The role of the renin–angiotensin–aldosterone system in cardiovascular homeostasis in normal man

E. HABER, J. SANCHO, R. RE, J. BURTON AND A. C. BARGER
Cardiac Unit, Massachusetts General Hospital and Departments of Medicine and Physiology, Harvard Medical School, Boston, Massachusetts, U.S.A.

Summary

1. To examine the role of angiotensin II in the maintenance of blood pressure and control of aldosterone secretion, eight normal human subjects were studied on a tilt table in sodium-replete and sodium-depleted states, before and after the administration of an angiotensin converting-enzyme inhibitor (CEI).

2. Administration of CEI was followed by a marked fall in blood pressure on tilting in sodium-depleted, but not in sodium-replete, subjects. CEI administration also resulted in a rise in plasma renin activity in the supine position, in the absence of haemodynamic change. The rise in plasma aldosterone observed both in response to tilting and sodium depletion did not occur after CEI, even though plasma renin activities were higher.

3. These results indicate that: (a) angiotensin II is essential for blood pressure control in the sodium-depleted individual; (b) angiotensin II exerts direct feedback control on renin secretion; (c) angiotensin II is the primary stimulus to aldosterone secretion in response to both sodium depletion and posture.

Key words: aldosterone, angiotensin, blood pressure, converting-enzyme inhibitor, renin, tilt table.

Introduction

The role of the renin–angiotensin system in the maintenance of normal blood pressure has been uncertain. The recent availability of effective competitive inhibitors of angiotensin-converting enzyme and of the action of angiotensin on its vascular receptors has permitted a critical examination of this question. Recent experiments in rats, rabbits and in trained, conscious dogs (Gavras, Brunner, Vaughan & Laragh, 1973; Samuels, Miller, Fray & Haber, 1973; Mimran, Guiod & Hollenberg, 1974) have demonstrated that angiotensin II is essential in the maintenance of normal blood pressure in the sodium-depleted but not in the sodium-replete animal. In the present experiments the role of renin in the maintenance of blood pressure and in the regulation of aldosterone in relation to posture is examined in normal man.

Methods

Human subjects

Eight normal subjects ranging in age from 19 to 27 years, including seven men and one woman, were studied. Subjects gave informed consent and the protocol of the investigation was approved by the institution’s human studies committee.

Group 1. Four subjects were maintained for 3 days on a 110 mmol Na–100 mmol K diet. On the subsequent day, subjects remained supine on a tilt table for 30 min, were tilted upright to 70° for 30 min and then permitted to remain supine for an additional 30 min. Heart rate and blood pressure were monitored. Blood samples were obtained at frequent intervals.

A single injection of converting-enzyme inhibitor (25 μmol/kg) was given intravenously 30 min after the first tilt and the earlier protocol was repeated. Subsequently, the subjects were either maintained on a 10 mmol Na–100 mmol K diet for 3 days (two subjects) or were given 80 mg of frusemide orally...
12 h before the study. Their mean weight loss was 2.67 ± 1.18 kg. The same experimental protocol as described above was then repeated.

Group 2. Four subjects were maintained first on a 110 mmol Na–100 mmol K diet for 5 days and then on a 10 mmol Na–100 mmol K diet. Before the experiment, 24 h urine sodium excretion was 138 ± 24 mmol on the high sodium diet and 15 ± 11 mmol on the low-sodium diet. Average weight loss was 2.16 ± 0.39 kg on sodium restriction. Each subject was studied on four separate experimental days, on 110 mmol Na diet, on 10 mmol Na diet, with and without CEI. In each study, after a supine equilibration period of 30 min, an injection of either CEI (25 mmol/kg) or diluent (placebo) was given. Fifteen minutes after the injection subjects were tilted to 70° for 7 min or until they felt faint.

Group 3. Five subjects were examined on a free diet and 12 h after the oral administration of 80 mg of frusemide (weight loss 1.54 ± 0.37 kg). After a 30 min period of blood pressure equilibration in the supine position, 12.7 μmol of CEI or diluent was administered, followed by a continuous infusion of CEI (12.7 μmol/min) or diluent. At 150 min the subjects were tilted upright for 7 min or until they fainted. The subjects were studied during four experimental sessions on separate days on a free diet with and without CEI and subsequent to frusemide with and without converting-enzyme inhibitor.

Plasma bradykinin concentrations were measured in two subjects in group 1 before and 5, 30 and 60 min after CEI, and in one subject in group 3 before and 15 and 150 min after CEI.

Analytical techniques

Plasma renin activities (PRA) were assayed by methods previously described (Haber, Koerner, Page, Kliman & Purnode, 1969). Plasma aldosterone determinations were done by a direct radioimmunoassay on plasma extract (Poulsen, Vetter, Sancho & Haber, 1974). Plasma bradykinin was determined by the method of Talamo, Haber & Austin (1969).

Converting-enzyme inhibitor

The converting-enzyme inhibitor utilized was the nonapeptide originally isolated from Bothrops venom having the sequence Tyr-Trp-Pro-Arg-Pro-Gln-Ile-Pro-Pro. Early experiments were performed with samples of this material kindly donated by Squibb (SQ 20,881). Later experiments were carried out with peptide synthesized in our laboratory, utilizing solid-phase synthetic techniques.

Results

Group 1

As is apparent from examination of Table 1, sodium-replete subjects underwent a modest narrowing of pulse pressure associated with tachycardia after 2 min of tilting. Identical changes on tilting were observed after administration of CEI, indicating that CEI did not have an effect on the haemodynamic response to tilting in the sodium-replete subject. After sodium depletion, these haemodynamic changes were exaggerated. After the administration of CEI in the sodium-depleted subject tilting resulted in a dramatic and significant fall in blood pressure (P<0.05) accompanied by a marked tachycardia.

The sodium-replete subjects showed a significant rise in PRA (P<0.05) and plasma aldosterone (P<0.01) during tilting. After CEI, PRA rose significantly higher on tilting (P<0.05), though there was no rise in plasma aldosterone. Sodium-depleted subjects had more dramatic rises in PRA and plasma aldosterone during control tilting studies. PRA was still further elevated on the tilt after CEI, though plasma aldosterone concentrations fell to baseline. These studies indicate that CEI administration resulted in a marked augmentation of the response of PRA to tilting, while completely blocking the response of plasma aldosterone.

Group 2

In order to exclude effects of diuresis independent of sodium depletion, haemodynamic studies were carried out in an additional group of four subjects who were sodium-depleted by diet alone. In this group, each tilting experiment was carried out on a separate day to exclude the effects of one experiment on a subsequent one. Table 1 confirms the haemodynamic observations made in group 1. Sodium-depleted subjects had a significantly greater fall in blood pressure (P<0.05) on tilting after CEI than did sodium-replete subjects.
Table 1. Effects of changes in posture of sodium-replete and sodium-depleted subjects on blood pressure, heart rate, plasma renin activity and plasma aldosterone concentration

Results are mean values ± SEM. Group 1: blood pressure, heart rate, PRA, plasma aldosterone: supine, 30 min; upright, maximal values. Group 2: supine blood pressure, heart rate before tilt; upright blood pressure, heart rate 2–3 min after tilt. Group 3: all supine blood pressure, heart rate, PRA, plasma aldosterone: control, 180 min; CEI or placebo, 150 min; upright blood pressure, pulse: 2–3 min.

<table>
<thead>
<tr>
<th>Na-replete</th>
<th>Na-depleted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>CEI</td>
</tr>
<tr>
<td>Supine</td>
<td>Upright</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>Systolic</td>
</tr>
<tr>
<td></td>
<td>Diastolic</td>
</tr>
<tr>
<td>Group 2</td>
<td>Systolic</td>
</tr>
<tr>
<td></td>
<td>Diastolic</td>
</tr>
<tr>
<td>Group 3</td>
<td>Systolic</td>
</tr>
<tr>
<td></td>
<td>Diastolic</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>67±5</td>
</tr>
<tr>
<td>Group 2</td>
<td>72±7</td>
</tr>
<tr>
<td>Group 3</td>
<td>59±2</td>
</tr>
<tr>
<td>PRA (ng h⁻¹ ml⁻¹)</td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>3.2±0.9</td>
</tr>
<tr>
<td>Group 3</td>
<td>1.1±0.3</td>
</tr>
<tr>
<td>Plasma aldosterone (pg/ml)</td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>156±55</td>
</tr>
<tr>
<td>Group 3</td>
<td>42±2</td>
</tr>
</tbody>
</table>

Group 3

In order to examine the persistence of the haemodynamic and hormonal effects of CEI, an infusion of CEI was continued for 150 min and subjects were tilted at the end of that period. Results in Table 1 confirm observations made in group 1 and group 2 at shorter intervals. As shown in the previous groups, there is no significant difference in upright blood pressure or heart rate in sodium-replete subjects before and after CEI. However, in sodium-depleted subjects a dramatic fall in blood pressure (P<0.05) was again observed on tilting after CEI administration. In the sodium-depleted subjects supine PRA was significantly higher than in control subjects after CEI (P<0.02), whereas plasma aldosterone concentrations were significantly lower (P<0.01). These results indicate that the dissociation of PRA and aldosterone seen on tilting in group 1 in response to CEI could also be observed in the supine position in group 3, suggesting that the rise in aldosterone in response to sodium depletion is also blocked by CEI.

No rise in bradykinin concentration was observed in any of the samples analysed.

Discussion

CEI previously has been demonstrated to block conversion of angiotensin I into II in man at doses similar to those used in this study (Collier, Robinson & Vane, 1973). Because of the short half-life of angiotensin II, within minutes after administration of CEI, the circulating amounts of this hormone should be negligible. From the data presented, it appears that angiotensin II is needed for the haemodynamic adjustment to upright tilting in sodium-depleted man; in its absence the sympathetic nervous system and other homeostatic mechanisms are inadequate to maintain blood pressure. Appropriate adrenergic response to hypotension is indicated by the invariable tachycardia observed when blood pressure falls. In the sodium-replete individual, other homeostatic mechanisms appear sufficient. It is unlikely that the other effect of CEI, inhibition of
bradykinin breakdown, is responsible for these observations since increase of plasma bradykinin concentration was not observed.

We have previously demonstrated that PRA rises rapidly on tilting (Oparil, Vassaux, Sanders & Haber, 1970). The data in these experiments show that plasma aldosterone follows with similar kinetics. CEI administration is associated with a significant increase in PRA in the supine position, more marked in sodium-depleted than in sodium-replete subjects at times when no significant haemodynamic change can be observed. This observation indicates that angiotensin II exerts negative feedback control on renin secretion.

After CEI administration, plasma aldosterone no longer follows the rise in PRA and remains either unchanged or falls either upon sodium depletion or tilting. These observations indicate that the major stimulus to aldosterone secretion in response to tilting or sodium depletion is angiotensin II. The earlier suggestion that angiotensin I may stimulate aldosterone secretion in vitro (Saruta, Cook & Kaplan, 1972) does not seem to be confirmed in vivo.

Acknowledgments

The skilful technical assistance of Virginia Lucas and Elizabeth Dimock is acknowledged. We also wish to thank Dr Richard Talamo for performing plasma bradykinin determinations. This work was supported by grant HL-14150 (SCOR) from the National Institutes of Health.

References


