

## Effect of Pyridoxine on the Depletion of Tissue Pyridoxal Phosphate by Carbidopa

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Vitamin B6

One or two hours after rats received a single dose (100 or 800 mg/kg, intraperitoneally) of carbidopa (MK-486;  $\alpha$ -methyl-L-dopa hydrazine), pyridoxal-5-phosphate (PLP) concentrations were significantly depressed in peripheral tissues (serum, liver, and muscle) and in hypothalami, but not in whole brains. Repeated administration of carbidopa (three 100 mg/kg doses per day for 3 days) lowered PLP concentrations in serum, liver, and muscle (by 88%, 51%, and 18%, respectively) among rats killed 2 hr after the final injection. PLP levels in brain and hypothalamus were also reduced significantly (by 22% and 18%, respectively) after this treatment. The activity of aromatic L-amino acid decarboxylase (AAAD) in hypothalamic homogenates (assayed in vitro) exhibited a parallel small decline;

its activity in brain homogenates, however, was not significantly changed. Administration of pyridoxine-HCl (200 mg/kg/day for 3 days) in addition to carbidopa blocked the fall in hypothalamic AAAD activity. Pyridoxine administration did not affect the inhibition of peripheral AAAD by carbidopa in vivo; it failed to interfere with carbidopa's blockade of decarboxylation of exogenous L-dopa (100 mg/kg, given intraperitoneally 1 hr before sacrifice). These findings suggest that large doses of carbidopa can, by depleting tissues of PLP, cause potentially undesirable nonspecific changes in pyridoxine-dependent enzymes. However, the coadministration of pyridoxine with carbidopa can maintain tissue PLP levels and protect against such enzyme changes.

**B**ECAUSE CARBIDOPA selectively inhibits the enzyme aromatic L-amino acid decarboxylase (AAAD) in peripheral tissues,<sup>1</sup> it increases the proportions of each dose of dopa that reaches the brain; this makes it a useful adjunct in the treatment of Parkinson's disease.<sup>2</sup> Carbidopa is capable of suppressing the decarboxylation of endogenous<sup>3</sup> as well as exogenous<sup>4,5</sup> dopa; the resulting inhibition of norepinephrine synthesis within sympathetic nerve terminals<sup>3</sup> may underlie carbidopa's ability to potentiate the antihypertensive actions of a number of chemically unrelated drugs in spontaneously hypertensive rats.<sup>6</sup>

Carbidopa is a hydrazine derivative of the amino acid L-dopa. It has been suggested<sup>7,8</sup> that its hydrazine group might bind chemically to pyridoxal-5-phosphate (PLP) to form a Schiff base (Fig. 1), as dopa and other amino acids and amines do.<sup>9,10</sup> Such binding between carbidopa and PLP has been demonstrated in vitro;<sup>11</sup> the second-order rate constant for formation of the Schiff base was found to be 20 times greater for carbidopa than for dopa. The admin-

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