Evidence for a Predominantly Central Hypotensive Effect of α-Methyldopa in Humans

ALEX BOBIK, GARRY JENNINGS, GRAHAM JACKMAN, CATHERINE ODDIE, AND PAUL KORNER

SUMMARY We examined the time course and extent to which central and peripheral mechanisms contribute to the short-term effects of a 500-mg oral dose of α-methyldopa on supine mean arterial pressure, cardiac output, and total peripheral resistance, as well as its effects on total urinary excretion of norepinephrine and its metabolites, in five subjects with essential hypertension. Total peripheral resistance was reduced significantly 1 hour after α-methyldopa administration and remained so for the ensuing 7 hours of the study (p < 0.05). A small but significant reduction in mean arterial pressure occurred 7 hours after the dose (p < 0.05), while cardiac output did not change significantly. Total 24-hour urinary norepinephrine and metabolite excretion was reduced by 8.1 μmol (35% compared with placebo). The relative distribution of urinary norepinephrine metabolites was unaffected by α-methyldopa, and the catecholamine metabolites of α-methyldopa, α-methylnorepinephrine and α-methylnormetanephrine did not account for this reduction. Competitive inhibition of methyldopa transport across the blood-brain barrier and into the central nervous system by large oral doses of isoleucine antagonized most of the effect of α-methyldopa. The effects on total peripheral resistance were completely abolished, and small, insignificant changes during the 7-hour study were similar to those observed after placebo. Changes in mean arterial pressure were not significant; however, 24-hour total urinary norepinephrine and metabolite excretion increased by 6.1 μmol to 22.7 μmol (24.7 μmol excreted after placebo). Adding benserazide to the α-methyldopa–isoleucine dose regimen in an attempt to inhibit any residual, presumably peripheral, effects of α-methyldopa caused little, if any, further antagonism. Our results suggest that short-term oral administration of α-methyldopa inhibits norepinephrine release from sympathetic nerves by central mechanisms, and the changes in mean arterial pressure, although small, are consistent with this hypothesis. The reductions in total peripheral resistance also appear to be centrally mediated.

(Hypertension 8: 16-23, 1986)

KEY WORDS • α-methyldopa • central nervous system • blood pressure • vasodilatation • norepinephrine metabolism

Both central and peripheral mechanisms have been suggested as the mechanism by which α-methyldopa reduces sympathetic activity and blood pressure.1-3 Recently, we have shown in conscious rabbits that α-methyldopa can reduce sympathetic activity and blood pressure by central and peripheral mechanisms.4,5 At doses in the rabbit approximately equivalent to those used clinically in humans, central mechanisms predominate, while at higher doses, central and peripheral mechanisms contribute equally to these effects. Several attempts have been made to evaluate the potential importance of central and peripheral antihypertensive sites of α-methyldopa’s action in humans.6,7 Since α-methyldopa must be metabolized to active metabolites within the central nervous system to exert centrally mediated hypotensive effects,4 these studies have concentrated on comparing the hypotensive effects of α-methyldopa before and after inhibition of central or peripheral dopa decarboxylase, or both. In general, these methods have not been able to attenuate the cardiovascular effects. Thus, the question of whether the central or the peripheral action of α-methyldopa is the more important in humans is still unanswered.

Recently, Zavisca and Wurtman8 reported that a cocktail of large, neutral amino acids administered intraperitoneally to spontaneously hypertensive rats could partially attenuate the fall in blood pressure produced by α-methyldopa. This effect appeared to be due to a reduction in the amount of α-methyldopa entering the brain.9 Indeed, Guroff and Udenfriend10 demon-

From the Clinical Research Unit, Alfred Hospital and Baker Medical Research Institute, Melbourne, Australia.
Address for reprints: Dr. A. Bobik, Baker Medical Research Institute, Commercial Road, Prahran, 3181, Victoria, Australia.
Received July 2, 1984; accepted June 12, 1985.

16
strated many years ago that large, neutral amino acids such as tyrosine, tryptophan, and isoleucine may compete with each other for active transport across the blood-brain barrier. Both \( \alpha \)-methyldopa and dopa appear to be transported by this system.\(^9\) \(^{11}\) Hence, in the present investigation we attempted to inhibit \( \alpha \)-methyldopa transport into the human brain to assess its peripheral and central actions on blood pressure and sympathethetic activity. We used large oral doses of isoleucine to inhibit \( \alpha \)-methyldopa’s entry into the brain. Isoleucine is relatively nontoxic when administered over short periods\(^{12}\) and has a high affinity for the transport system of the blood-brain barrier.\(^{10}\)

Our study consisted of examining the effects of placebo and various doses of \( \alpha \)-methyldopa administered orally to subjects with essential hypertension on sympathetic activity, blood pressure, and its determinants. We examined the time course of changes in these circulatory parameters as well as the effects on excretion of norepinephrine (NE) and its metabolites 1) after oral administration of \( \alpha \)-methyldopa, 2) while antagonizing the transport of \( \alpha \)-methyldopa across the blood-brain barrier with isoleucine, 3) after the \( \alpha \)-methyldopa and isoleucine regimen was followed by peripheral dopa decarboxylase inhibition with a small dose of benzerazide, and 4) after placebo.

### Subjects and Methods

Five subjects (four men and one woman) with mild to moderate essential hypertension and a mean age of 38 years (range, 23–51 years) were studied. These subjects had no cardiac or renal failure, no signs or symptoms of coronary insufficiency, and no liver damage, positive Coombs’ test, or history of hemolytic anemia. They had not been treated with any antihypertensive agents during the 3 weeks preceding the study. All subjects gave their informed consent. The study protocol had been previously approved by the Alfred Hospital Clinical Research Ethics Committee. Protein intake was restricted to less than 30 g during each study day, and subjects were instructed to abstain from a diet rich in protein on the day before each study.

### Plasma \( \alpha \)-Methyldopa

Plasma \( \alpha \)-methyldopa concentrations were estimated from blood collected into a solution of glutathione (30 mg/ml) and ethylenediaminetetraacetic acid (EDTA; 100 mg/ml), pH 6.8 to 7.0, in the proportion of 20 \( \mu \)l of solution per milliliter of blood. Blood was collected from each subject 30 minutes before administering \( \alpha \)-methyldopa and at hourly intervals thereafter for 8 hours. The \( \alpha \)-methyldopa was estimated electrochemically after high-pressure liquid chromatography using a slight modification of the methods of Ong et al.\(^{13}\) and Jackman et al.\(^{14}\)

### Urinary Norepinephrine and Metabolites

Urine was collected for 24 hours after each dose of \( \alpha \)-methyldopa or placebo into a container containing 10 ml of 6 N hydrochloric acid. Total (free and conjugated) norepinephrine (NE), \( \alpha \)-methylnorepinephrine, \( \alpha \)-methyldopamine, normetanephrine, and \( \alpha \)-methylnormetanephrine in urine were estimated by high-pressure liquid chromatography with fluorescence detection after acid hydrolysis as we have previously described.\(^{15}\) \(^{16}\)

Glycol metabolites of NE, 3,4-dihydroxyphenylethylene glycol (DHPG), and 3-hydroxy-4-methoxynaphthylglycol (MHPG) were estimated in urine after hydrolysis of their conjugates with a mixture of \( \beta \)-glucuronidase and arylsulfatase (Gluisulase), previously purified according to the method of Jarrige.\(^{17}\) In brief, 100 \( \mu \)l of urine was added to 200 \( \mu \)l of 1 M sodium acetate, pH 6.5, containing 2% disodium EDTA, 10 \( \mu \)l of 0.1% sodium metabisulfite, and approximately 0.25 IU of purified Glusulase. The mixture was incubated at 37°C for 3 hours, and DHPG and MHPG were then extracted into 5 ml of ethylacetate. After centrifugation at 1000 \( g \), the ethylacetate layer was transferred to a tube containing 3 ml of hexane and 500 \( \mu \)l of 0.1% disodium EDTA and the glycols were extracted into the aqueous phase. The DHPG and MHPG were then separated and quantified by high-pressure liquid chromatography with fluorescence detection. Extraction recoveries for the two glycols ranged between 45 and 55%.

3-Methoxy-4-hydroxymandelic acid (VMA) was extracted from 50 \( \mu \)l of urine after the addition of 20 \( \mu \)l of 0.1% disodium EDTA into 5 ml of diethyl ether. The VMA was reextracted from the ether into 100 \( \mu \)l of 0.1 M sodium phosphate, pH 7.5, containing 0.1% disodium EDTA. The pH of the aqueous extract containing VMA was adjusted to 4 to 5 with 75 \( \mu \)l of 0.1 M phosphoric acid before high-pressure liquid chromatography.

All extracts containing catecholamines and metabolites were assayed by high-pressure liquid chromatography on a Varian instrument (Model 5000; Palo Alto, CA, USA) equipped with a Schoeffel fluorimeter (Model FS970; Westwood, NJ, USA) with excitation wavelength set at 200 nm and emission wavelength selected with a Corning 7-60 glass filter (bandpass 320–400 nm; Corning, NY, USA). The mobile phase (flow, 2 ml/min) for the catecholamines was 10 mM perchloric acid/acetonitrile (99:1 by volume). Retention times for NE, \( \alpha \)-methylnorepinephrine, and \( \alpha \)-methyldopamine averaged 3.0, 3.5, and 12 minutes respectively. To estimate normetanephrine and \( \alpha \)-methylnormetanephrine, the mobile phase consisted of 2 mM sodium dihydrogen phosphate and 10 mM sodium hydroxide instead of acetonitrile (85:15 by volume). Retention times for normetanephrine and \( \alpha \)-methylnormetanephrine averaged 4.5 and 5.5 minutes respectively.

The DHPG and MHPG were chromatographed in a mobile phase (flow, 2 ml/min) consisting of 10 mM perchloric acid/acetonitrile (99:1 by volume). Retention times were 2.6 and 6.0 minutes respectively. The mobile phase for VMA was 0.1 M sodium dihydrogen phosphate containing 3 mM acetic acid (flow, 2 ml/min). Retention time of VMA was 2.8 minutes.
Four minutes after each injection, the acetonitrile concentration was increased linearly over 3 minutes to 15% to elute residual chromatographing material. Appropriate standards were carried through all assay procedures.

**Hemodynamic Measurements**

Each subject’s heart rate was measured continuously using an electrocardiograph (Avionics, Los Angeles, CA, USA). Mean arterial pressure (MAP) was measured with an automated sphygmomanometer (Dynamap, Critikon, Tampa, FL, USA). Cardiac output was measured noninvasively by a carbon dioxide rebreathing method using the Fick principle. The method has been previously validated in our laboratory, when its accuracy and reproducibility were evaluated in 13 subjects. The regression line relating thermodilution and the indirect carbon dioxide rebreathing method of cardiac output was linear with a slope of 0.98 and regression coefficient of 0.92. The standard error (SE) of a single observation was 7%. Hemodynamic measurements and blood collection were performed after the subject had been lying supine for 20 minutes; blood pressure and cardiac output values used are the mean of at least three similar measurements at a given time.

**Protocol**

Each subject attended the laboratory on four study days, which were separated by at least 1 week. The order of the four treatments was randomized. On each occasion we measured 1) the time course of changes in resting hemodynamics, heart rate, MAP, cardiac output, and total peripheral resistance; 2) NE excretion and metabolism; and 3) α-methyl dopa bioavailability. The oral drug treatments consisted of 1) 500 mg of α-methyldopa alone; 2) 500 mg of α-methyldopa given 30 minutes after oral pretreatment with 14 g of isoleucine, and followed by further doses of isoleucine given 2 hours (7 g) and 4 hours (5 g) after the initial dose of isoleucine; 3) 500 mg α-methyldopa plus 200 mg benserazide and the same amounts of isoleucine given at the same times; and 4) placebo.

On the morning of each study day and following an overnight fast, a cannula was inserted into the subject’s forearm vein for blood sampling, after which the subject rested for 20 minutes. Control MAP, heart rate, and cardiac output were measured in the supine position and a blood sample was collected. Resting supine hemodynamic measurements were repeated 1, 3, and 7 hours after administration of α-methyldopa or placebo. Blood samples were collected hourly for 8 hours for α-methyldopa analysis. Urine was collected for catecholamine and metabolite excretion for 24 hours; the collection period was timed from α-methyldopa or placebo administration.

**Pharmacokinetic and Statistical Analysis**

Pharmacokinetic analyses were performed as previously described. The area under the plasma α-methyldopa concentration-time curves (AUC) between zero and 8 hours was calculated using the trapezoidal method. Statistical analyses were performed by two-way and three-way analysis of variance. Significant F tests were followed by examining the significance of differences between control measurements and those made at various times after a particular α-methyldopa regimen using least-significant differences. Results are expressed as either mean ± standard error of the mean (SEM) or mean ± standard error of the difference (SED) calculated from the analysis of variance.

**Results**

**α-Methyldopa Pharmacokinetics**

With all three α-methyldopa regimens peak plasma concentrations were achieved 2 to 3 hours after drug administration and then declined; the half-time was approximately 2 hours (Figure 1). Addition of isoleucine to α-methyldopa did not significantly affect its bioavailability: the AUC averaged 24.9 ± 5.8 μg·hr/ml after α-methyldopa alone and 18.6 ± 2.4 μg·hr/ml after α-methyldopa and isoleucine (p > 0.05). Isoleucine also had no apparent effect on the peripheral metabolism of α-methyldopa by dopa decarboxylase. Cumulative 24-hour urinary excretion of α-methyldopamine averaged 72 ± 12 μmol after administering α-methyldopa alone and 68 ± 7 μmol after α-methyldopa and isoleucine (p > 0.05). Adding 200 mg of benserazide to the isoleucine and α-methyldopa regimen to inhibit peripheral dopa decarboxylase significantly reduced α-methyldopamine excretion from 72 ± 12 to 18 ± 2 μmol (p < 0.001; Figure 2). Despite this reduction, benserazide had little overall effect on either the absorption or elimination of α-methyldopa from plasma (see Figure 1). After administering α-methyldopa with isoleucine plus benserazide, the AUC averaged 23.4 ± 4.1 μg·hr/ml, which was similar to that achieved after administering α-methyldopa alone and was not significantly different (p > 0.05).

**Urinary Excretion of Catecholamines and Metabolites**

The α-methylcatecholamine metabolites of α-methyldopa may influence the metabolism and clearance of NE, and the most reliable method of estimating NE release during α-methyldopa therapy is to measure the excretion of all its major metabolites. We measured the excretion of VMA, MHPG, DHPG, normetanephrine, and NE. After placebo administration, the subjects’ total NE metabolite excretion varied from 13.4 to 31.4 μmol/24 hr (mean, 24.7 μmol/24 hr; Table 1). Excretion of VMA and MHPG contributed approximately 89% to this value. The 24-hour urinary excretion of catecholamine metabolites was reduced by about 35% after a single 500-mg oral dose of α-methyldopa (Figure 3). Reductions in MHPG excretion averaged 37% (p < 0.05); VMA, 46% (p < 0.02); and DHPG, 41% (p < 0.05). Although the excretion of NE and normetanephrine tend-
ed to be reduced, these changes were not significant (0.1 < p > 0.05).

The reduction in the excretion of NE metabolites (8.9 μmol/24 hr) did not appear to be a consequence of replacement of endogenously released NE by α-methylnorepinephrine. Since excretion of α-methylnorepinephrine and its major metabolite, α-methylnormetanephrine, totaled only 0.86 ± 0.20 μmol/24 hr after the dose of α-methyldopa. However, since α-methylnorepinephrine and α-methylnormetanephrine are most likely the result of intraneuronal metabolism of α-methyldopa and, possibly, of α-methylnorepinephrine release during sympathetic nerve activation, we have added these to the NE metabolite values to assess biochemically the effects of α-methyldopa on sympathetic function (Figure 4). After adding these values to the NE metabolite excretion values (to equal total NE and metabolite excretion), the reduction in excretion was still 33% (p < 0.02) after administering α-methyldopa.

Administration of isoleucine in conjunction with α-methyldopa antagonized approximately 90% of the reduction in total NE and metabolite excretion observed after α-methyldopa. After isoleucine administration, the total NE and metabolite excretion increased to 22.7 μmol/24 hr (p < 0.01, compared with α-methyldopa dose; see Figure 4). Isoleucine had little effect on the 24-hour excretion of α-methylnorepinephrine and α-methylnormetanephrine, whose combined totals averaged 0.85 ± 0.09 μmol/24 hr. Addition of benserazide to the dose regimen also resulted in attenuation of the fall in total NE and metabolite excretion following α-methyldopa: Total NE and metabolite excretion increased to 21.3 μmol/24 hr, compared with 16.7 μmol/24 hr after α-methyldopa alone.

### Table 1. The 24-Hour Urinary Excretion Rates for Norepinephrine and Its Metabolites After Administering Placebo

<table>
<thead>
<tr>
<th>Patient</th>
<th>NE (μmol/24 hr)</th>
<th>NMN (μmol/24 hr)</th>
<th>DHPG (μmol/24 hr)</th>
<th>MHPG (μmol/24 hr)</th>
<th>VMA (μmol/24 hr)</th>
<th>Total (μmol/24 hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.29</td>
<td>0.68</td>
<td>0.51</td>
<td>9.02</td>
<td>2.93</td>
<td>13.43</td>
</tr>
<tr>
<td>2</td>
<td>1.35</td>
<td>1.87</td>
<td>1.86</td>
<td>11.14</td>
<td>13.60</td>
<td>29.82</td>
</tr>
<tr>
<td>3</td>
<td>0.26</td>
<td>0.41</td>
<td>1.32</td>
<td>11.48</td>
<td>18.00</td>
<td>31.47</td>
</tr>
<tr>
<td>4</td>
<td>0.25</td>
<td>0.76</td>
<td>1.62</td>
<td>3.26</td>
<td>11.50</td>
<td>17.39</td>
</tr>
<tr>
<td>5</td>
<td>0.55</td>
<td>0.95</td>
<td>0.59</td>
<td>19.20</td>
<td>10.10</td>
<td>31.39</td>
</tr>
</tbody>
</table>

Mean ± SEM 0.54 ± 0.19 0.93 ± 0.22 1.18 ± 0.24 10.82 ± 2.28 11.23 ± 2.20 24.7 ± 3.14

NE = norepinephrine; NMN = normetanephrine; DHPG = 3,4-dihydroxyphenylethylene glycol, MHPG = 3-hydroxy-4-methoxyphenylethylene glycol, VMA = vanillylmandelic acid
FIGURE 3 The 24-hour excretion of norepinephrine and its metabolites after placebo (○) and after a 500-mg oral dose of α-methyldopa (□). Results are the means ± SEM.

μmol/24 hr after α-methyldopa alone (0.06 < p > 0.05; see Figure 4).

Circulatory Effects

Supine MAP was lower after α-methyldopa administration. The fall in MAP was already apparent 1 hour after α-methyldopa administration in some subjects, while in others it became manifest somewhat later. Seven hours after the dose, the reduction in MAP was approximately 8 mm Hg (p < 0.05, compared with control; Table 2). As can be seen in Table 2, neither heart rate nor cardiac output was significantly affected by α-methyldopa (p > 0.05 compared with predose control values). Thus, the fall in MAP was due to a reduction in total peripheral resistance (TPR; p < 0.05). This effect on TPR was already apparent 1 hour after α-methyldopa administration and persisted for the entire 7-hour study (see Table 2). No significant

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Time Course of Changes in Mean Arterial Pressure, Total Peripheral Resistance, Heart Rate, and Cardiac Output After Oral Administration of Placebo and α-Methyldopa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose regimen</td>
<td>Supine MAP (mm Hg)</td>
</tr>
<tr>
<td>Control</td>
<td>1 hr</td>
</tr>
<tr>
<td>Placebo</td>
<td>103 ±5 9</td>
</tr>
<tr>
<td>α-MD</td>
<td>105 ±6 7</td>
</tr>
<tr>
<td>α-MD + isoleucine</td>
<td>107 ±4 5</td>
</tr>
<tr>
<td>α-MD + isoleucine + benserazide</td>
<td>108 ±8 5</td>
</tr>
</tbody>
</table>

Results are means ± SEM. MAP = mean arterial pressure, TPR = total peripheral resistance, HR = heart rate, CO = cardiac output, α-MD = α-methyldopa. *p < 0.05, †p 1 < p > 0.05.
changes in the various hemodynamic parameters were observed after placebo administration.

Administration of isoleucine with α-methyldopa attenuated most of the fall in MAP and TPR observed after α-methyldopa administration. Supine MAP tended to fall 7 hours after α-methyldopa administration; however, this reduction was not statistically significant ($p > 0.05$). The small fluctuations in TPR were not statistically significant and were similar to those observed after placebo administration. Cardiac output was unaffected.

Addition of benserazide to the dose regimen tended to produce a fall in MAP 7 hours after the α-methyldopa dose ($p < 0.05$ compared with control values). Part of this fall in MAP appeared to be mediated by a small reduction in TPR ($0.10 < p > 0.05$ compared with control values). Cardiac output was unaltered (see Table 2).

**Discussion**

Our results suggest that acutely administered α-methyldopa lowers blood pressure and TPR and reduces sympathetic activity in humans by acting predominantly within the central nervous system. Approximately 90% of the reduction in total NE and metabolite excretion as well as the fall in TPR was antagonized by administering large doses of isoleucine before α-methyldopa and then 2 and 4 hours later to maintain high concentrations of the amino acid while α-methyldopa concentrations were high. This antagonism is likely the result of competitive inhibition of α-methyldopa's transport across the blood-brain barrier. These results support our hypothesis, derived from animal experiments, but their importance in humans has not been critically investigated. Day and Rand proposed that, after metabolic conversion to α-methylnorepinephrine in sympathetic nerves, α-methyldopa can partially replace NE stores and then act as a "false transmitter." This action was suggested from in vitro experiments indicating that α-methylnorepinephrine was a much weaker α-adrenergic agonist than NE. If such a mechanism were to occur in humans, one might expect the reduction in NE metabolite excretion to be compensated for by a roughly equivalent amount of α-methylnorepinephrine or its metabolite, α-methylnormetanephrine. In the present study, however, excretion of α-methylnorepinephrine and α-methylnormetanephrine only accounted for approximately 10% of the reduction in total NE and metabolite excretion. This finding suggests that while some replacement of NE stores by metabolism of α-methyldopa to α-methylnorepinephrine occurs in humans after short-term administration, the release of α-methylnorepinephrine, rather than NE, from sympathetic nerves cannot account for the reduction in sympathetic activity or TPR following α-methyldopa administration.

Similar conclusions recently have been drawn from experiments in rabbits, which examined the effects of intravenous α-methyldopa on plasma NE levels as well as plasma and tissue α-methylnorepinephrine levels. Taken together, these biochemical results present strong evidence against a false transmitter type of mechanism being responsible for a substantial part of α-methyldopa's actions in humans.

A small, peripheral, presynaptic effect of α-methylnorepinephrine cannot be excluded by our results. Isoleucine antagonized approximately 90% of the fall in urinary catecholamine and metabolite excretion and virtually all the reduction in TPR after α-methyldopa administration. The remaining 10% or so could be due to presynaptic inhibition of NE release. α-Methylnorepinephrine inhibits NE release from sympathetic nerves in vitro pharmacological preparations by selectively activating presynaptic α-adrenergic receptors. Whether α-methylnorepinephrine is actively released from sympathetic nerves to subsequently inhibit NE release or passively diffuses to inhibit release of NE during nerve stimulation is not known. The finding that α-methylnorepinephrine and α-methylnormeta-

### Table 2. (continued)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>1 hr</th>
<th>2 hr</th>
<th>3 hr</th>
<th>4 hr</th>
<th>5 hr</th>
<th>6 hr</th>
<th>7 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HR (beats/min)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>69 ± 4</td>
<td>69 ± 4</td>
<td>69 ± 4</td>
<td>66 ± 4</td>
<td>66 ± 4</td>
<td>66 ± 4</td>
<td>66 ± 4</td>
<td>66 ± 4</td>
<td>66 ± 4</td>
</tr>
<tr>
<td>73 ± 3</td>
<td>76 ± 6</td>
<td>66 ± 6</td>
<td>66 ± 6</td>
<td>66 ± 6</td>
<td>66 ± 6</td>
<td>66 ± 6</td>
<td>66 ± 6</td>
<td>66 ± 6</td>
</tr>
<tr>
<td>73 ± 3</td>
<td>68 ± 4</td>
<td>70 ± 4</td>
<td>70 ± 4</td>
<td>70 ± 4</td>
<td>70 ± 4</td>
<td>70 ± 4</td>
<td>70 ± 4</td>
<td>70 ± 4</td>
</tr>
<tr>
<td>71 ± 4</td>
<td>74 ± 2</td>
<td>72 ± 2</td>
<td>76 ± 2</td>
<td>76 ± 2</td>
<td>76 ± 2</td>
<td>76 ± 2</td>
<td>76 ± 2</td>
<td>76 ± 2</td>
</tr>
<tr>
<td><strong>CO (L/min/m²)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.75 ± 0.14</td>
<td>5.24 ± 0.28</td>
<td>4.98 ± 0.19</td>
<td>5.48 ± 0.39</td>
<td>5.48 ± 0.39</td>
<td>5.48 ± 0.39</td>
<td>5.48 ± 0.39</td>
<td>5.48 ± 0.39</td>
<td>5.48 ± 0.39</td>
</tr>
<tr>
<td>5.13 ± 0.29</td>
<td>5.82 ± 0.41</td>
<td>5.47 ± 0.38</td>
<td>5.52 ± 0.31</td>
<td>5.52 ± 0.31</td>
<td>5.52 ± 0.31</td>
<td>5.52 ± 0.31</td>
<td>5.52 ± 0.31</td>
<td>5.52 ± 0.31</td>
</tr>
<tr>
<td>5.11 ± 0.47</td>
<td>5.64 ± 0.34</td>
<td>4.75 ± 0.36</td>
<td>5.37 ± 0.24</td>
<td>5.37 ± 0.24</td>
<td>5.37 ± 0.24</td>
<td>5.37 ± 0.24</td>
<td>5.37 ± 0.24</td>
<td>5.37 ± 0.24</td>
</tr>
<tr>
<td>5.39 ± 0.62</td>
<td>5.37 ± 0.43</td>
<td>5.32 ± 0.23</td>
<td>5.40 ± 0.33</td>
<td>5.40 ± 0.33</td>
<td>5.40 ± 0.33</td>
<td>5.40 ± 0.33</td>
<td>5.40 ± 0.33</td>
<td>5.40 ± 0.33</td>
</tr>
</tbody>
</table>
nephrine excretion were unaltered after the various \( \alpha \)-methyldopa regimens, despite alterations in the level of sympathetic activity, suggests that most of the \( \alpha \)-methylnorepinephrine is released from adrenergic nerves by passive diffusion. This possibility requires further investigation.

Several attempts have been made to antagonize the hypotensive action of \( \alpha \)-methyldopa in humans with inhibitors of dopa decarboxylase. In the present study, we attempted to abolish any residual, presumably peripheral, effects of \( \alpha \)-methyldopa by adding a small dose of benserazide to the isoleucine. Although benserazide inhibits central as well as peripheral dopa decarboxylase, central inhibition has not been achieved, even after administering doses five times larger than those used in our study.7 The addition of benserazide to isoleucine appeared to have little further effect on urinary NE and metabolite excretion, TPR, or cardiac output. Seven hours after \( \alpha \)-methyldopa administration, however, MAP decreased. Since the fall in TPR at this time was only marginal (0.10 < \( p > 0.05 \) compared with control), this effect most likely is related to cardiac output, which showed no tendency to rise, a trend seen on the other three study days.

It has been suggested that both \( \alpha \)-methyldopa and clonidine act at similar sites within the central nervous system. A comparison of the hemodynamic results of our study and those reported for clonidine indicates that, if the two drugs do act at common sites, their relative affinity for these sites differs. Clonidine tends to lower blood pressure by reducing cardiac output and has little or no effect on TPR. In contrast, acute therapeutic doses of \( \alpha \)-methyldopa that are administered orally, as in the present study, or intravenously, and chronic, oral doses lower blood pressure by reducing peripheral resistance. We did not investigate whether higher oral doses also reduced cardiac output.

Both drugs reduced NE and metabolite excretion. Martin et al. reported reductions in NE and metabolite excretion during therapy with clonidine similar to those found in the present study. Neither clonidine nor \( \alpha \)-methyldopa significantly altered the metabolic profile of NE. However, while these metabolic studies indicate that both drugs reduce sympathetic activity, regional studies on NE spillover from various organs will be required to locate precisely which organs are affected by the two drugs.

In summary, our results have demonstrated that therapeutic oral doses of \( \alpha \)-methyldopa administered acutely to hypertensive subjects reduce NE release from sympathetic nerves by actions within the central nervous system. The reductions in TPR also appear to be due predominantly to central mechanisms. The responses in MAP, although small, are consistent with \( \alpha \)-methyldopa exerting its hypotensive effect predominantly by acting on the central nervous system. Our urinary NE and metabolite studies suggest that less than 10% of \( \alpha \)-methyldopa's effects on NE release are due to peripheral mechanisms.

References


Evidence for a predominantly central hypotensive effect of alpha-methyldopa in humans.
A Bobik, G Jennings, G Jackman, C Oddie and P Korner

Hypertension. 1986;8:16-23
doi: 10.1161/01.HYP.8.1.16

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1986 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/8/1/16

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/