of the nine patients reported worsening of parkinsonian symptoms after the high-protein diet, and three of them also experienced dyskinesias or increased restlessness after the high-carbohydrate meal. After the balanced meal, only one subject developed dyskinesias, although another felt especially energized ("like Popeye after spinach"). Of the nine patients, only two were unaffected by the dietary manipulations.

**Motor performance.** There was a significant correla-

Table 2. Mean plasma levodopa levels (nmol/ml) in nine patients with PD before and after ingesting carbidopa/levodopa with breakfasts of different nutrient composition

Time	High carbohydrate	High protein	Balanced
Before meal	1.95 ± 0.67	1.82 ± 0.51	1.88 ± 0.56
After 1 hr	3.38 ± 0.62	4.57 ± 0.96	3.45 ± 1.06
After 2 hrs	3.55 ± 0.84	2.35 ± 0.32	2.26 ± 0.59

Repeated measures ANOVA:  
 Diet:  $p = 0.75$ .  
 Time:  $p = 0.011$ .  
 Diet × time:  $p = 0.17$ .

tion between the patients' subjective assessment of treatment response and pegboard performance ( $r = 0.64$ ,  $p = 0.0001$ ) and also sentence length ( $r = 0.48$ ,  $p = 0.0001$ ). The pegboard score differed according to the type of breakfast eaten, with a significant diet by time interaction ( $p = 0.028$ ). With the balanced diet, performance improved steadily over 2 hours, whereas performance peaked at 1 hour and declined at 2 hours after both the high-protein and high-carbohydrate meals. A similar but nonsignificant trend was observed with an increase in sentence length. Two hours after eating, as sentence length increased, writing time decreased by 10% after the carbohydrate and balanced diets, but increased by 5% after the protein meal. The levodopa:LNAA ratio correlated significantly with clinical performance on the pegboard test ( $r = 0.40$ ,  $p = 0.001$ ) and sentence length ( $r = 0.30$ ,  $p = 0.006$ ).

**Discussion.** This study indicates that in PD patients receiving levodopa/carbidopa, plasma LNAA levels remain stable for 2 hours after a balanced meal containing a carbohydrate:protein ratio of 5:1. Such a balanced diet in the management of PD fulfills two requirements: the diet is nutritionally complete, and it stabilizes plasma LNAA levels for titrating levodopa dosages. An analogy may be drawn from the treatment of diabetes in which the optimal control of blood glucose depends on the timing and nature of the diet as well as the dose and type of insulin. Similarly, the management of PD should include attention to a balanced diet as well as to the levodopa dose and schedule. Prior recommendations for PD diets have focused entirely on restricting protein consumption to 0.5 g/kg body weight/d<sup>5</sup> or omitting protein at breakfast and lunch and providing this nutrient only in the evening.<sup>6</sup> The recommended daily allowance for protein is 0.75 to 0.8 g/kg body weight/d,<sup>9</sup> and even this intake may be inadequate in the elderly to prevent negative nitrogen balance.<sup>10</sup> Our data suggest that it is not necessary to limit protein intake of patients with PD to achieve stable levels of levodopa and LNAAs, and therefore a predictable plasma levodopa:LNAA ratio. In susceptible patients, consumption of meals containing carbohydrate, but lacking sufficient protein, can cause signs of levodopa toxicity (dyskinesias), probably because too much drug suddenly enters the brain.<sup>8</sup> When presented in a ratio of 5:1, the divergent effects of carbohydrate

and protein consumption are balanced and the plasma LNAA levels remain stable. Equally important for chronic treatment, the balanced diet used in this study, if consumed for the other meals, would provide sufficient protein (60 g/d, equivalent to 0.86 g/kg for a 70-kg adult) to meet recommended daily requirements.<sup>9</sup>

The focus of our study was nutritional and biochemical; additional research will be required in order to explore the clinical consequences of the balanced carbohydrate:protein diet in minimizing fluctuations in motor activity. That performance on the pegboard test after the balanced diet was superior than after either the high-protein or high-carbohydrate meals is a preliminary finding, but suggests that the balanced diet does not worsen and may, in fact, enhance motor performance.

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