Diet and Uptake of Aldomet by the Brain: Competition with Natural Large Neutral Amino Acids

Abstract. *The rise in levels of aldomet in the brains of rats after an injection of the α-methylated amino acid was depressed when large neutral amino acids, but not acidic amino acids, were coadministered with the drug. This result suggests that aldomet is transported into brain by the carrier for natural large neutral amino acids. The prior ingestion of a carbohydrate meal, which lowers levels of neural amino acids in the serum, enhanced the uptake of aldomet into brain; the consumption of a protein-containing meal inhibited the subsequent uptake of aldomet into the brain. Antecedent diet can thus affect the availability of aldomet to the central nervous system; the mechanism of this effect probably involves the blood-brain barrier uptake system for large neutral amino acids.*

Aldomet, a drug used widely in the treatment of hypertension, differs structurally from the neutral amino acid L-dopa only by the addition of a methyl group on the α-carbon. Dopa is a large neutral amino acid, as are such other aromatic and branched-chain amino acids as phenylalanine and leucine; these amino acids all share a common transport system, located at the blood-brain barrier, which mediates their uptake into the brain (*1*, *2*). Because aldomet is a close analog of dopa, its uptake into the central nervous system (CNS), where it is thought to exert its therapeutic effects (*3*), might also be mediated by this same carrier. If so, then the therapeutic potency of aldomet might be influenced by factors that normally modify the uptake of large neutral amino acids into brain (for example, the diet). We now report that aldomet does appear to compete with natural large neutral amino acids for brain uptake, and that food ingestion, which has previously been shown to affect the brain's uptake of such large neutral amino acids as tryptophan and phenylalanine (*4*), also significantly alters aldomet uptake into this organ.

Groups of male Sprague-Dawley rats (Charles River Laboratories; 175 to 250 g) were exposed to light (*5*) from 8 a.m. to 8 p.m. daily and given free access to water and food (Charles River rat, mouse, and hamster maintenance formula). Late in the afternoon of the day before an experiment, the food was removed from the cages. The next morning the animals received aldomet either alone (50 mg/kg or 237 μmole/kg intraperitoneally) or in combination with large neutral or acidic amino acids (708 μmole/kg) (*6*). Groups of animals were killed 7, 30, or 60 minutes later, and blood samples and brains were quickly removed. The brains were immediately frozen on Dry Ice; the blood samples were centrifuged and the serums were frozen. Aldomet was measured fluorimetrically, after Dowex chromatography (*7*).

In experiments involving food ingestion, rats that had been fasted overnight were given free access in the morning to either a protein-free diet or a diet containing 40 percent casein (*8*); 90 minutes later, they received an intraperitoneal injection of aldomet (25 or 50 mg/kg) and were killed 30 minutes thereafter. The food was present throughout the entire 2-hour period; the animals each consumed about 10 g of either diet.

Brain aldomet levels increased rapidly after a single injection of the drug (50 mg/kg; Fig. 1); peak levels were attained by 60 minutes (later time points are not shown). The coadministration of large

Table 1. Effect of food ingestion on aldomet uptake into the rat brain. Groups of six male Sprague-Dawley rats were fasted overnight; the next morning they were given free access to either a carbohydrate-fat diet (no protein) or a similar diet containing 40 percent protein (casein). Ninety minutes after diet presentation, they received an intraperitoneal injection of aldomet and were killed 30 minutes later. The food was not removed during the last 30-minute period. Control animals received no food during the experimental period, but continued to have access to water. Data are presented as means ± standard error and were analyzed by analysis of variance and the Neuman-Keuls test.

Diet group	Aldomet dose (mg/kg)	Aldomet level	
		Serum (μg/ml)	Brain (μg/g)
Control	25	10.2 ± 0.6	2.3 ± 0.1
Carbohydrate	25	7.7 ± 0.1	5.8 ± 0.4*
Casein	25	9.8 ± 0.4	1.4 ± 0.1*
Control	50	25.2 ± 1.7	6.3 ± 0.4
Carbohydrate	50	17.1 ± 1.8	11.3 ± 0.3*
Casein	50	24.4 ± 5.3	4.3 ± 0.4*

*$P < .01$ compared to control values.

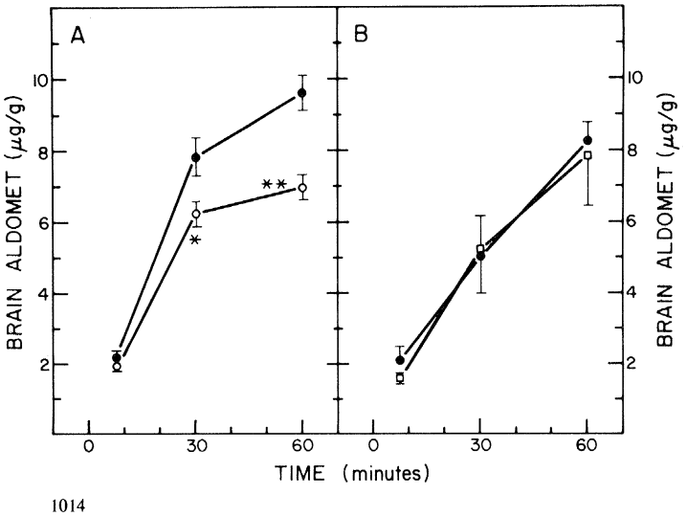

Fig. 1. The effect of coadministering aldomet with either neutral or acidic amino acids on the rise in brain aldomet levels following its administration to rats. Groups of five fasting rats received aldomet alone (50 mg/kg) or in combination with either large neutral amino acids or acidic amino acids, as described in the text. They were then killed at the indicated times, and their serums and brains were analyzed for aldomet content. Vertical bars represent standard errors of the mean. Data were analyzed by two-way analysis of variance: (*), $P < .05$; (**), $P < .01$. Aldomet concentrations in the brains of rats injected with aldomet alone were compared to the concentrations in rats injected with aldomet in combination with large neutral amino acids. The experiments summarized in (A) and (B) were performed on different days; that different lots of animals were used probably accounts for the slight differences in the brain levels measured in animals receiving aldomet alone. (●) Animals receiving aldomet alone; (○) rats receiving aldomet plus neutral amino acids; (□) animals receiving aldomet plus acidic amino acids.

neutral amino acids with aldomet was associated with marked reductions in the levels of aldomet in the brain 30 and 60 minutes after injection (Fig. 1A; open circles). However, the injection of the same number of moles of acidic amino acids with aldomet had no effect on the rise in brain aldomet levels after injection (Fig. 1B; open squares). In serum, the highest aldomet concentrations in all groups were noted after 7 minutes (40 to 50 μg/ml); these concentrations declined by 60 minutes to 10 to 20 μg/ml (not shown). Concentrations of aldomet in the serums of animals receiving neutral or acidic amino acids did not differ from those receiving aldomet alone at any time tested. These data support the hypothesis that large neutral amino acids, but not acidic amino acids, in the circulation compete with aldomet for brain uptake.

The ingestion of a carbohydrate meal increases brain tryptophan uptake and levels by lowering the serum concentrations of competing large neutral amino acids relative to serum tryptophan (*9*). Protein ingestion raises the concentrations of these competitors in the serum as well as that of tryptophan; thus brain tryptophan levels do not rise, and may even fall (*10*). Aldomet uptake into brain was similarly influenced by the diet (Table 1): carbohydrate ingestion prior to aldomet administration markedly elevated the proportion of an injected dose present in the brain 30 minutes after injection, even though serum aldomet levels were higher in the fasting animals. In contrast, protein ingestion decreased brain aldomet levels 30 minutes after injection, even though serum aldomet levels were almost identical to those of fasting control animals. This effect occurred at both of the aldomet dose levels.

These data thus suggest that aldomet is transported into the brain by the same system used by the large neutral amino acids that occur naturally in proteins and in the bloodstream. Another synthetic α-methylated amino acid, α-methyltyrosine, is probably also transported into the brain by the carrier for large neutral amino acids (*2*).

The finding that aldomet competes for brain uptake with natural large neutral amino acids suggested to us that aldomet uptake might also be modified by antecedent diet. Carbohydrate ingestion was thus found to enhance aldomet uptake into brain, probably because the resulting secretion of insulin lowered the serum concentrations of most of the competing large neutral amino acids (*9*). Similarly, protein ingestion suppressed aldomet uptake into brain, presumably by elevating the serum concentrations of these competing amino acids (*10*). While a direct effect of insulin on CNS aldomet uptake cannot be ruled out by our data alone, insulin appears to have little, if any, *direct* effect on the CNS uptake of natural large neutral amino acids (*2, 11*).

Aldomet apparently exerts its antihypertensive effects via an action on the CNS (*3*). If so, then the serum neutral amino acid pattern (and the diet) would influence both the uptake of aldomet into brain and its potency in lowering blood pressure. Some observations tend to support this hypothesis: the coadministration of doses of large neutral amino acids, which suppress aldomet uptake into the CNS, also antagonizes the drug's antihypertensive effect in spontaneously hypertensive rats (*12*). One might thus expect protein ingestion to have a similar effect (*13*). Our data might also explain why the efficacy of L-dopa in the treatment of Parkinson's disease is reduced by the ingestion of high-protein diets (*14*). Dopa is transported into brain via the large neutral amino acid carrier (*2*); high circulating levels of other competitors, associated with the ingestion of high-protein meals, might suppress dopa uptake into brain and thus diminish its actions in the CNS.

Hence, antecedent diet, by affecting serum amino acid pattern, can significantly influence the availability of amino acid drugs to the brain. A knowledge of how diet modifies serum amino acid levels (particularly the neutral amino acids) is thus useful in formulating dietary strategies to enhance the uptake into the CNS of important, centrally acting amino acid drugs such as aldomet.

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References and Notes

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5. Vita-Lite, 300 μw/cm²; Duro-Test Corp., North Bergen, N.J.
6. The neutral amino acids tyrosine, phenylalanine, leucine, isoleucine, and valine were coadministered with aldomet, each at a dose of 20 mg/kg, that is, a total dose of 100 mg/kg (708 μmole/kg). When acidic amino acids were coadministered with aldomet, aspartate and glutamate were injected, in equimolar amounts, at a total dose of 708 μmole/kg, intraperitoneally. All amino acids were dissolved or suspended in saline; the injection volume was always 1.0 ml.
7. C.-M. Lo, M.-L. Kwok, R. J. Wurtman, *Neuropharmacology* **15**, 395 (1976). For aldomet determinations in serum, 0.2 ml was precipitated in 9.8 ml of 0.4*N* perchloric acid containing 0.2 percent EDTA and sodium metabisulfite (3 mg/100 ml); the subsequent procedure was identical to that for brain samples. Although 3-*O*-methyldopa, a metabolite of aldomet, elutes from Dowex with aldomet, it was found not to interfere in the subsequent fluorimetric determination of the drug.
8. Protein-free diet ingredients (g/kg, dry weight): dextrose, 267; sucrose, 219; dextrin, 267; Mazola oil, 150; salt mixture [Q. Rogers and A. E. Harper, *J. Nutr.* **87**, 267 (1965)], 40; vitamin diet fortification mixture (ICN Nutritional Biochemicals, Cleveland), 22; and agar, 35. The agar was mixed with 1000 ml of hot water prior to the addition of the other ingredients. The 40 percent casein diet differed only by the inclusion of casein (400 g/kg) in lieu of an equivalent amount of carbohydrate (dextrose, sucrose, and dextrin in equal amounts).
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