Plasma Chromogranin A
Initial Studies in Human Hypertension
DANIEL T. O’CONNOR

SUMMARY  Chromogranin A is the major catecholamine storage vesicle soluble protein costored and coreleased by exocytosis with catecholamines. Immunoreactive chromogranin A circulates in human plasma, where it may reflect changes in exocytotic sympathoadrenal activity. We measured plasma chromogranin A concentration in normotensive control subjects as well as in untreated essential (primary) hypertensive subjects and subjects with several varieties of secondary hypertension. Plasma chromogranin A concentration was higher in subjects with essential hypertension (n = 32) than in normal controls (n = 18; 198 ± 32 versus 129 ± 12 ng/ml [mean ± SEM]; p < 0.05), and was also elevated in subjects with hypertension secondary to renal parenchymal disease (n = 9; 192 ± 36 ng/ml; 0.05 < p < 0.1) and those with pheochromocytoma (n = 11; 1614 ± 408 ng/ml; p < 0.01). In essential hypertensive subjects (n = 5), short-term suppression of sympathetic outflow with oral guanabenz (4 mg) reduced plasma chromogranin A concentration within 30 to 60 minutes, while the blood pressure response was more gradual and was maximal at 3 hours. The results suggest that plasma chromogranin A is, at least in part, under neural control and that there may be an excess of exocytotic sympathoadrenal activity in essential hypertension. These initial studies are now being expanded to larger subject groups. (Hypertension 7 [Suppl I]: 1-76-1-79, 1985)

KEY WORDS • chromogranin A • chromaffin granule • hypertension • pheochromocytoma • sympathetic nervous system

BIOCHEMICAL assessment of sympathoadrenal activity in intact organisms is fraught with methodological difficulties.1 Chromogranin A is a protein costored and coreleased by exocytosis with catecholamines from their storage vesicles in the adrenal medulla and sympathetic nerve.2-4 We have recently explored the measurement of human plasma chromogranin A as a means of probing the sympathoadrenal system and have found that its concentration varies as a function of exocytotic sympathoadrenal activity.5 Here, we present our initial data on plasma chromogranin A in primary and secondary hypertension and its acute response to antihypertensive treatment.

Materials and Methods
Chromaffin vesicles were isolated by sucrose density gradient centrifugation of homogenates of human pheochromocytoma and normal human adrenal medulla, as previously described.6,7 Chromogranin A was isolated from the soluble chromaffin vesicle lysate of a human pheochromocytoma, as previously described.7 Chromogranin A was quantitated by a soluble phase, double-antibody, equilibrium radioimmunoassay, as previously described.8 The assay had intraassay and interassay coefficients of variation of 5 and 15%, and did not cross-react appreciably with other catecholamine storage vesicle soluble constituents.

Heparinized plasma was obtained from male subjects who were in the supine position for 20 to 30 minutes. The 18 normotensive control subjects were healthy, white male volunteers (mean age, 38 ± 2 years), consistently normotensive (diastolic blood pressure < 90 mm Hg), and receiving no medications. The 32 essential (primary) hypertensive subjects were consistently hypertensive (diastolic blood pressure > 90 mm Hg) and receiving no medications. The 32 essential (primary) hypertensive subjects were consistently hypertensive (diastolic blood pressure > 90 mm Hg in the outpatient clinic) white men (mean age, 50 ± 2 years) with no evidence of hypertensive target organ damage or secondary hypertension after an evaluation that included history, physical examination, and laboratory investigations (electrocardiogram, chest x-ray film, urinalysis, hemogram, and serum chemistry values). The 11 pheochromocytoma subjects (mean age, 41 ± 5 years) had blood drawn before operative removal of the tumors, with the diagnosis subsequently verified pathologically.
Chromogranin A/ O'Connor

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Chromogranin A concentration was elevated in patients with essential hypertension (Table 1; p < 0.05), although there was considerable heterogeneity among the essential hypertensive subjects. Although the essential hypertensive subjects as a group were older than the normotensive controls (p < 0.01; see Table 1), plasma chromogranin A concentration did not correlate significantly with age in either the normotensive (r = 0.25) or the essential hypertensive subjects (r = 0.20). As previously reported, subjects with pheochromocytoma, as a group, had a marked elevation in plasma chromogranin A levels (p < 0.01). Subjects with hypertension secondary to renal parenchymal disease also had a modest elevation in plasma chromogranin A levels (0.05 < p < 0.1).

Results

Chromogranin A was quantitated by radioimmunoassay (Figure 1), which assessed immunoreactivity by parallel displacement of tracer 125I-labeled chromogranin A from antibody by chromogranin A in human catecholamine storage vesicles as well as unextracted plasma from both normotensive and hypertensive humans.

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Five of the essential hypertensive subjects remained recumbent for at least 30 minutes with an antecubital venous catheter in place. Blood pressure, heart rate, and plasma chromogranin A levels were measured before and periodically up to 6 hours after a single oral dose of 4 mg of guanabenz, a centrally acting \(\alpha_2\)-adrenergic agonist that acts by diminishing peripheral sympathoadrenal activity.8

Radioimmunoassay results and curves were analyzed by a weighted, nonlinear regression program7 on a VAX 11/780 computer (Digital Equipment Corporation, Maynard, MA). Descriptive and inferential statistics were generated with a statistics software module on a TI-99/4A computer (Texas Instruments, Dallas, TX). Results are reported as mean values ± SEM.

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Table 1 Plasma Chromogranin A Concentrations in the Human Subject Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Age (yr)</th>
<th>Blood pressure (mm Hg, systolic/diastolic)</th>
<th>Plasma chromogranin A (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotensive control subjects</td>
<td>18</td>
<td>38 ± 2</td>
<td>112 ± 7 / 76 ± 2</td>
<td>129 ± 12</td>
</tr>
<tr>
<td>Hypertensive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Essential (primary)</td>
<td>32</td>
<td>50 ± 2*</td>
<td>155 ± 4* / 101 ± 1*</td>
<td>198 ± 32†</td>
</tr>
<tr>
<td>Secondary Pheochromocytoma</td>
<td>11</td>
<td>41 ± 5</td>
<td>137 ± 5* / 83 ± 6</td>
<td>1614 ± 408*</td>
</tr>
<tr>
<td>Renal parenchymal</td>
<td>9</td>
<td>57 ± 2*</td>
<td>150 ± 5* / 94 ± 5*</td>
<td>192 ± 36‡</td>
</tr>
</tbody>
</table>

Values are means ± SEM

All subjects were untreated, except those with pheochromocytoma, who were receiving phenoxybenzamine, 5 to 70 mg orally, twice daily.

Blood pressures listed here were obtained at the time of plasma sampling.

* p < 0.01, † p < 0.05, ‡ 0.05 < p < 0.1, versus the value in the normotensive control group.
In response to 4 mg (the usual starting dose) of oral guanabenz in five previously untreated essential hypertensive subjects (Figure 2), plasma chromogranin A concentration fell acutely by approximately 50%. The fall was fairly maximal within 30 to 60 minutes after administration, whereas the fall in blood pressure occurred more gradually and was maximal by 3 hours. Both plasma chromogranin A levels and blood pressure remained suppressed for at least 6 hours after administration of the drug. There was no change in heart rate.

In vitro, guanabenz did not interfere with the assay in any concentrations tested (up to 10 ng/ml).

Discussion

These studies provide evidence that mean plasma chromogranin A concentration is elevated in essential (primary) hypertensive subjects, as well as in subjects with hypertension secondary to renal parenchymal disease, and confirm our previous observation that mean plasma chromogranin A concentration is markedly elevated in subjects with pheochromocytoma. The assessment of plasma chromogranin A concentration may provide a means of evaluating changes in sympathoadrenal activity as well as their mechanism—exocytotic versus nonexocytotic. As has been pointed out, many questions remain about the ability of plasma chromogranin A concentrations to mirror such changes. First of all, changes in plasma chromogranin A levels generally are modest (10-20% of baseline) in response to sympathoadrenal manipulations.

Second, since immunoreactive chromogranin is found in both adrenal medullary and sympathetic neuronal catecholamine storage vesicles, it is not yet possible to state whether plasma chromogranin A emerges principally from an adrenal medulla or a sympathetic neuronal source, or from both. Finally, chromogranin immunoreactivity is found in a variety of peptide hormone producing tissues. Among the endocrine glands, however, the adrenal medulla contains at least 20- to 30-fold more chromogranin immunoreactivity (µg/g of tissue) than any other source.

A few points suggest that the plasma chromogranin A elevation in essential hypertension is not simply the result of hypertension but may reflect increased sympathoadrenal tone in essential hypertension. First, the plasma chromogranin A elevation was acutely suppressible by inhibiting sympathetic outflow (see Figure 2). Second, the fall in plasma chromogranin A after guanabenz administration temporally preceded the fall in blood pressure (see Figure 2).

An elevation of plasma chromogranin A concentration in essential hypertension is consistent with recent observations documenting an elevation of plasma norepinephrine levels in early essential hypertension and further suggests that the excessive norepinephrine release is exocytotic in origin. We have not yet accumulated sufficient numbers of normotensive and hypertensive subjects for meaningful age stratification of the plasma chromogranin data, nor have we investigated whether the essential hypertensive- and normotensive plasma chromogranin A level differences reflect an
alteration in exocytotic release versus the less likely possibility of a change in plasma clearance of the protein. It should be noted that there was considerable heterogeneity of plasma chromogranin A concentration in the essential hypertensive group, as evidenced by the substantial standard error of the mean in this group (see Table 1).

The plasma chromogranin A elevation in renal hypertension, although of borderline statistical significance (see Table 1), also suggests sympathoadrenal overactivity in such hypertension, a finding compatible with findings on elevated plasma norepinephrine levels in renal hypertension. As we have not yet investigated plasma chromogranin A levels in normotensive patients with renal insufficiency, we cannot yet exclude the possibility that renal disease per se elevates plasma chromogranin A levels, perhaps by diminishing a renal component of the protein’s disposition or plasma clearance.

In conclusion, an elevation of plasma chromogranin A concentration in essential hypertension, coupled with its short-term suppression by sympathetic outflow inhibition, suggests an excess of exocytotic sympathoadrenal activity in this disorder. Further studies are in progress to define more precisely the origin and specificity of the observed elevation and to expand these initial studies to larger subject groups.

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References


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