Dopaminergic Control of Prolactin and Blood Pressure: Altered Control in Essential Hypertension

JAMES R. SOWERS, M.D., MICHAEL NYBY, M.S., AND KEITH JASBERG, B.S.

SUMMARY This study examines the influence of dopamine on plasma catecholamine, prolactin (PRL), and mean arterial pressure (MAP) responses to upright posture and isometric handgrip exercise and the recumbent circadian PRL and MAP patterns in essential hypertension. Nine men with sustained essential hypertension and nine age- and weight-matched normotensive controls were studied after they had reached metabolic equilibrium on a constant intake of 100 mEq sodium and 80 mEq potassium. The hypertensive group, but not the normotensive group, displayed a PRL response to upright posture and handgrip. Hypertensives and normotensives had similar basal supine catecholamine levels and similar epinephrine and dopamine responses to posture and handgrip. The hypertensives had greater \((p < 0.01)\) norepinephrine (NE) responses to posture and handgrip than did the normotensives. Bromocriptine (BEC) depressed supine basal MAP in the hypertensives but not in the normotensives. BEC markedly decreased the basal PRL levels in both groups. BEC eliminated the PRL response to posture in the hypertensives and depressed the NE response to posture and handgrip to a greater extent \((p < 0.01)\) in the hypertensives than in the normotensives. In the control period, a clear circadian rhythm of PRL and MAP was noted in both groups. In both groups an increase in PRL concentration occurred between 60 to 90 minutes after sleep onset, and was followed by several larger secretory episodes resulting in progressively higher levels during the night with peak values occurring at the end of the sleep period, generally at 0500 to 0600 hours. During the hour after awakening, a fall in PRL concentration began, and lowest levels were reached at approximately 1100 hours in both groups. The mean 24-hour PRL levels in the hypertensive group \((12.6 \pm 0.5 \text{ ng/ml})\) were higher \((p < 0.01)\) than in the normotensives \((10.8 \pm 0.4 \text{ ng/ml})\). During the waking hours, there was a correlation \((r = 0.57, p < 0.01)\) between recumbent PRL levels and MAP. BEC therapy lowered MAP levels throughout the 24 hours in the hypertensive group. BEC also eliminated the circadian rhythm of PRL secretion. Thus, circadian variations in PRL secretion and blood pressure appear to be modulated by a central and/or peripheral dopaminergic mechanism. Decreased dopaminergic activity in essential hypertension may account, in part, for aberrances in PRL secretion and elevated blood pressure in this disease state. (Hypertension 4: 431-438, 1982)

KEY WORDS • dopamine • plasma catecholamine • prolactin • upright posture • isometric handgrip • bromocriptine • circadian rhythm • essential hypertension

Prolactin (PRL) secretion is modulated to a considerable extent by the central tuberoinfundibular-dopaminergic (TIDA) system. Accordingly, any stimulation of TIDA activity reduces PRL secretion from pituitary lactotropes and mechanisms leading to decreased tuberoinfundibular-neuronal secretion of dopamine (DA) increase PRL secretion. Evidence has accumulated that this PRL-regulating mechanism may also participate in blood pressure regulation. It has been reported that treatment of essential hypertensives with the dopamine agonist bromocriptine (BEC) causes parallel decreases in plasma PRL, sympathetic tone, and blood pressure. It has recently been observed that BEC treatment in the spontaneously hypertensive rat, a model for human essential hypertension, is associated with a parallel lowering of prolactin and blood pressure. These observations have led to the speculation that the antihypertensive effects of dopamine agonists, such as BEC, are due to elevation of central dopaminergic activity or to depression of PRL levels that have been reported to be high in the spontaneously hypertensive rat model as well as in hypertensive humans.

Supine basal unstimulated PRL levels have been reported to be elevated and normal in patients with essential hypertension. However, measurement
of a single plasma PRL level may be very misleading in view of PRL responsiveness to various conditions, including mental and physical stress, decreased plasma osmolality, and sleep. Blood pressure, as previously proposed, demonstrates circadian variability. Further, blood pressure during waking hours is dependent on many factors including posture, mental and physical stress, and other stimuli. If PRL levels serve as an index of central adrenergic discharge and adrenergic modulation of blood pressure, then patients with essential hypertension may have increased PRL responsiveness to various conditions, including sleep and upright posture, a stimulus that markedly affects the adrenergic nervous system. In the present study we have compared the PRL, catecholamine, and blood pressure responses to posture and isometric exercise and recumbent PRL and blood pressures over 24 hours in patients with essential hypertension and age-, weight-, and sex-matched normotensive controls before and after BEC treatment. Our purpose was to determine if reduced central dopaminergic activity contributes to the maintenance of essential hypertension.

Methods

Subjects

Nine Caucasian men with sustained essential hypertension, aged 22–46 years, whose supine blood pressure while not taking medications were 140/95 mm Hg or greater on the majority of observations for at least 1 year, were taken off of all medications for 3 weeks prior to the study. Secondary causes of hypertension were excluded by means of history, physical examination, creatinine clearance, and rapid sequence urograms. Nine healthy Caucasian normotensive men, aged 24–45, with three consecutive normal blood pressure readings, were also studied.

Protocol

Control studies (subjects on no medications) as well as BEC studies were performed on Days 4 and 5 or 7 and 8 of a constant diet of 100 mEq sodium and 80 mEq potassium. During the BEC period, subjects received 2.5 mg BEC orally three times daily. The order of control and BEC periods were varied for each of the two groups. During each period, serum electrolytes and 24-hour urinary sodium were measured on Day 4 of the constant diet.

Upright Posture and Isometric Handgrip Exercise

At 0800 hours, on Day 4 or 7 of the constant diet, 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, epinephrine (E), dopamine (DA), and PRL. Blood samples for these measurements were collected after the subjects had assumed an upright posture for 5 and 10 minutes, and after 5 minutes of isometric handgrip exercise consisting of a workload of 30% of maximum voluntary contraction. Blood pressures were determined with a mercury sphygmomanometer at the same time as blood collections.

24-Hour Recumbency Studies

All subjects underwent a 24-hour period of habituation on Day 3 of the constant diet in a sound-proofed room containing a viewing room, with simulated blood sampling through an indwelling venous catheter and blood pressure monitoring by an Arteriosonde instrument (Hoffman-La Roche; Nutley, New Jersey) every 30 minutes. On either Day 5 or 8 of the constant diet, patients were given three meals at 0800, 1200, and 1800 hours and noncaffeinated fluids on request. An indwelling venous catheter was inserted in an antecubital vein at 0700 hours and blood sampling begun at 0800 hours. The venous catheter was connected to a sampling line passing through a port in the wall and maintained patent by slow saline drip. Blood samples (1 ml) were collected every 30 minutes, and blood pressure was monitored and recorded by Arteriosonde. Mean arterial blood pressure (MAP) was calculated as the diastolic pressure plus one-third of the pulse pressure. Lights were turned off at 2200 hours and on again at 0700 hours. Sleep was monitored clinically as previously described.

### Table 1. Supine Serum Sodium and Potassium, 24-hour Urine Sodium, and Supine Blood Pressure in Nine Hypertensive and Nine Normotensive Subjects in Control and Bromocriptine Periods While on a 100 mEq Sodium Diet (Mean ± SEM)

<table>
<thead>
<tr>
<th></th>
<th>Hypertensives</th>
<th>Normotensives</th>
<th>Hypertensives</th>
<th>Normotensives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum sodium (mEq/liter)</td>
<td>141 ± 1</td>
<td>140 ± 1</td>
<td>140 ± 1</td>
<td>140 ± 1</td>
</tr>
<tr>
<td>Serum potassium (mEq/liter)</td>
<td>4.3 ± 0.2</td>
<td>4.4 ± 0.2</td>
<td>4.5 ± 0.3</td>
<td>4.5 ± 0.3</td>
</tr>
<tr>
<td>24-hour urinary sodium (mEq)</td>
<td>92 ± 10</td>
<td>96 ± 12</td>
<td>103 ± 17</td>
<td>99 ± 16</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>108 ± 6</td>
<td>83 ± 5</td>
<td>99 ± 5*</td>
<td>80 ± 4</td>
</tr>
</tbody>
</table>

*p < 0.05 for comparison between the control and bromocriptine periods.
TABLE 2. Mean (± SEM) Norepinephrine, Epinephrine and Dopamine Response to Upright Posture and Isometric Handgrip in Nine Normotensive Subjects and Nine Patients with Essential Hypertension Before (control) and After Bromocriptine (BEC)

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Measurements</th>
<th>Baseline</th>
<th>5 min</th>
<th>10 min</th>
<th>Handgrip</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotensives</td>
<td>Control Norepinephrine (pg/ml)</td>
<td>289 ± 16</td>
<td>330 ± 28</td>
<td>470 ± 50</td>
<td>545 ± 60</td>
</tr>
<tr>
<td></td>
<td>BEC</td>
<td>175 ± 15</td>
<td>190 ± 20</td>
<td>340 ± 40</td>
<td>444 ± 60</td>
</tr>
<tr>
<td>p value</td>
<td>&lt; 0.01</td>
<td>&lt; 0.01</td>
<td>&lt; 0.01</td>
<td>&lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>Hypertensives</td>
<td>Control Norepinephrine (pg/ml)</td>
<td>302 ± 18</td>
<td>460 ± 60</td>
<td>630 ± 70</td>
<td>750 ± 85</td>
</tr>
<tr>
<td></td>
<td>BEC</td>
<td>190 ± 17</td>
<td>200 ± 21</td>
<td>360 ± 50</td>
<td>475 ± 65</td>
</tr>
<tr>
<td>p value</td>
<td>&lt; 0.01</td>
<td>&lt; 0.01</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Normotensives</td>
<td>Control Epinephrine (pg/ml)</td>
<td>16.8 ± 3.2</td>
<td>17.6 ± 3.4</td>
<td>18.0 ± 3.3</td>
<td>17.4 ± 3.5</td>
</tr>
<tr>
<td></td>
<td>BEC</td>
<td>1.8 ± 0.3</td>
<td>1.7 ± 0.4</td>
<td>1.8 ± 0.5</td>
<td>1.9 ± 0.4</td>
</tr>
<tr>
<td>p value</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Hypertensives</td>
<td>Control Epinephrine (pg/ml)</td>
<td>21.7 ± 3.4</td>
<td>22.2 ± 3.6</td>
<td>23.4 ± 3.7</td>
<td>22.8 ± 3.6</td>
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<tr>
<td></td>
<td>BEC</td>
<td>1.9 ± 0.4</td>
<td>1.8 ± 0.4</td>
<td>1.9 ± 0.5</td>
<td>2.0 ± 0.5</td>
</tr>
<tr>
<td>p value</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Normotensives</td>
<td>Control Dopamine (pg/ml)</td>
<td>61 ± 28</td>
<td>62 ± 24</td>
<td>70 ± 28</td>
<td>92 ± 34</td>
</tr>
<tr>
<td></td>
<td>BEC</td>
<td>20 ± 8</td>
<td>22 ± 14</td>
<td>29 ± 19</td>
<td>51 ± 30</td>
</tr>
<tr>
<td>p value</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Hypertensives</td>
<td>Control Dopamine (pg/ml)</td>
<td>55 ± 27</td>
<td>76 ± 24</td>
<td>72 ± 29</td>
<td>114 ± 43</td>
</tr>
<tr>
<td></td>
<td>BEC</td>
<td>30 ± 20</td>
<td>29 ± 21</td>
<td>30 ± 24</td>
<td>58 ± 35</td>
</tr>
<tr>
<td>p value</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

*p values are for statistical comparisons between control and BEC periods.

Measurements

Prolactin was measured by a homologous double isotope radioimmunoassay using reagents provided by the National Institute of Arthritis, Metabolism, Digestive Diseases (NIAMDD). Sensitivity of this assay is 1.0 ng/ml and the intraassay coefficient of variance (CV) is 5%. Plasma NE, E, and DA were determined using a single isotope radioenzymatic assay. The sensitivity of this assay is 10.0 pg/ml for NE and E, and 15.0 pg/ml for DA. The intraassay CV is 8% and the interassay CV is 11.3% for the DA assay. All blood samples for catecholamines 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. Serum and urinary sodium and serum potassium were measured by atomic absorption spectrophotometry. Dunnett multiple comparison analysis technique was used to compare blood pressure and hormonal responses to posture and handgrip and time-related changes in the two groups. Time-related comparisons between PRL, NE, and MAP were made using the repeated sampling analysis of variance method. Chronobiological characteristics of PRL, NE, and MAP during 24-hour periods in each of the two groups before and after BEC were determined by chronobiological statistical methods as previously outlined. With this procedure, the rhythm is characterized by the following parameters: 1) acrophase — crest of the cosine function used to approximate the rhythm; 2) mesor — rhythm adjusted to a 24-hour average; 3) amplitude — the difference between the maximum value measured at acrophase and the mesor in the cosine curve.

Results

On the fourth day of the control and treatment periods, there was no difference in serum sodium or potassium in the two groups (table 1). Both groups displayed similar 24-hour urinary sodium excretion in both periods. The 24-hour sodium secretion data suggest that both groups were in balance on the constant sodium intake. The hypertensive group had a lower (p < 0.05) supine MAP in the BEC period than in the control period. However, supine MAP was not different in the control and BEC period in the normotensive group.

Posture and Handgrip

Table 2 illustrates mean catecholamine responses to upright posture and isometric handgrip. Hypertensive patients and normotensive subjects had similar basal plasma NE, but the hypertensive group had greater (p < 0.01) NE responses to 5 and 10 minutes of upright posture and 5 minutes of isometric handgrip exercise.
After BEC treatment, there was a reduction \((p < 0.01)\) in basal plasma NE in both normotensives and hypertensives. The hypertensive group had a greater \((p < 0.01)\) reduction in NE response to 10 minutes of upright posture and 5 minutes of isometric handgrip than the normotensive group. Plasma E levels were similar in the two groups, and neither group displayed an E response to posture or handgrip (table 2). BEC therapy markedly suppressed \((p < 0.01)\) E levels in both groups. Basal supine plasma DA levels and DA responses to posture and handgrips were not significantly different in the hypertensive and the normotensive subjects. Reduction of DA following BEC was not significant because of large variability in the DA measurements.

Basal supine PRL levels were similar in the hypertensives \((9.9 \pm 0.8 \text{ ng/ml})\) and the normotensives \((8.6 \pm 0.8 \text{ ng/ml})\) (fig. 1). Hypertensive subjects had PRL responses \((p < 0.01)\) to upright posture and isometric handgrip exercise which were not observed in the normotensives. Following BEC therapy, PRL was markedly suppressed \((p < 0.001)\) in both groups, and there was no PRL response to posture and handgrip in either group. In the hypertensives, the MAP increased \((p < 0.05)\) from a basal level of 108.6 ± 4.0 to 120 ± 4.9 mm Hg after 10 minutes of upright posture and further increased \((p < 0.01)\) to 127 ± 7.9 mm Hg after isometric handgrip exercise. Basal supine MAP in the normotensives \((82 \pm 4 \text{ mm Hg})\) did not increase with posture, but rose \((p < 0.05)\) to 97 ± 5.1 mm Hg after isometric handgrip. Thus, MAP rises after isometric handgrip were similar for both groups. Basal supine MAP was reduced \((p < 0.05)\) by 10% after BEC in the hypertensives, but there was no such reduction in the normotensives. There were similar reductions \((p < 0.01)\) in MAP responses to posture and handgrip in both hypertensives and normotensives.

**24-Hour Recumbency Studies**

Figure 2 demonstrates the mean 24-hour recumbent PRL levels in the nine normotensives and nine hypertensives. The 24-hour recumbent PRL levels in the normotensives displayed the following chronobiological characteristics: the mesor was 5.2 ± 0.4 ng/ml, the amplitude was 2.5 ± 0.3 ng/ml, and the acrophase was 0230 hours. The hypertensives displayed similar chronobiological characteristics: the mesor was 6.1 ± 0.5 ng/ml, the amplitude was 2.7 ± 0.3 ng/ml, and the acrophase was 0130 hours. Sleep onset generally occurred between 2230 and 2330 hours and all nine normotensives and nine hypertensives displayed increments in PRL concentrations between 60 to 90 minutes after sleep onset. These increments were followed by a series of larger secretory episodes resulting in progressively higher levels during the night with peak values occurring at the end of the sleep period \((0500 \text{ to } 0600 \text{ hours})\). During the hour following awakening \((0600 \text{ to } 0700 \text{ hours})\), a fall in PRL began, with the lowest levels being reached at approximately 1100 hours in both groups at which time the levels were approximately 70% of mean 24-hour values. PRL release in both groups during the waking period was also characterized by secretory episodes whose amplitudes were less than during sleep. The 24-hour mean concentrations of PRL in the hypertensive subjects \((12.6 \pm 0.5 \text{ ng/ml})\) were greater \((p < 0.05)\) than in the normotensives \((10.8 \pm 0.4 \text{ ng/ml})\). PRL levels were correlated with clock time throughout the 24-hour cycle in the normotensives \((r = 0.36, p < 0.01)\) and the hypertensives \((r = 0.38, p < 0.01)\).

After BEC treatment in the nine hypertensive patients, the mean 24-hour PRL concentration was suppressed \((p < 0.001)\) to 1.3 ± 1.2 ng/ml (fig. 3). Very small PRL fluctuations were observed over the 24-hour period, and a circadian rhythm was not present. After BEC, the mean 24-hour PRL concentration in the normotensives was suppressed to 1.1 ± 0.1 ng/ml, and the circadian rhythm was eliminated (data not shown).

The relationship between 24-hour MAP and PRL concentrations in the nine hypertensive patients is illustrated in figure 4. During the waking hours \((0700 \text{ to } 2200 \text{ hours})\) there was a correlation \((r = 0.63, p <
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0.01) between MAP and PRL in hypertensives. However, during sleep (2200 to 0700 hours) there was a negative correlation ($r = -0.44$, $p < 0.05$) between MAP and PRL in the hypertensives. As for the PRL, the MAP was linearly correlated with clock time in the hypertensives ($r = 0.35$, $p < 0.05$) and normotensives ($r = 0.34$, $p < 0.05$) across the 24-hour study period. The 24-hour MAP in the nine hypertensive patients displayed the following chronobiological characteristics: the mesor was 110.2 ± 3.2 mm Hg, the amplitude 10.8 ± 2.4 mm Hg, and the acrophase was 1600 hours. The range of the MAP in the hypertensive group was 24 mm Hg (97 to 121 mm Hg). The 24-hour MAP circadian variations in the hypertensives generally paralleled those seen in the normotensives, with lowest MAP occurring shortly after the onset of sleep (2200 to 2300 hours) until shortly before awakening. BEC treatment suppressed ($p < 0.05$) MAP in the hypertensive patients, but not the normotensive subjects over the 24-hour sampling period (fig. 5).

Discussion

The results of this study suggest that the control of PRL secretion may be altered in essential hypertension. Our observation that morning basal supine PRL levels are similar in patients with essential hypertension to those observed in normotensive controls is in agreement with several previous studies. In this investigation, we observed a PRL response to posture and isometric exercise in patients with essential hypertension but not in normotensive control subjects. Meier et al. have previously reported a PRL response to posture that was not present in normotensives. More important, we observed that mean PRL levels in patients with essential hypertension...
were significantly higher over a 24-hour recumbent period than in normotensive controls. These differences were not due to differences in sex, age, or sodium homeostasis, all of which can affect PRL secretion. Although there is no known direct contribution of PRL to blood pressure in man, there is indirect evidence that it may play a role in sodium retention. In normotensive controls, there is a decrease in urinary sodium clearance in hypertensive patients. This observation suggests that sodium clearance is not directly related to PRL levels during sleep in the hypertensive patients. This observation suggests that sodium clearance during sleep is not directly related to the ambient plasma PRL levels. Indeed, it is more likely that hyperprolactinemia, rather than having hypertensive properties itself, reflects decreased central dopaminergic activity which may play a role in the pathogenesis of essential hypertension. PRL secretion displays a nyctohemeral rhythm in patients with essential hypertension as well as in normal individuals. In both hypertensives and normotensives PRL levels were observed to rise after the sleep-related acrophase at 0230 hours in normotensives and 0130 hours in hypertensives is similar to the data previously reported. Although the hypertensives generally had higher recumbent PRL levels than the normotensives, the differences were minimal between 0300 and 0600 hours, the time when PRL levels were at their highest in both groups. Parker et al. evidenced a temporal relationship between REM-non-REM sleep cycles and PRL nadir and peaks, showing that non-REM intervals coincided with plasma PRL surges. Because of the relationship between sleep cycles and central dopaminergic function, the authors proposed a relationship between activation of hypothalamic dopaminergic activity during REM sleep and decreased activity during REM sleep and associated PRL nadirs and peaks. Thus, if patients with essential hypertension have decreased dopaminergic activity, differences in PRL secretion from that of normal individuals would be expected to be minimized at a time when dopaminergic inhibition of PRL is at its lowest, i.e., between 0300 and 0600 hours when PRL levels are at their highest.

Our observation that BEC reduces resting recumbent supine blood pressure in awake patients with essential hypertension, but not in normotensives, is in accordance with previous reports. That BEC lowers recumbent blood pressure in hypertensives but not in normotensives has led to the speculation that reduced central and peripheral dopaminergic activity may be a factor in the development and maintenance of essential hypertension. Accordingly, BEC may produce antihypertensive effects by increasing central dopaminergic activity thereby decreasing sympathetic outflow and thus adrenal medullary and sympathetic nerve secretion of NE. The greater effect of BEC on plasma catecholamine response to posture and to isometric exercise in hypertensives is in accord with the concept of decreased central dopaminergic activity in essential hypertension. Thus, our observation of a greater effect of BEC on PRL and catecholamine responses to posture and exercise, and 24-hour recumbent blood pressures, in patients with essential hypertension is further evidence that a common mechanism, perhaps central dopaminergic activity, governing response of PRL and catecholamines to posture and stress and circadian variations of blood pressure is important in maintaining essential hypertension.

Blood-pressure-lowering effects of BEC could be mediated, in addition to central dopaminergic effects, by peripheral mechanisms. Dopamine agonist properties of BEC also result in peripheral inhibitory effects on sympathetic nerve activity. This inhibitory effect has been localized to autonomic sympathetic ganglia and postganglionic sympathetic nerves. Additionally, BEC has vascular postsynaptic alpha-antagonistic properties, which may result in direct peripheral vasodepressor effects. However, our observation that BEC appears to suppress plasma E and DA, as well as NE, suggests that BEC inhibits the release of these catecholamines from the adrenal medulla. As adrenal catecholamine release is controlled by central adrenergic discharge, this suggests that BEC acts primarily by inhibiting central sympathetic nerve outflow rather than by inhibition of peripheral NE release. The observation that blockade of peripheral dopamine receptors with domperidone, a selective peripheral dopamine antagonist, does not prevent the blood-pressure-lowering effects of BEC also suggests that it acts mainly through a central mechanism rather than by peripheral effects.

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