Dopaminergic Modulation of Pressor and Hormonal Responses in Essential Hypertension

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SUMMARY Hormonal and mean arterial pressure (MAP) responses to posture, isometric handgrip, angiotensin II (AI1), adrenocorticotrophic hormone (ACTH), and metoclopramide (MCP), a dopamine (DA) antagonist, were examined in nine men with essential hypertension and nine age- and weight-matched normotensive men on a constant 100 mEq sodium and 80 mEq potassium intake before and after 4 days of administration of the DA agonist, bromocriptine (BEC; 2.5 mg three times a day). BEC depressed supine basal MAP in the hypertensives, and decreased MAP response to posture and isometric exercise in both groups. There were similar reductions ($p < 0.01$) in basal supine norepinephrine (NE) in the two groups. Hypertensives displayed greater ($p < 0.01$) NE responses to posture and exercise than the normotensives. BEC decreased the NE response to 10 minutes of upright posture and exercise more in hypertensives ($p < 0.01$) than in normotensives. Hypertensives had greater ($p < 0.05$) plasma aldosterone (PA) responses to exercise than normotensives, but following BEC, the responses were similar. BEC did not affect basal PRA or PRA responses to posture and exercise in the two groups. PA responses to ACTH and MCP were similar in both groups, but the hypertensives displayed greater ($p < 0.01$) PA responses to AI1. BEC suppressed PA responses to AI1 ($p < 0.01$) and high dose ACTH ($p < 0.05$) to a similar extent in both groups. The prolactin as well as the PA response to DA antagonism with MCP was similar in the two groups. These results suggest that dopaminergic control of NE secretion may be altered in essential hypertension. Blood pressure lowering effects of BEC in patients with essential hypertension may be related, in part, to depression of sympathetic nervous system activity. (Hypertension 4: 424-430, 1982)

KEY WORDS • bromocriptine • metoclopramide • adrenocorticotrophic hormone • angiotensin II • posture • isometric exercise • catecholamines • aldosterone • prolactin • hypertensives • plasma renin activity

EVIDENCE has accumulated that reduced central and peripheral dopaminergic activity may be a factor in the maintenance of essential hypertension in man and experimental animal models of essential hypertension. Bromocriptine (BEC), a central and peripheral dopamine agonist, causes orthostatic hypotension in normal persons and significantly reduces blood pressure in spontaneously hypertensive rats and in patients with essential hypertension. The observation that BEC lowers resting supine blood pressure in hypertensives but not in normotensives has led to the speculation that dopaminergic mechanisms might be involved in the development and maintenance of essential hypertension.

BEC administration to normal individuals resulted in suppression of plasma aldosterone (PA) responses to angiotensin II (AI1) in two studies, but was not observed to affect PA response to AI1 in another study. However, BEC did not alter basal nor stimulated levels of plasma renin activity (PRA). Basal recumbent norepinephrine (NE) and epinephrine (E) as well as the NE response to upright posture and isometric exercise were decreased in normal subjects and hypertensives after short-term administration of BEC. Prolactin (PRL) secretion was markedly suppressed after BEC administration in normotensives as well as in patients with essential hypertension.

In the present study, we have examined the dopaminergic control of NE, PA, PRL, and blood pressure in hypertensives compared to normotensive subjects. We have also compared hormonal and pressor responses to upright posture, to isometric handgrip, graded doses of AI1 and ACTH, and to the dopamine antagonist, metoclopramide (MCP), in patients with essential hypertension and normotensive subjects before and during BEC administration.
Materials and Methods

Nine men, 25 to 57 years of age, with sustained essential hypertension were taken off all medication for 3 weeks prior to the study.12 Nine age- and weight-matched normotensive men on no medications were also studied. Control studies (subjects on no medications) as well as the BEC studies were performed on Days 4 to 7 of a 100 mEq sodium and 80 mEq potassium diet. During the BEC period, subjects received 2.5 mg BEC orally three times daily. The order of test during control and BEC periods was varied among subjects from each of the two groups. During each period, serum electrolytes and 24-hour sodium were measured on Day 4 of the diet. The study protocol was as follows.

Upright Posture and Isometric Handgrip Exercise

At 0800 hours, subjects assumed a supine position, and a needle was placed in the left antecubital vein for blood collection. The needle was maintained patent by infusion of 5% dextrose and water at 1 ml/min. At 0900 hours, basal supine blood samples were collected for determination of NE, E, dopamine (DA), PRA, PA, and PRL. Subjects then assumed upright posture for 10 minutes, followed by 5 minutes of isometric handgrip exercise consisting of a workload of 30% maximum voluntary contraction. Blood samples for the above measurements were collected, and blood pressures were determined with a mercury sphygmomanometer after 5 and 10 minutes of standing and after 5 minutes of isometric handgrip exercise.

Angiotensin II Infusion

Subjects assumed a supine position at 0800 hours, and needles were placed in antecubital veins for blood sampling and AII infusion. After a 60-minute supine period, AII (Hypertension, Ciba, Summit, New Jersey) was infused at 0.5, 1, and 2 ng/kg-min during three sequential 30-minute periods. Blood samples for PA were obtained at the end of the 90-minute control period at the end of each infusion period. These doses and time periods have been shown to produce peak, stable aldosterone levels within 20 minutes of the infusion.14 Blood pressures were measured at 5-minute intervals with an automatic blood pressure device (Arteriosonde, Roche Laboratories, Santa Ana, California). Mean arterial blood pressure (MAP) was calculated as the diastolic blood pressure plus one-third of the pulse pressure.

ACTH Infusion

After 60 minutes in a supine position with needles positioned in each antecubital vein, adrenocorticotrophic hormone (ACTH) (Cortrosyn, Organon Pharmaceuticals, West Orange, New Jersey) was infused at rates of 12.5, 25, and 50 mIU/30 min during three sequential 30-minute periods. These doses of ACTH have been demonstrated to produce threshold aldosterone responses.16 Blood sampling for PA was performed at 0, 30, 60, and 90 minutes.

Metoclopramide Test

After 60 minutes in the supine position, a 10 mg i.v. bolus dose of MCP was given, and blood samples were collected at 0, 5, 10, 15, 30, 45 and 60 minutes for measurement of PA and PRL.

Measurements

Plasma NE was determined in duplicate samples using a single isotope radioenzymatic assay.6 The sensitivity of this assay is 10.0 pg/ml. Data on pooled samples in consecutive assays yields a between assay coefficient of variation of 8% to 12%. All blood samples for NE were collected in prechilled heparinized tubes and centrifuged at 4°C within 15 minutes. Plasma samples were immediately stored at −100°C and analyzed within 2 weeks. Aldosterone was extracted from plasma samples using 15-fold volumes of methylene chloride and was separated from other steroids by means of a Sephadex LH-20 column. The extracted aldosterone was measured by radioimmunoassay using an antiserum provided by the National Institute of Arthritis, Metabolism, Digestive Diseases (NIAMDD).8 PRA was measured by radioimmunoassay of angiotensin I generated during a 60 min incubation in the presence of angiotensinase inhibitors at pH 7.4 and at 37°C.16 Sensitivity of this assay is 0.2 ng/ml-hr13 and the intraassay coefficient of variation (CV) is 5.9%. Prolactin was measured by a homologous double isotope radioimmunoassay using reagents provided by the NIAMDD.17 Sensitivity of this assay is 1.0 ng/ml and the intraassay CV is 5%.

Statistics

A two-way analysis of variance was used to compare NE, PRA, PA, PRL, and blood pressure responses to acute stimuli in the two groups of subjects before and after BEC, and determination of statistical significance of responses to each stimulus was made using Dunnett’s test18 after logarithmic transformation of data.

Results

On the fourth day of the control and treatment periods, there was no difference in serum sodium or potassium in the two groups, as previously described.12 Both groups displayed similar 24-hour urinary sodium excretion in both periods. The 24-hour sodium excretion showed that both groups were in balance on the constant sodium intake. Supine MAP was not different in the control and BEC period in the normotensive group. However, the hypertensive group had a lower (p < 0.05) supine MAP in the BEC treatment period.

Posture and Handgrip

Figure 1 illustrates mean plasma NE responses to upright posture and isometric handgrip. The hypertensive patients and the normotensive subjects had similar basal plasma NE, but the hypertensive group
had greater \( (p < 0.01) \) NE responses (peak-baseline) to 5 and 10 minutes of upright posture and 5 minutes of isometric handgrip exercise. After BEC treatment, there was a 33\% reduction \( (p < 0.01) \) in basal plasma NE in the hypertensives and a 37\% reduction \( (p < 0.01) \) in the normotensive group. In the hypertensive group, the reduction in NE responses to 10 minutes of posture and 5 minutes of isometric handgrip were greater \( (p < 0.01) \) than the reductions in the normotensive group. Thus, after BEC the NE responses to upright posture and isometric handgrip were not different for the hypertensive and the normotensive groups.

The hypertensive group displayed MAP responses to upright posture, but the normotensive group displayed no rise in MAP during the 10 minutes (fig. 1). The rises in MAP after isometric handgrip were similar for the hypertensives and normotensives. Basal supine MAP was reduced \( (p < 0.05) \) by 10\% after BEC in the hypertensive group. There was not a significant reduction in MAP after BEC in the normotensive group (fig. 1). In the hypertensive group there was a 19\%, 17\%, and 18\% reduction \( (p < 0.01) \) in MAP responses to 5-minute posture, 10-minute posture, and 5-minute isometric handgrip, respectively. In the normotensive group there was a 20\%, 18\%, and 21\% reduction \( (p < 0.01) \) in MAP responses. Thus, BEC therapy reduced the MAP responses to a similar extent in both groups.

Figure 2 demonstrates the PA response to upright posture and isometric handgrip in the hypertensive and normotensive groups. PA was similar in the two groups in the supine and upright positions. Hypertensive patients demonstrated greater \( (p < 0.05) \) PA responses to upright posture and isometric exercise than the normotensives. BEC therapy reduced \( (p < 0.01) \) the PA responses by 24\%, 27\%, and 39\%, respectively, in the hypertensive group, and 28\%, 41\%, and
28% in the control group. Following BEC therapy the PA responses to isometric exercise were similar in the two groups. Although basal supine PRA levels were similar in the two groups, the normotensives displayed greater ($p < 0.05$) responses after 10 minutes of upright posture and 5 minutes of isometric exercise than did the hypertensives (table 1). BEC therapy did not significantly affect basal supine PRA or PRA responses to upright posture and isometric exercise in the two groups.

Angiotensin II and ACTH Infusion

Figure 3 demonstrates the PA response to graded dose infusion of AII. The hypertensive patients demonstrated greater ($p < 0.01$) PA responses to the 1.0 ng/kg/min and the 2.0 ng/kg/min doses of AII than the normotensive subjects. BEC therapy suppressed ($p < 0.01$) the PA responses to 1.0 ng/kg/min and 2.0 ng/kg/min doses of AII in both the hypertensives and the normotensives. PA responses to graded doses of ACTH were similar in the two groups (fig. 4). BEC therapy reduced ($p < 0.05$) the PA response to the 50 mIU min dose of ACTH in both the hypertensive and the normotensive group.

Metoclopramide Responses

PA responses to metoclopramide in the two groups before and after BEC therapy are demonstrated in figure 5. The two groups had similar PA responses to metoclopramide, and BEC did not affect the PA responses in either group. Both basal plasma PRL and plasma PRL responses to metoclopramide were similar in the two groups (fig. 6). Following BEC therapy, PRL was markedly suppressed ($p < 0.001$), and the PRL response to metoclopramide was eliminated in the two groups.
Table 1. Mean (± SEM) Plasma Renin Activity (PRA) Response to Upright Posture and Isometric Handgrip in Nine Normotensive Subjects and Nine Patients with Essential Hypertension before (Control) and After BEC

<table>
<thead>
<tr>
<th>Subjects' response</th>
<th>Plasma renin activity response (ng/ml/hr):</th>
<th>Baseline</th>
<th>5 min</th>
<th>10 min</th>
<th>Handgrip</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normotensives</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>1.4 ± 0.5</td>
<td>2.6 ± 0.9</td>
<td>3.5 ± 0.9</td>
<td>3.5 ± 1.0</td>
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</tr>
<tr>
<td>Bromocriptine</td>
<td>1.2 ± 0.4</td>
<td>2.3 ± 1.0</td>
<td>3.3 ± 1.0</td>
<td>3.5 ± 1.1</td>
<td></td>
</tr>
<tr>
<td>Hypertensives</td>
<td>0.8 ± 0.3</td>
<td>1.1 ± 0.4</td>
<td>1.7 ± 0.4</td>
<td>1.5 ± 0.4</td>
<td></td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>0.7 ± 0.3</td>
<td>1.1 ± 0.4</td>
<td>1.5 ± 0.5</td>
<td>1.3 ± 0.4</td>
<td></td>
</tr>
</tbody>
</table>

Discussion

The more pronounced lowering of basal blood pressure by BEC in hypertensive patients than in normotensives is in agreement with previous observations.1-3 Our observation that basal supine plasma NE levels were similar in essential hypertensives and age-, sex-, and weight-matched controls is in agreement with some previous studies,19-21 and differs from others in which increased basal supine plasma NE levels were reported for hypertensive patients.5,22,23 Our observation that posturally induced plasma NE responses were greater in hypertensive patients is in agreement with the previous observations.13 The greater effect of BEC on NE responses to posture observed in this study and previously8 and greater effect of BEC on PRL8,13 in patients with essential hypertension are consistent with the concept of decreased central dopaminergic activity playing a role in the maintenance of essential hypertension.

Figure 5. Mean (± SEM) plasma aldosterone responses to metoclopramide in nine patients with essential hypertension and nine normal subjects before and after bromocriptine.

Figure 6. Mean (± SEM) plasma prolactin responses to metoclopramide in nine patients with essential hypertension and nine normal subjects before and after bromocriptine.
Basal levels of PRA and PA were similar in the normotensive controls and patients with essential hypertension. However, the hypertensives displayed greater PA responses to posture and isometric exercise as well as to All infusion. Indeed, increased PA responses to posture and exercise occurred despite the fact that PRA, and presumably endogenous All, responses were somewhat less in the essential hypertensive patients. It has previously been reported that some essential hypertensive patients, particularly those with low PRA, have increased PA responses to All when studied under conditions of moderate to high sodium intake.24-28 On the other hand, decreased PA responses to All have been reported in essential hypertensives when sodium intake was markedly restricted.27 Williams et al.28 have suggested that this apparent discrepancy is probably related to the fact that the sodium-dependent swing in adrenal All responsiveness in essential hypertensives is smaller than normal. They concluded from their studies employing a converting enzyme inhibitor, a competitive All antagonist, and All infusions that altered adrenal responsiveness to All in essential hypertensive patients is secondary to a change in the interaction of All with its adrenal receptor. Results of our present study support the concept that essential hypertensives with normal levels of PRA when maintained on a moderate sodium intake have increased adrenal responsiveness to All.

Administration of BEC did not result in a significant reduction of basal PRA in either group, consistent with the previous observation that BEC does not decrease PRA levels in normotensive subjects.8-10 BEC resulted in suppression of PA responses to upright posture, isometric handgrip, and to All in both hypertensives and normotensives without affecting renin release in either group. Edwards et al.29 had previously demonstrated that BEC inhibits the expected increase in PA without affecting the normal increase in PRA following furosemide administration in normal subjects. Thus, suppression of All-mediated aldosterone release by BEC appears to be controlled by a mechanism independent of the effects on renin secretion. PA responses to ACTH were only moderately suppressed at the highest dose of ACTH used in this study, in agreement with the observations of Birkhauser et al.9 A recent observation that both NE and E stimulate aldosterone secretion in bovine glomerulosa cell suspensions30 suggests that BEC could have suppressed the PA response to posture, All, and to a lesser extent, ACTH, by decreasing catecholamine secretion. Owing to the proximity of the adrenal medulla to the cortex and the interposition of a portal circulation, adrenomedullary secretion of catecholamines may modulate aldosterone response to acute stimuli. Since BEC decreased catecholamine secretion to a similar degree in hypertensives and normotensives, this could explain the similar suppression of BEC on aldosterone responses to posture, exercise, All, and ACTH in both groups.

Recently, evidence has accumulated that dopaminergic modulation of aldosterone secretion is altered in states of increased salt retention and hypertension. Patients with primary aldosteronism have been reported to have elevated plasma levels and urinary excretion of DA.30 Dopaminergic antagonism has been reported to result in an excessive rise of aldosterone in secondary hyperaldosteronism.31 Exaggerated aldosterone responses to MCP have also been observed in spontaneously hypertensive rats (SHR).6 These disease states in humans and experimental animals are characterized by high normal to elevated aldosterone levels and low PRA. It has been suggested that the dissociation of renin and aldosterone secretion in these disease states may be the result of increased tonic dopaminergic activity, as DA appears to have a greater inhibitory effect on aldosterone than on renin secretion.6 In the present study administration of metoclopramide resulted in similar PA and PRL responses in hypertensive subjects and normotensive controls before and after BEC therapy. These data do not rule out the possibility that decreased dopaminergic activity may play a role in the pathogenesis of essential hypertension. Rather, they suggest that aldosterone and PRL responses to pharmacologic DA antagonism may not be a good index of central dopaminergic activity.

Acknowledgments

We thank Pamela Joyce for excellent skills in preparing this manuscript, and Ronald Marciano, P.A., for clinical assistance in performing these studies.

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Dopaminergic modulation of pressor and hormonal responses in essential hypertension.
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Hypertension. 1982;4:424-430
doi: 10.1161/01.HYP.4.3.424

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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