Dopamine Selectively Inhibits Aldosterone Responses to Angiotensin II in Humans

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SUMMARY Previous studies have suggested that dopamine may have an important role as an inhibitor of aldosterone secretion in humans. Recent studies have also suggested that the adrenergic nervous system may have an important role in controlling aldosterone secretion. The present study investigated the effects of dopamine on aldosterone secretion in response to angiotensin II, with and without pretreatment with propranolol, and to adrenocorticotropic hormone, another known stimulator of aldosterone secretion. Nine normal subjects in balance at 10 mEq sodium intake received dopamine (4 µg/kg/min) or vehicle for 270 minutes on 2 consecutive days on three separate occasions. After 120 minutes of dopamine infusion, the subjects received a 30-minute intravenous infusion of angiotensin II (in cumulative doses of 0.5, 1, 2, 4, and 6 pmol/kg/min), angiotensin II after oral pretreatment with propranolol, or adrenocorticotropic hormone (in cumulative doses of 0.5, 1, 2, and 5 U/hr). Aldosterone responses to 2, 4, and 6 pmol/kg/min of angiotensin II (without propranolol) were greater in vehicle-treated than in dopamine-treated subjects (p < 0.05), as was the slope of the angiotensin II–vehicle dose-response curve (0.46, p < 0.05). Propranolol suppressed the aldosterone response to angiotensin II, but dopamine still inhibited the response. Aldosterone and cortisol secretion were stimulated equally by adrenocorticotropic hormone in dopamine-treated and vehicle-treated groups. These results suggest that dopamine selectively inhibits the aldosterone response to angiotensin II and that this response is not mediated by the activity of dopamine at β-adrenergic receptors.

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KEY WORDS • aldosterone • dopamine • aldosterone secretion • angiotensin II • β-adrenergic receptors

ALDOSTERONE, the primary sodium-retaining hormone in humans, is regulated by several known stimulating factors, including potassium, adrenocorticotropic hormone (ACTH), and angiotensin II. We have demonstrated previously that dopamine may be an important inhibitor of aldosterone secretion. Dopamine inhibited angiotensin II–stimulated aldosterone secretion in normal human subjects in metabolic balance at low sodium intake but had no observable effect on sodium-replete subjects. Other experimental evidence for the inhibitory role of dopamine includes the demonstration that the dopamine antagonist metoclopramide stimulates aldosterone secretion without affecting the known stimulators of aldosterone secretion. Dopamine blocks this action of metoclopramide in a dose-dependent manner and also has been shown to inhibit angiotensin II–stimulated aldosterone secretion in bovine adrenal cells in vitro. The finding that metoclopramide enhances angiotensin II–stimulated aldosterone secretion in rats and humans on a high sodium diet is consistent with the hypothesis that endogenous dopamine inhibits aldosterone secretion.

The adrenergic nervous system also has been implicated in the control of aldosterone secretion. In vivo adrenergic agents secondarily stimulate aldosterone secretion by acting primarily at β-adrenergic receptors on renal juxtaglomerular cells to stimulate renin secretion and thus enhance angiotensin formation. Since dopamine has β-adrenergic as well as dopaminergic effects, dopamine may exert a non-specific stimulatory action at β-adrenergic receptors to inhibit aldosterone secretion directly.

The present study was undertaken to investigate the...
specificity of dopamine’s ability to inhibit angiotensin II-mediated aldosterone secretion in vivo in humans by assessing 1) the ability of dopamine to inhibit angiotensin II–induced increases in circulating aldosterone in sodium-depleted normal subjects, 2) the effect of β-adrenergic blockade with propranolol on dopaminergic inhibition of aldosterone secretion, and 3) the effect of dopamine on ACTH-induced aldosterone secretion.

Subjects and Methods

The ability of dopamine to inhibit angiotensin II–induced increases in circulating aldosterone levels was studied in nine normal white men (age, 20–30 years) with normal arterial blood pressure and no history of renal disease. These subjects and the study protocol differed from those reported previously. The protocol was approved by the Human Experimentation Committee of the University of Virginia Medical Center, and written informed consent was obtained from all subjects. For 7 days before the experiment began, the subjects received a diet containing 10 mEq sodium, 60 mEq potassium, 1 g of protein per kilogram body weight, and 2680 cal/day at the Clinical Research Center. Consecutive 24-hour urine samples were collected for each day of the diet and analyzed for sodium, potassium, and creatinine.

The nine subjects were studied in the following manner. No food was given after 2400 before Day 1 of the study, when the subjects assumed the supine position until completion of the study. At 0530 on Day 1, a heparin lock for obtaining blood samples was placed in each subject’s left antecubital vein and an intravenous infusion of 5% glucose solution at 1 ml/min was begun in the right antecubital vein. At 0600, the subjects completed 24-hour urine collections, and blood pressure monitoring with an Arteriosonde (Hoffman-LaRoche, Nutley, NJ, USA) was initiated and continued every 2 minutes until the study ended. At 0630 and 0700 (−30 and 0 minutes of the study), control blood samples were obtained for determination of serum sodium, potassium, and prolactin concentrations, plasma renin activity (PRA), and cortisol and aldosterone concentrations. After completion of blood sampling at 0700, an intravenous infusion of either 5% glucose solution (vehicle), 0.1 ml/min, or dopamine, 4 μg/kg/min, was initiated with a Harvard infusion pump (S. Natick, MA, USA) and continued for 270 minutes. The dose of dopamine was selected on the basis of approximately 75% inhibition of metoclopramide-induced aldosterone responses in previous studies. Blood sampling was repeated at 30-minute intervals throughout the remainder of the study. After completion of the blood sampling at 0900, five 30-minute infusions of angiotensin II at successively increasing dose levels (0.5, 1, 2, 4, and 6 pmol/kg/min) were performed. The angiotensin II infusions were performed on each of 2 consecutive study days, in the presence of dopamine on one day and vehicle on the other day. The order of administration of vehicle and dopamine was randomized, and the subjects and laboratory technicians were unaware of which agent was being administered on either day. The dose of angiotensin II was selected to span from threshold through a midrange of the angiotensin II–aldosterone dose-response curve; the maximum response could not be achieved because of the limitations of the rise in blood pressure.

To assess the effect of propranolol-induced β-adrenergic blockade on dopaminergic inhibition of aldosterone secretion, six of the original nine subjects consumed the 10 mEq sodium diet for 7 days after 4 weeks on an ad libitum diet. The subjects also took propranolol, 40 mg p.o., at 12-hour intervals during the diet and were studied in a manner identical to that described for the angiotensin II–dopamine studies. The dose of propranolol was selected on the basis of its ability to abolish completely the increase in heart rate from supine to upright posture for 2 minutes.

To assess the effect of dopamine on ACTH-induced aldosterone secretion, the same six subjects again consumed a 10 mEq sodium diet for 7 days after 4 weeks on an ad libitum diet. The subjects were then studied in a manner identical to that described for the angiotensin II–dopamine studies except that ACTH (0.5, 1, 2, and 5 U/hr) was substituted for the five 30-minute angiotensin II infusions. The dose of ACTH was selected to span from threshold through maximum aldosterone responses.

Serum sodium and potassium concentrations were measured by flame photometry (Model 143; Instrumentation Laboratories, Watertown, MA, USA). Plasma aldosterone concentration was measured by using the method of Buhler et al. After incubation, PRA was determined by radioimmunoassay of angiotensin I, as detailed by Sealey et al. Plasma cortisol was measured by specific radioimmunoassay. Serum prolactin was measured by the method of Sinha et al. All samples collected on dopamine and vehicle study days were assayed simultaneously for each protocol. The intraassay coefficients of variation were 6% for plasma aldosterone concentration; 6% for PRA; 8% for plasma cortisol concentration; and 5% for serum prolactin concentration. The sensitivities of these assays were 0.5 ng/dl for plasma aldosterone concentration; 0.1 ng angiotensin I per milliliter per hour for PRA; 1 μg/dl for plasma cortisol concentration; and 3 ng/ml for serum prolactin concentration.

Values obtained at 0630 and 0700 (−30 and 0 minutes of the study) before the administration of any pharmacological agents were used as control values for statistical comparisons. Data are expressed as means ± 1 SE. Statistical analysis was performed using analysis of variance, and a p value less than 0.05 was considered significant. Dose-response curves under different experimental conditions were assessed for differences using linear regression analysis with a test of homogeneity of slopes (partial F must exceed p < 0.005).
Results

The characteristics of the subjects in sodium balance on Day 6 of a constant low sodium diet before each set of experiments are summarized in Table 1; no differences in urinary sodium excretion, serum sodium, serum potassium, blood pressure, plasma cortisol, or serum prolactin were noted. Before the angiotensin II–dopamine study, however, plasma aldosterone concentrations were significantly lower before vehicle infusion than before dopamine infusion (p < 0.05). Before the ACTH-dopamine study, PRA was significantly lower before dopamine infusion than before vehicle infusion (p < 0.05).

Responses to Angiotensin II and Dopamine Infusion

During the initial 120 minutes of the angiotensin II–dopamine study in which dopamine or vehicle was infused, plasma aldosterone concentrations did not vary significantly from baseline and were not different between the two treatment groups. Thereafter, plasma aldosterone concentration increased progressively in vehicle-treated subjects (p < 0.05) with each cumulative dose increase of angiotensin II, while in dopamine-treated subjects it did not increase significantly from baseline until 210 minutes (Figure 1). Plasma aldosterone concentration at 2, 4, and 6 pmol/kg/min of angiotensin II was lower in dopamine-treated than in vehicle-treated subjects (p < 0.05). The slope of the angiotensin II–vehicle dose-response curve (0.46) was significantly greater than that of the angiotensin II–dopamine dose-response curve (0.26; p < 0.05).

Values for plasma cortisol, serum potassium, serum sodium, serum prolactin, and PRA throughout the study are shown in Figure 2. Cortisol values in dopamine-treated subjects were significantly higher (p < 0.05) than in vehicle-treated subjects at 180, 210, and 240 minutes. Potassium concentration was higher at 30 minutes in dopamine-treated subjects and higher at 210 minutes in vehicle-treated subjects (p < 0.05). Sodium values were not different at any time during the study. In dopamine-treated subjects, prolactin was suppressed from baseline (p < 0.05) by 150 minutes and levels were significantly less than in vehicle-treated subjects from 180 to 270 minutes (p < 0.05). Each incremental dose of angiotensin II suppressed PRA in a stepwise fashion. The PRA was significantly lower than baseline values by 150 minutes on the dopamine infusion day and by 210 minutes on the vehicle infusion day (p < 0.05). There were no significant between-group differences in PRA or systolic blood pressure at any time during the study. Systolic blood pressure rise occurred significantly from baseline by 150 minutes in response to angiotensin II on the dopamine infusion day and by 240 minutes on the vehicle infusion day. Diastolic blood pressure did not change on the dopamine infusion day with angiotensin II but rose

Table 1. Characteristics of Subjects on Day 6 of a Constant Low Sodium Diet Before Angiotensin II or Adrenocorticotropic Hormone Studies

<table>
<thead>
<tr>
<th>Variable</th>
<th>Angiotensin II</th>
<th>Propanolol–Angiotensin II</th>
<th>ACTH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dopamine</td>
<td>Vehicle</td>
<td>Dopamine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dopamine</td>
</tr>
<tr>
<td>24-hour urine sodium (mEq)</td>
<td>15 ± 2</td>
<td>18 ± 4</td>
<td>11 ± 3</td>
</tr>
<tr>
<td>Serum sodium (mEq/L)</td>
<td>142 ± 1</td>
<td>142 ± 1</td>
<td>140 ± 1</td>
</tr>
<tr>
<td>Serum potassium (mEq/L)</td>
<td>3.8 ± 0.1</td>
<td>3.8 ± 0.1</td>
<td>4.1 ± 0.1</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>106 ± 3</td>
<td>111 ± 3</td>
<td>109 ± 1</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>69 ± 2</td>
<td>71 ± 2</td>
<td>60 ± 2</td>
</tr>
<tr>
<td>Plasma renin activity (ng ANG I/ml/hr)</td>
<td>3.2 ± 0.6</td>
<td>2.7 ± 0.5</td>
<td>3.6 ± 0.7</td>
</tr>
<tr>
<td>Plasma aldosterone (ng/dl)</td>
<td>39 ± 6*</td>
<td>23 ± 5</td>
<td>29 ± 5</td>
</tr>
<tr>
<td>Plasma cortisol (µg/dl)</td>
<td>13 ± 2</td>
<td>13 ± 1</td>
<td>13 ± 2</td>
</tr>
<tr>
<td>Serum prolactin (ng/ml)</td>
<td>7.3 ± 1.6</td>
<td>6.4 ± 1.0</td>
<td>9.7 ± 2.1</td>
</tr>
</tbody>
</table>

Values are means ± 1 SE. ACTH = adrenocorticotropic hormone; BP = blood pressure; ANG I = angiotensin I.

*p < 0.05, compared with values in vehicle-treated subjects.
significantly by 210 minutes on the vehicle day. In the final two time periods, diastolic blood pressure was higher in vehicle-treated than in dopamine-treated subjects (p < 0.05).

Responses to Propranolol Pretreatment and Angiotensin II and Dopamine Infusion

After administration of propranolol (40 mg p.o., b.i.d.) for 5 days, resting supine pulse rate decreased from 70 ± 3 to 54 ± 6 beats/min (p < 0.005) and standing pulse rate decreased from 77 ± 3 to 67 ± 3 beats/min (p < 0.01). Systolic and diastolic blood pressures were not changed significantly by propranolol.

Propranolol blunted the aldosterone response to angiotensin II infusion (p < 0.01; n = 6 with paired data; Figure 3). This observation was made by comparing the slope of the angiotensin II–aldosterone dose-response relationship in the six subjects in the absence (open circles in Figure 1) and presence of propranolol (open circles in Figure 3). Plasma aldosterone concentration did not increase significantly at any dose of angiotensin II in the presence of propranolol and dopamine, but it did increase significantly (p < 0.05) at angiotensin II doses of 0.5, 4.0, and 6.0 pmol/kg/min in the presence of propranolol and vehicle. In the presence of propranolol, dopamine infusion significantly blunted aldosterone responses to angiotensin II at doses of 2, 4, and 6 pmol/kg/min compared with values obtained during vehicle administration.

Cortisol values were significantly higher (p < 0.05) in dopamine-treated subjects than in vehicle-treated subjects only at 60 minutes (Figure 4) and did not vary significantly from baseline at any time in either treatment group. Potassium and sodium values were not different between groups at any time during the study. Prolactin values were significantly suppressed from baseline by dopamine throughout the study, and these values were significantly less than those obtained in the presence of vehicle from 60 to 270 minutes. The PRA was suppressed in the vehicle-treated group at 210 to 270 minutes (p < 0.05) but was not suppressed from baseline in the dopamine-treated group. There was no between-group difference in PRA at any time during the study. Systolic blood pressure rose significantly from baseline by 120 minutes on the dopamine infusion day and by 240 minutes on the vehicle infusion day in response to angiotensin II. Systolic blood pressure was higher with dopamine infusion than with vehicle infusion at 120 minutes (p < 0.05). Diastolic blood pressure did not change on the dopamine infusion day but rose significantly by 240 minutes on the vehicle infusion day (p < 0.05). No between-group differences in blood pressures were noted.
DOPAMINE INHIBITS ALDOSTERONE/Carley and Drake

DOPAMINE INHIBITS ALDOSTERONE/Cariy and Drake

Figure 4. Hormonal and electrolyte responses to dopamine or vehicle infusion and cumulative doses of angiotensin II in six normal volunteers pretreated with propranolol and in metabolic balance at 10 mEq sodium, 60 mEq potassium intake. Asterisk indicates values during dopamine infusion significantly different from values during vehicle infusion (p < 0.05).

Responses to Adrenocorticotropic Hormone and Dopamine Infusion

During the initial 120 minutes of the study in which dopamine or vehicle was infused, plasma aldosterone concentration was significantly higher (p < 0.05) in vehicle-treated than in dopamine-treated subjects at 90 and 120 minutes (Figure 5). However, during the rest of the study with progressive ACTH infusions, there was no difference in plasma aldosterone concentration between the two treatment groups. Plasma aldosterone concentration increased significantly from baseline by 120 minutes in the vehicle-treated group and by 150 minutes in the dopamine-treated group. The slopes of the ACTH-dopamine (0.32) and the ACTH-vehicle (0.22) dose-response curves were similar.

Plasma cortisol levels rose progressively with each increasing dose of ACTH and were significantly higher than baseline values at all doses of ACTH (Figure 6). There were no between-group differences in cortisol levels at any time during the study. Serum potassium values were similar throughout the study except at 30 minutes, when the levels were higher with vehicle than with dopamine infusion. Serum sodium levels were similar throughout the study. Serum prolactin was suppressed from baseline at 30 minutes of dopamine infusion (p < 0.05), and levels were undetectable at 60 minutes (see Figure 6). Prolactin concentration was significantly lower with dopamine than with vehicle infusion at 60 and 120 minutes. The PRA was similar between groups throughout the study except at 30 minutes when it was significantly less in the presence of dopamine. Blood pressure did not vary from baseline except on the dopamine treatment day, when diastolic blood pressure was lower than baseline at 120, 210, and 240 minutes (p < 0.05). No difference in blood pressure was noted between the two treatment groups except at 90 minutes, when the diastolic blood pressure was higher with vehicle than with dopamine infusion (p < 0.05).

Discussion

The results of the present study demonstrate in normal, sodium-restricted humans that 1) dopamine inhibits aldosterone responses to angiotensin II, 2) dopaminergic suppression of angiotensin II-induced
aldosterone secretion is unaffected by β-adrenergic blockade, and 3) dopamine does not attenuate ACTH-induced aldosterone secretion. These results suggest that dopamine selectively inhibits aldosterone responses to angiotensin II in humans.

Our finding that dopamine inhibited aldosterone responses to angiotensin II in the low sodium balance state is consistent with previous studies by our group. Administration of dopamine to normal subjects in the normal or high sodium balance state is not accompanied by any significant inhibition of angiotensin II-induced aldosterone responses. In the sodium-restricted state, however, dopamine significantly reduces the slope of the angiotensin II–aldosterone dose response curve to a value that is indistinguishable from that observed during high sodium intake. Conversely, Aguilera and Catt have demonstrated in sodium-loaded rats that the dopamine antagonist metoclopramide markedly increases the ability of angiotensin II to increase aldosterone secretion in vivo. This action of metoclopramide was completely abolished by dopamine administration, which suggests that the effects of metoclopramide on aldosterone secretion are due to its dopamine antagonist properties.

Taken together, these results suggest that dopamine may modulate alterations in angiotensin-induced aldosterone secretion with changes in sodium balance. Thus, angiotensin would induce large increases in aldosterone secretion during low sodium intake, when dopaminergic activity is low, and relatively small increases in aldosterone secretion during high sodium intake, when dopaminergic activity is increased. Indirect evidence in experimental animals and in humans, showing that urinary dopamine excretion is directly proportional to sodium intake, supports this hypothesis. Further studies of the effects of variations in sodium intake on the activity of dopaminergic neurons supplying the adrenal cortex as well as on adrenocortical dopamine content and turnover in experimental animals are warranted to determine the mechanism and site of action of dopamine on angiotensin-induced aldosterone secretion.

In the present study, dopaminergic suppression of angiotensin II–induced aldosterone secretion was still present after β-adrenergic blockade with propranolol. The degree of β-adrenergic blockade at cardiac receptors was monitored by heart rate responses, which were reduced significantly in both the supine and upright positions. Although aldosterone responses to angiotensin II during β-adrenergic blockade clearly were inhibited by dopamine compared with responses elicited by vehicle, aldosterone responses to angiotensin II were reduced by propranolol whether or not dopamine was given. The reduction of aldosterone response to angiotensin II in the presence of β-adrenergic blockade could be related to reduction of β-adrenergic stimulation of renin release from renal juxtaglomerular cells, with secondary reduction in circulating angiotensin II. The octapeptide is known to serve as a permissive factor in addition to an acute stimulator of aldosterone biosynthesis. However, PRA was not suppressed significantly by propranolol administration in the present study. Thus, another mechanism could be responsible for the suppressant effect of propranolol on angiotensin II–induced aldosterone responses. Irrespective of the mechanism of propranolol to inhibit aldosterone responses to angiotensin II, the present data demonstrated that dopamine does not suppress angiotensin II–induced aldosterone secretion by means of a β-adrenergic action.

Another major finding of the present study was that dopamine did not inhibit ACTH-stimulated aldosterone secretion in sodium-restricted normal subjects. Under identical conditions, dopamine effectively inhibited angiotensin-stimulated aldosterone secretion. Thus, the effect of dopamine appears to be selective for angiotensin-mediated responses. Although the effect of dopamine on potassium-induced aldosterone secretion has yet to be determined, we postulate on
the basis of current information that dopaminergic mechanisms impair aldosterone secretion by selective impairment of angiotensin-induced responses.

Alterations of other factors known to influence aldosterone secretion were not responsible for the inhibitory effects of dopamine observed in the present study. Changes in circulating sodium and potassium concentrations did not appear to explain the observed changes in plasma aldosterone concentration. In the angiotensin II–dopamine study, plasma cortisol (a monitor of circulating ACTH) was elevated in the dopamine-treated subjects relative to the vehicle-treated subjects at 180, 210, and 240 minutes. Thus, a possible elevation of ACTH secretion may have partially masked the full suppressant effect of dopamine on aldosterone secretion. Although the higher plasma cortisol concentrations in the dopamine studies may have been related to stress, no clinical effects suggestive of stress occurred during dopamine administration.

In the propranolol–angiotensin II–dopamine study and the ACTH-dopamine study, the data excluded a role for cortisol (and ACTH) in explaining the changes in plasma aldosterone concentration. The influence of the endogenous renin-angiotensin system was removed by administration of progressive pharmacological doses of angiotensin II. The ability of dopamine to suppress prolactin secretion at the pituitary lactotroph also was monitored: prolactin was suppressed significantly by dopamine in each study. In the ACTH-dopamine study, dopamine appeared to suppress basal plasma aldosterone concentrations, but this effect was not observed in the angiotensin II–dopamine or the propranolol–angiotensin II–dopamine studies. Thus, the effect, if any, of dopamine on basal aldosterone secretion is unclear.

As dopamine does not cross the blood-brain barrier, a central nervous system mechanism of action of dopamine to inhibit aldosterone secretion is unlikely. More likely is a peripheral effect of dopamine, either directly at the adrenal cortex or indirectly by way of an action on aldosterone stimulating factor, a 26,000 molecular weight glycoprotein of anterior pituitary origin. The former concept is supported by the recent demonstration of specific dopamine receptors in adrenal zona glomerulosa cells in vitro, in which dopamine has been shown to inhibit angiotensin II–stimulated aldosterone secretion. The possibility that dopamine increased aldosterone metabolic clearance rate by means of its vasodilator effect in the hepatic vasculature is unlikely, since Hanson et al. have demonstrated that the dose of dopamine employed in this study does not alter aldosterone metabolic clearance.

In conclusion, we have shown that dopamine selectively inhibits aldosterone responses to angiotensin II. The possibility that primary alterations in endogenous dopamine production may be responsible for physiological and pathophysiological modification of aldosterone responses to angiotensin II awaits future investigation.

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