

## FACILITATION OF LEVODOPA-INDUCED DYSKINESIAS BY DIETARY CARBOHYDRATES

*To the Editor:* The symptoms of a patient with Parkinson's disease on a particular regimen of levodopa, alone or with a decarboxylase inhibitor, can vary markedly, adequate or inadequate control alternating with drug toxicity.<sup>1</sup> On the assumption that levodopa acts by being converted to dopamine within the corpus striatum, this variability has been attributed to metabolic factors, such as suppression by dietary protein of levodopa's intestinal absorption or transport across the blood-brain barrier,<sup>2-4</sup> since these processes are inhibited by the large neutral amino acids (LNAA) in protein that compete with circulating dopa for the transport macromolecules.<sup>5,6</sup>

We examined plasma levels of dopa and LNAA along with the clinical responses to levodopa in a subject consuming test meals designed to alter plasma levels of LNAA. At a given plasma dopa level, this ratio varied almost threefold, and its variations correlated well with clinical findings. The subject, a 59-year-old physician with a 12-year history of Parkinson's disease, customarily undermedicated himself to minimize dyskinesic side effects. During this study, he followed his usual regimen of 100 mg of levodopa and 25 mg of

carbidopa six times per day (Fig. 1, solid triangles) and 5 mg of bromocriptine three times per day. He consumed isocaloric test meals (Fig. 1, open triangles), consisting of a high-carbohydrate breakfast (80 g of sucrose, no protein); a high-protein lunch (80 g); a dinner with an intermediate protein content (40 g); and the next day, a high-protein breakfast (80 g). The intake of levodopa transiently increased plasma levodopa levels, except for the 3 p.m. dose, which produced no drug peak, possibly because of the inhibition of its intestinal absorption by the high-protein lunch. Although all plasma levodopa peaks were similar, the high-carbohydrate breakfast, by raising plasma insulin and thus reducing plasma LNAA, greatly elevated the ratio of dopa to LNAA; this effect was temporally associated with dyskinesic symptoms. Conversely, after the high-protein breakfast, the ratio of dopa to LNAA was less than half as high ( $4.4 \times 10^{-3}$  vs.  $10.5 \times 10^{-3}$ ), and this coincided with symptoms of undermedication. With similar plasma dopa levels, the ratios of dopa to LNAA varied between  $10.5 \times 10^{-3}$  and  $3.9 \times 10^{-3}$ , depending on the composition of the meal most recently ingested.

These findings indicate that a high-carbohydrate meal may trigger symptoms of dopa toxicity in patients receiving this drug. This effect does not depend on plasma dopa levels, but rather on the plasma ratio of dopa to LNAA, which rises markedly after carbohy-

Figure 1. Symptoms (Panel A), Plasma Levels of LNAA (Panel B), and Plasma Dopa Levels and the Ratios of These Levels to Those of the LNAA (Panel C) during a 30-Hour Period in a Patient with Parkinson's Disease Receiving Levodopa at the Times Indicated (Solid Triangles).

Meals containing various amounts (0 to 80 g) of carbohydrate (Carb.) and protein (Prot.) were consumed at 8 a.m., noon, and 5 p.m. (open triangles). Values above the line in Panel A denote symptoms of drug overdose (dyskinesias), and those below the line symptoms of undermedication.

drate ingestion. The possibility that dyskinesic episodes may be precipitated by high-carbohydrate, low-protein meals should be considered before drug doses are adjusted for patients with Parkinson's disease. Such a state might be induced, for example, by a breakfast consisting of fruit juice, a sweet roll, and coffee with sugar. The relation of diet to "on-off" phenomena in Parkinson's disease has recently been emphasized by Eriksson et al.<sup>7</sup>

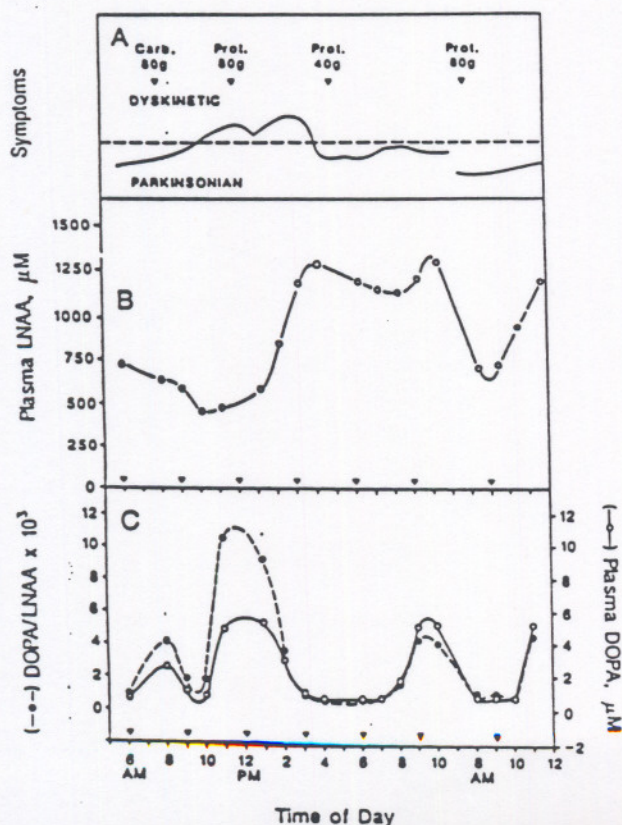
RICHARD WURTMAN, M.D.  
BENJAMIN CABALLERO, M.D.

Cambridge, MA 02139 Massachusetts Institute of Technology

EDWIN SALZMAN, M.D.  
Harvard Medical School

Boston, MA 02114

1. Marsden CD, Parkes JD. "On-off" effects in patients with Parkinson's disease on chronic levodopa therapy. *Lancet* 1976; 1:292-6.
2. Cozias GC, Mens I, Papavasiliou PS. Overview of present treatment of parkinsonism with L-dopa. *Adv Neurol* 1973; 2:265-77.
3. Wade DN, Mearick FT, Birkett DJ, Morris J. Variability of L-dopa absorption in man. *Aust NZ J Med* 1974; 4:138-43.
4. Nutt JG, Woodward WR, Hammerstad JP, Carter JH, Anderson JL. The "on-off" phenomenon in Parkinson's disease: relation to levodopa absorption and transport. *N Engl J Med* 1984; 310:483-8.
5. Waide LA, Katzman R. 3-O-Methyl-dopa uptake and inhibition of L-dopa transport at the blood-brain barrier. *Life Sci* 1975; 17:131-6.
6. Wurtman RJ. Effects of dietary amino acids, carbohydrates and choline on neurotransmitter synthesis. *Mt Sinai J Med (NY)* 1988; 55:75-86.
7. Eriksson T, Granerus A-K, Linde A, Carlsson A. "On-off" phenomenon in Parkinson's disease: relationship between dopa and other large neutral amino acids in plasma. *Neurology* 1988; 38:1245-8.



#776

New Eng. J. Med. 319:1288-89, 1988