Effect of Methyldopa on Brain Cholinergic Neurons Involved in Cardiovascular Regulation
A Study in Conscious Spontaneously Hypertensive Rats

Jerry J. Buccafusco

SUMMARY Chemical stimulation of brain cholinergic neurons in many species can produce hypertension. Recent studies in this laboratory have demonstrated that clonidine inhibits this central cholinergic pressor response by inhibiting the biosynthesis of brain acetylcholine. This study was designed to determine whether methyldopa, like clonidine, could inhibit brain cholinergic neurons involved in cardiovascular regulation in freely-moving spontaneously hypertensive rats (SHR). Intravenous (i.v.) injection of methyldopa (50–200 mg/kg) produced a dose-related fall in blood pressure (29/15–54/33 mm Hg) in SHR. Intracerebroventricular (i.c.v.) injection of hemicholinium-3 (HC-3) in SHR evoked a fall in arterial pressure through inhibition of acetylcholine synthesis. Doses of HC-3 (10 µg, or 15 µg, i.c.v.) and methyldopa (50 mg/kg, i.v.) were administered to produce small reductions in arterial pressure in SHR (7–14 mm Hg diastolic, respectively). When the two agents were injected simultaneously, however, a greater than additive response was obtained (p < 0.05). Central injection of echothiophate (a long-acting cholinesterase inhibitor) to potentiate brain cholinergic activity resulted in a sustained hypertensive response (>40 mm Hg) in SHR for at least 150 minutes. Simultaneous injection of or pretreatment with methyldopa (100 mg/kg, i.v.) inhibited the pressor response to echothiophate over a time course similar to its antihypertensive response in untreated SHR. Methyldopa, however, was completely ineffective in altering the hypertensive response to central injection of carbachol (1 µg, i.c.v.). This difference in methyldopa susceptibility between the indirect-acting (echothiophate) and direct-acting (carbachol) cholinergic agonists may be related to an inhibiting effect of methyldopa on brain acetylcholine release. These data support our previous studies with clonidine and suggest a cholinergic component in the antihypertensive action of these drugs. (Hypertension 6: 614–621, 1984)

KEY WORDS • methyldopa • spontaneously hypertensive rats

The antihypertensive actions of drugs like clonidine and methyldopa are believed to be mediated through the activation of brain adrenergic receptors.1, 2 These receptors, however, do not appear to be located either presynaptically or postsynaptically upon central adrenergic neurons, since the antihypertensive effect of clonidine is not affected by drug treatments which cause depletion of brain catecholamines or which destroy adrenergic nerve endings.2, 3 Likewise, the hypotensive action of methyldopa is unaffected following severe depletion of brain catecholamines.6 Recent studies in this laboratory have demonstrated that clonidine produces a marked inhibition of brain acetylcholine (ACh) synthesis through stimulation of central α2-adrenergic receptors.7, 8 We have hypothesized that these α2-adrenergic receptors may be located on cholinergic nerve terminals, as they are known to exist on parasympathetic, postganglionic nerve endings where they serve to inhibit acetylcholine release.9, 10 These studies may explain the common "anticholinergic" side effects, such as drowsiness and dry mouth, which are experienced by patients on clonidine and methyldopa therapy. Since their antihypertensive actions do not appear to be mediated through central catecholaminergic neurons, but require intact α2-adrenergic receptors, it is conceivable that inhibition of central cholinergic activity via central α2-adrenergic stimulation also may play a part in lowering blood pressure.

In support of this hypothesis are the following findings: 1) chemical stimulation of brain cholinergic receptors in several species including humans (for review11) produces a hypertensive response. 2) The centrally mediated pressor response to cholinesterase

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Supported by Grant HL 30046 from the National Heart, Lung, and Blood Institute.

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Received July 15, 1983; revision accepted March 14, 1984.
Inhibitors is greatly potentiated in spontaneously hypertensive rats (SHR) as compared to their normotensive controls.\textsuperscript{3,13,14} 3) Inhibition of brain ACh synthesis with subsequent depletion of ACh levels, as well as blockade of central muscarinic receptors, results in a decreased arterial pressure in unanesthetized SHR.\textsuperscript{13-15}

The purpose of the present study was to determine whether methyldopa, like clonidine, could interact with central cholinergic neurons involved in cardiovascular regulation. Experiments were performed in freely-moving SHR to examine the dose-response and antihypertensive profile of methyldopa in this animal model. This is the first report to my knowledge of the effects of intravenous (i.v.) administration of methyldopa in the SHR. The cardiovascular responses to inhibition and augmentation of central cholinergic activity were examined in these animals in the presence or absence of methyldopa.

Methods

Male SHR of the Wistar strain were obtained from Taconic Farms Inc., Germantown, New York. The animals were housed in a special barrier room separated from other rat strains and allowed free access to tap water and food (Wayne Lab Blocks). At the time of the experiments the rats were 15 to 18 weeks old. They were maintained on a 12-hour-light/12-hour-dark cycle before and after the surgical procedures.

Surgical Procedures

Rats were anesthetized with methohexital sodium (60 mg/kg, i.p.) and placed in a stereotaxic frame according to the coordinate systems provided by Konig and Klippel.\textsuperscript{16} A 28-gauge Teflon cannula guide was permanently implanted in the skull and directed at the left lateral cerebral ventricle, as described previously.\textsuperscript{17} Rats were allowed at least 5 days to recover from this procedure.

Animals were then reanesthetized with methohexital, and a catheter (PE 50) was implanted in the left iliac artery with its tip at the origin of the abdominal aorta. The catheter was exteriorized at the nape of the neck, passed through a spring support, and connected to a water-tight swivel for the direct recording of arterial blood pressure. A second catheter was implanted in the right jugular vein and brought out at the nape of the neck to permit i.v. injection of drug solutions. The swivel cannula was mounted 30 cm above the cage in which the animal remained for the duration of the experiment. The venous catheter was filled with saline and plugged with a 22-gauge stainless steel stilette. The arterial line was continuously flushed (8.6 ml/day) with saline containing 50 units/ml of sodium heparin. The animal was allowed to recover for at least 24 hours before the first blood pressure recording.

Experimental Procedures

Arterial blood pressure (BP) was recorded from unanesthetized, freely moving rats by connecting the arterial line to a Statham P23Gb pressure transducer (Oxnard, California) connected to a Coulbourn Instrument. This is the first report to my knowledge of the effects of intravenous (i.v.) administration of methyldopa in the SHR. The cardiovascular responses to inhibition and augmentation of central cholinergic activity were examined in these animals in the presence or absence of methyldopa.

Drugs were administered i.v. by connecting a 3-way stopcock to the venous line. Methyldopa or vehicle was delivered by a Harvard syringe pump (South Natick, Massachusetts) at the rate of approximately 0.3 ml/min up to a maximum volume of 1 ml. Although methyldopa most often has been administered orally (p.o.) or intraperitoneally (i.p.), the i.v. route was chosen to preclude any variability in the rates of absorption from nonvascular sites; and to avoid handling of the animal during drug administration. All other drugs given i.v. were administered as a bolus. In all cases the catheter was flushed with 0.2 ml of saline.

Drugs were injected centrally by the intracerebroventricular (i.c.v.) route in a volume of 10 µl through a 28-gauge stainless steel injection cannula. The cannula was connected via Tygon microtubing to a Hamilton syringe. The drugs were dissolved in normal saline, and the injection cannula was inserted through the guide into the ventricle without disturbing the animal. Drug solutions were administered through a Harvard syringe pump set to deliver at the rate of 10 µl/30 sec.

Experimental Protocol

Rats were divided into three groups to determine 1) the effect of partial central inhibition of ACh synthesis with hemicholinium-3 (HC-3) on the hypotensive response to methyldopa; 2) the effect of methyldopa on the centrally-induced hypertensive response to an indirect acting cholinergic agonist, echothiophate; and 3) the effect of methyldopa on the centrally-mediated hypertensive response to a direct-acting cholinergic agonist, carbachol. No animal was used more than once in an experiment unless specifically stated.

Drugs

Methyldopa was obtained from Merck Sharp & Dohme (West Point, Pennsylvania) and administered as methyldopate hydrochloride. This methylester of methyldopa was used primarily for its increased solubility. Preliminary experiments with both compounds revealed a similar profile for their antihypertensive responses in the SHR. Norepinephrine bitratrate, tyramine hydrochloride, angiotensin II, HC-3, and carbachol chloride were obtained from Sigma Chemical Company (St. Louis, Missouri). Echthiophate iodide was generously supplied by Ayerst Laboratories (New York, New York). All drug doses refer to their respective salts.

Statistics

Values are presented as means ± SEM. The difference between means of two groups was estimated by
using Student's *t* test for unpaired data (or in cases where each animal served as its own control, a *t* test for paired data was used) and was considered significant when *p* < 0.05 (two-tailed analysis). Comparisons between means of several populations were performed by analysis of variance (ANOVA) or an ANOVA for repeated measures.

**Results**

Preinjection values for systolic blood pressure, diastolic blood pressure, and heart rate recorded from the 60 unanesthetized SHR averaged, respectively, 204 ± 3 mm Hg, 131 ± 3 mm Hg, and 373 ± 5 bpm. Basal levels were not significantly different among the various subgroups in each experiment.

**Cardiovascular Response to Intravenous Methyldopa**

Intravenous injection of methyldopa produced a transient increase in blood pressure, which returned to preinjection levels within 5 minutes after the 50 and 100 mg/kg doses. In the case of the 200 mg/kg dose, the initial pressor phase was evident for up to 30 minutes after the start of the injection (Figure 1). Arterial pressure was increased by 34 ± 3/27 ± 2, 36 ± 4/26 ± 4, and 45 ± 2/34 ± 2 mm Hg respectively, following 50, 100, and 200 mg/kg of methyldopa. By 60 to 90 minutes, however, all doses resulted in a significant, dose-related fall in blood pressure, which became maximal by 2 hours. In a few experiments carried out for longer time periods, blood pressure began to return toward baseline at 3 hours. Injection of methyldopa vehicle (up to 1 ml/animal) produced no significant alteration in arterial pressure. Systolic blood pressure was maximally reduced by 29 to 54 mm Hg and diastolic by 15 to 33 mm Hg over the three doses tested (Figure 1).

The hypotensive response to methyldopa in all cases was associated with a dose-related increase in heart rate (Figure 2). This response peaked by about 60 minutes and returned toward control levels by 150 minutes. Heart rate was maximally increased by 95 to 145 bpm over the three doses tested.

**Effect of Hemicholinium-3 on the Hypotensive Response to Methyldopa**

Inhibition of brain ACh synthesis can be produced by i.c.v. injection of HC-3. Injection of 20 μg of this substance leads to depletion of brain ACh levels and produces a marked fall in blood pressure in SHR. In this experiment, 10 or 15 μg of HC-3 was injected i.c.v. to produce a modest reduction in blood pressure, in this case a maximum decrease in diastolic pressure of 9 ± 2 and 15 ± 3 mm Hg, respectively. The entire profile of the hypotensive response is illustrated in Figure 3. Also depicted is the response to 50 mg/kg of methyldopa, i.v. alone and in combination with either the 10 or 15 μg dose of HC-3. ANOVA revealed a significant between-groups difference for the three curves that represented 10 μg HC-3 alone, methyldopa alone, and 10 μg HC-3 plus methyldopa, *F* = 4.69

![Figure 1. Effect of methyldopa vehicle (squares) and methyldopa 50 mg/kg (triangles), 100 mg/kg (circles), and 200 mg/kg (diamonds) on blood pressure of SHR. Each point represents the mean of five to eight experiments. Max refers to the average value ± SEM of the maximal decrease in blood pressure obtained over the entire time course. The curves for each dose exhibited a significant between-treatment component, *F* = 15.2 (3,21), *p* < 0.01 systolic; *F* = 4.3 (3,21), *p* < 0.05 diastolic.](http://hyper.ahajournals.org/doi/pdf/10.1161/01.hyp.6.5.616)

![Figure 2. Effect of methyldopa vehicle (squares) and methyldopa 50 mg/kg (triangles), 100 mg/kg (circles), and 200 mg/kg (diamonds) on heart rate. Each point represents the mean of five to eight experiments. Max refers to the average value ± SEM of the maximal increase in heart rate obtained over the entire time course. The curves for each dose exhibited a significant between-treatment component, *F* = 20.6 (3,21), *p* < 0.01.](http://hyper.ahajournals.org/doi/pdf/10.1161/01.hyp.6.5.616)
METHYLDOPA AND CENTRAL CHOLINERGIC BP CONTROL/Buccafusco

(2,18), p < 0.05; and for the three curves representing 15 µg HC-3 alone, methyldopa alone, and 15 µg HC-3 plus methyldopa, F = 4.14 (2,14), p < 0.05. Inspection of Figure 3 reveals that the combined treatment was responsible for these differences. There was also a significant interactive component for the two groups of curves, F = 3.58 (18,171), p < 0.01, by ANOVA. The curves representing HC-3, 15 µg, methyldopa, and HC-3, 15 µg + methyldopa also exhibited a significant between-treatment component, F = 4.34 (18,126), p < 0.01.

Effect of Methyldopa on the Pressor Response to Central Cholinergic Stimulation

Results from the previous experiment suggested the possibility that methyldopa may, like HC-3, inhibit the function of central cholinergic neurons involved in blood pressure regulation. Heuristically, therefore, methyldopa should inhibit the hypertensive response induced by activation of these cholinergic neurons. In this series of experiments, activation of central cholinergic receptors either indirectly with echothiophate, a long-acting acetylcholinesterase inhibitor, or directly with carbachol, a direct receptor agonist, produced an elevation of arterial pressure in freely moving SHR (Figures 4–6). The ability of methyldopa to alter this response to central cholinergic activation was evaluated. To rule out a possible peripheral sympatholytic action of methyldopa which could inhibit these pressor responses, three SHR were injected intravenously with norepinephrine, tyramine, and angiotensin at doses that produced blood pressure increases equal in magnitude to echothiophate and carbachol (i.c.v.). After control responses to the vasoactive agents were obtained, methyldopa (100 mg/kg, i.v.) was injected, and 1 hour later the series of vasoactive agents was administered.

In contrast to their similar vascular actions, HC-3 and methyldopa evoked opposite changes in heart rate. Methyldopa produced a maximum increase of 95 bpm, and HC-3 (10 µg) produced a maximum decrease of 29 bpm (Table 1). Combined treatment resulted in a maximum increase of 64 bpm, which was not significantly different from the response obtained from methyldopa alone.

**Table 1. Effects of Various Drug Regimens on Heart Rate in Spontaneously Hypertensive Rats**

<table>
<thead>
<tr>
<th>Drug regimen</th>
<th>No. of rats</th>
<th>Predrug level (bpm)</th>
<th>Maximum HR change (bpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methyldopa, 50 mg/kg i.v.</td>
<td>7</td>
<td>357 ± 12</td>
<td>95 ± 14</td>
</tr>
<tr>
<td>HC-3, 10 µg i.c.v.</td>
<td>7</td>
<td>393 ± 21</td>
<td>29 ± 7</td>
</tr>
<tr>
<td>Methyldopa + HC-3</td>
<td>7</td>
<td>385 ± 11</td>
<td>64 ± 14</td>
</tr>
<tr>
<td>Methyldopa, 100 mg/kg i.v.</td>
<td>5</td>
<td>399 ± 12</td>
<td>96 ± 11</td>
</tr>
<tr>
<td>Echothiophate, 50 ng i.c.v.</td>
<td>5</td>
<td>360 ± 11</td>
<td>60 ± 12</td>
</tr>
<tr>
<td>Methyldopa + echothiophate</td>
<td>5</td>
<td>395 ± 26</td>
<td>97 ± 19</td>
</tr>
<tr>
<td>Carbachol, 1 µg</td>
<td>6</td>
<td>355 ± 12</td>
<td>77 ± 14</td>
</tr>
<tr>
<td>Methyldopa + carbachol</td>
<td>6</td>
<td>491 ± 12*</td>
<td>79 ± 11</td>
</tr>
</tbody>
</table>

Data obtained from carbachol experiments were from a group of six rats; each animal served as its own control. HC-3 = hemicholinium-3.

*Value obtained 1 hour after methyldopa pretreatment.
repeated. The data from this experiment are presented in Table 2. Methyldopa pretreatment did not significantly alter the pressor response to any of the three vasoactive agents. Therefore, any peripheral effects of methyldopa would be of no consequence in the subsequent experiments with echothiophate and carbachol.

Central (i.c.v.) injection of 50 ng of echothiophate in freely-moving SHR evoked an immediate increase in arterial pressure, which was maintained for at least 150 minutes (Figure 4). Simultaneous administration of echothiophate (50 ng, i.c.v.) and methyldopa (100 mg/kg, i.v.) resulted in a transient increase in blood pressure which decayed rapidly and was significantly lower than the echothiophate alone response by 90 minutes and which fell to below pretreatment levels by 120 minutes. Echothiophate also elicited a fall in heart rate of 60 bpm, which was abolished in the presence of methyldopa (Table 1).

As with the inhibitory action of methyldopa administered simultaneously with echothiophate, pretreatment with methyldopa (100–200 mg/kg) 1 hour prior to the cholinesterase inhibitor also attenuated the echothiophate-induced pressor response (Figure 5). The 200 mg/kg dose of methyldopa was slightly, but not statistically more effective than the 100 mg/kg dose. The inhibitory effect of methyldopa was even more apparent at the later time points. ANOVA of the times 60–90 minutes after echothiophate for the three groups revealed, for example, a significant between-group component: $F = 10.4$ (2,12), $p < 0.01$ for diastolic pressure changes.

Central (i.c.v.) injection of 1 µg of carbachol in freely-moving SHR evoked an immediate increase in arterial pressure similar in magnitude to that evoked by 50 ng of echothiophate. The response duration was much shorter, however, with blood pressure returning to preinjection levels by 80 minutes (Figure 6). The effect of methyldopa was determined by pretreating animals with 100 or 200 mg/kg, i.v. of methyldopa followed 1 hour later by carbachol (1 µg, i.c.v.). The data illustrated in Figure 6 indicate, unlike its effect on the echothiophate pressor response, that methyldopa produced no significant alteration of the carbachol-induced pressor response. Even at the later time points ANOVA revealed no significant between-group differences for 60–80 minutes: $F = 2.5$ (2,15), $p > 0.05$ for diastolic pressure changes.
Table 2. Response to Vasoactive Agents Before and 1 Hour Following Methyldopa Administration in Spontaneously Hypertensive Rats (SHR)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Increase in blood pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>42 ± 4 52 ± 6 38 ± 3 62 ± 3 52 ± 9</td>
</tr>
<tr>
<td>Methyldopa</td>
<td>48 ± 7 63 ± 3 47 ± 6 65 ± 5 60 ± 1</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>27 ± 4 30 ± 5 32 ± 4 40 ± 3 43 ± 4</td>
</tr>
<tr>
<td>Methyldopa</td>
<td>32 ± 4 38 ± 4 27 ± 4 43 ± 6 52 ± 3</td>
</tr>
</tbody>
</table>

Data were derived from three animals and expressed as the mean change in arterial pressure ± SEM. Each vasoactive agent was injected i.v. at the specified dose before and 1 hour after 100 mg/kg methyldopa injected i.v. ANG = angiotensin.

Discussion

For several years, methyldopa has been administered i.v. in the treatment of essential hypertension when parenteral medication is indicated and in the initial treatment of hypertensive crises. Generally, when methyldopa is slowly infused over a 30- to 60-minute period, arterial pressure is reduced within 3 hours, and heart rate is unchanged or occasionally decreased. Although one potential cardiovascular adverse reaction associated with intravenous methyldopa is a "paradoxical" pressor response. Although this side effect can be minimized by employing a slow infusion rate, animal studies have demonstrated that this side effect is potentially lethal. Also, Blower and co-workers observed a sustained pressor response during a prolonged infusion in the anesthetized, normotensive dog. It is possible that the severity of this side effect may increase with the severity of the hypertensive disease. In the present study, marked pressor responses that often increased systolic pressure to 250 mm Hg were observed following i.v. methyldopa. In our preliminary studies, we found that rapid injection of the higher doses resulted in the death of several SHR. The mode of lethality was not due to the pressor response per se, since other hypertensive agents that evoked comparable pressor responses did not cause death. While the nature of this response is not well understood, our results indicate that the SHR would be a good animal model for further study.

One difference between the clinical response and that obtained in SHR is the cardioacceleration which occurred during the decrease in blood pressure. LeDoux and co-workers, who observed a similar response following i.p. injection of methyldopa in SHR, suggested that the tachycardiac response might be activated reflexly in response to baroreceptor stimulation accompanying the fall in arterial pressure. While the baroreceptor reflex may contribute to this response, our time course data (Figure 2) clearly indicated that heart rate increased prior to a significant fall in blood pressure (Figure 1) and then declined toward baseline while the blood pressure was still maximally decreased. This temporal dissociation between the tachycardiac and antihypertensive response of methyldopa suggests a direct chronotropic effect of the drug on the heart. In at least one clinical report where a pressor response to i.v. methyldopa was observed, an increase in heart rate accompanied the increase in blood pressure. These observations may be consistent with the action of a peripheral metabolite of methyldopa on the heart, as suggested by Nijkamp and co-workers.

With the cardiovascular profile to i.v. methyldopa in SHR defined, the remainder of the study was designed to examine any possible interaction of methyl-
methyldopa with brain cholinergic systems involved in cardiovascular regulation. Studies by this author and other workers have demonstrated that the maintenance of elevated blood pressure in SHR is at least partially dependent upon an intact, functioning, brain cholinergic system. This can be readily demonstrated following i.c.v. injection of HC-3. The ability of HC-3 to accentuate the antihypertensive action of methyldopa suggests that the two agents may act on the same substrate to decrease blood pressure. While the ACh depleting actions of HC-3 are well known, data from this study indicate that, like clonidine, methyldopa may also inhibit the biosynthesis of ACh. This is not the first report of an anti-ACh drug potentiating the cardiovascular actions of methyldopa. In 1976 DeJong and Nijkamp reported that systemic injection of atropine greatly potentiated the fall in blood pressure following local microinjection of methylnorepinephrine into the nucleus tractus solitarii of anesthetized, vagotomized rats.

Central injection of cholinesterase inhibitors evokes a pressor response in rats which is dependent upon intact, functioning stores of brain ACh. Interference with the synthesis or release of brain ACh blocks the pressor response to inhibition of brain acetylcholinesterase, but not the pressor response to direct-acting cholinergic agonists. The ability of methyldopa to block the pressor response to central injection of echothiophate, but not that to carbachol, is consistent with the concept that methyldopa, like clonidine, can inhibit the release of brain ACh. In support of this hypothesis are the results of a study recently completed in this laboratory (unpublished) which demonstrated that methyldopa can produce a marked inhibition of brain ACh turnover rates in certain brain regions.

Whether drugs like clonidine and methyldopa lower blood pressure via their central "anticholinergic" effects cannot yet be determined since the findings obtained thus far are primarily correlative. However, it is apparent that while the antihypertensive response to methyldopa is prevented by drugs that destroy brain catecholaminergic nerve endings, this response is unaffected by drugs that cause depletion of endogenous brain catecholamines. The implication of these findings is that methyldopa, like clonidine, stimulates (presumably via its active metabolite methylnorepinephrine) alpha-adrenergic receptors on noncatecholaminergic neurons to evoke its antihypertensive action. Evidence from this laboratory and others (cited above) suggests that these adrenergic receptors may be located on cholinergic neurons. The fact that methyldopa reversed the pressor response to echothiophate with a similar onset of action (in about 1 hour) as its antihypertensive response in untreated animals suggests that methyldopa must first be biotransformed to an active metabolite to inhibit cholinergic neurons (e.g., clonidine that is not biotransformed can inhibit brain cholinergic neurons in less than 20 minutes). This strongly implies that adrenergic neurons either directly innervate or are closely juxtaposed to these cholinergic neurons. This hypothesis of a cholinergic link in the antihypertensive action of clonidine and methyldopa is intriguing, but it may not complete the entire story. For example, anticholinergic drugs, while being antihypertensive agents, do not lower blood pressure significantly in normotensive animals, whereas clonidine and methyldopa may produce hypotension. It is possible, however, that at least one component leading to neurogenic hypertension is mediated through altered brain cholinergic activity.

Acknowledgments
The author thanks Laura F. Shuster for skillful technical assistance and Jennie Doby for expert typing of this manuscript.

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Hypertension. 1984;6:614-621
doi: 10.1161/01.HYP.6.5.614

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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