SHORT COMMUNICATION

Studies on aldosterone responsiveness to angiotensin II during clinical variations in calcium metabolism in normal man

M. G. BIANCHETTI, C. BERETTA-PICCOLI, P. WEIDMANN, K. BOEHRINGER, L. LINK AND J. J. MORTON*  
Medizinische Poliklinik, University of Berne, Switzerland, and *MRC Blood Pressure Unit, Western Infirmary, Glasgow, Scotland, U.K.

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Summary

1. Angiotensin II was infused at stepwise increasing dose rates (2, 4 and 10 pmol min⁻¹ kg⁻¹) in 12 normal subjects. Infusions were performed in the presence of normocalcaemia, mild hypercalcaemia induced by concomitant calcium gluconate infusion, and after 2 weeks of treatment with nifedipine.

2. Pre-infusion plasma levels of angiotensin II, renin or aldosterone were not altered by acute mild hypercalcaemia or administration of nifedipine. The angiotensin II-induced increases in plasma aldosterone were also similar under the three study conditions.

3. Variations in calcium metabolism occurring under clinical conditions appear to play a minor role in modulating the angiotensin II-dependent pathway of aldosterone regulation in normal man.

Key words: aldosterone, angiotensin II, calcium, nifedipine.

Introduction

Experiments in vitro indicated that calcium may modify the responsiveness of aldosterone production to corticotropin, angiotensin II (ANG II) or potassium [1, 2]. However, the relevance of this cation in the regulation of aldosterone metabolism in man has not been clarified. Acute hypercalcaemia induced by intravenous infusion did not modify plasma aldosterone levels in subjects with mildly impaired renal function [3] but caused aldosterone stimulation in patients with terminal renal failure [4]. On the other hand, in six normal subjects the responsiveness of aldosterone to ANG II was reported to be blunted acutely after administration of a single dose of the calcium inhibitor nifedipine [5]. Whether and to what extent such an effect may persist in the stable phase of pharmacological intervention with calcium antagonists is unknown. Therefore, the present study was undertaken to assess the influence of a mild elevation in plasma calcium or of nifedipine given for 2 weeks on aldosterone responsiveness to ANG II in normal subjects.

Methods

Twelve normal subjects (four females and eight males, aged 20–30 years) were studied. All were healthy volunteers with a blood pressure consistently below 140/90 mmHg, and had normal plasma creatinine levels. The subjects, who had given their informed consent to the study, were instructed to ingest a normal diet, avoiding very high or low sodium intakes [6]. Under these dietary conditions, urinary sodium and potassium averaged 188 ± SEM 29 and 78 ± 8 mmol/24 h respectively on the first day and 168 ± 21 or 72 ± 8 mmol/24 h on the last day of the study.

The following procedures were performed after an overnight fast on three different mornings (08.00–12.00 hours) within 3–5 days:

(A) After a 60 min equilibration period with glucose (5%) infusion (6 ml/h by constant
infusion pump) in the supine position, ANG II (Hypertensin) was infused at stepwise increasing dose rates of 2, 4 and 10 pmol min$^{-1}$ kg$^{-1}$ during 20 min each. At the end of the equilibration period, basal blood pressure and heart rate were obtained and blood was collected from the arm contralateral to the infusion for determination of plasma sodium, potassium, calcium, renin activity, ANG II and aldosterone levels. Plasma ANG II, aldosterone and, at the highest dose rate, calcium levels were measured at the end of each ANG II infusion step.

(B) After the equilibration period described above (procedure A), calcium gluconate was infused at constant rate (8.3 μmol of calcium min$^{-1}$ kg$^{-1}$) during 120 min. Blood pressure, heart rate, plasma renin, aldosterone and calcium levels were determined at the end of the equilibration and of the calcium infusion periods.

(C) After a 60–120 min equilibration period with intravenous infusion of calcium gluconate at constant rate (8.3 μmol of calcium min$^{-1}$ kg$^{-1}$) in the supine position, ANG II was infused in addition to calcium gluconate at increasing dose rates of 2, 4 and 10 pmol min$^{-1}$ kg$^{-1}$ during 20 min each. Blood was collected at the end of the equilibration period and of each ANG II infusion step for determination of plasma calcium, ANG II and aldosterone levels.

(D) After completion of these procedures, the subjects were started on oral nifedipine, 10–20 mg thrice daily (mean dose 48 ± 3 mg/day). The lower dose had to be used in five subjects, who developed headache at the higher doses. After 2 weeks of nifedipine treatment, ANG II infusion study was performed according to procedure (A) protocol. All subjects took the usual morning dose of nifedipine before the test.

Blood pressure and heart rate were monitored at 1–2 min intervals during procedures (A)–(D). Plasma sodium and potassium were determined by flame photometer, calcium by Autoanalyzer, ANG II, aldosterone and renin activity by radioimmunoassay [7–9]. Data were analysed by analysis of variance and modified t-test; regressions were compared by analysis of covariance.

Results

Under basal conditions (procedure A), mean pre-ANG II infusion blood pressure and heart rate were 109/65 ± 3/2 mmHg and 65 ± 3 beats/min; plasma sodium, potassium, calcium and renin activity averaged 139 ± 1 mmol/l, 4.0 ± 0.1 mmol/l, 2.27 ± 0.02 mmol/l and 1.4 ± 0.4 nmol h$^{-1}$ ml$^{-1}$ respectively. These values were unaltered after 2 weeks of nifedipine treatment (procedure D) (108/61 ± 3/2 mmHg, 66 ± 4 beats/min, 139 ± 1 mmol/l, 4.1 ± 0.1 mmol/l, 2.25 ± 0.02 mmol/l and 1.2 ± 0.2 nmol h$^{-1}$ ml$^{-1}$). Blood pressure, heart rate, plasma calcium and renin measured before calcium infusion (procedure B), and blood pressure, heart rate and plasma renin activity measured before the combined calcium ANG II infusion (procedure C), were comparable with the corresponding values obtained before procedures (A) and (D). However, during the calcium infusion preceding the combined calcium–ANG II infusion, plasma calcium increased from 2.25 ± 0.02 to 2.64 ± 0.04 mmol/l (P < 0.01).

Pre-infusion plasma levels of ANG II and aldosterone were similar when measured before ANG II infusion (procedure A), the combined calcium–ANG II infusion (procedure C) or the ANG II infusion under nifedipine (procedure D) (Fig. 1). The increase in plasma ANG II during ANG II infusion was comparable in the three procedures (Fig. 1); the increase in plasma ANG II was accompanied by a parallel increase in plasma aldosterone, which was highly significant (P < 0.01) already at the lowest ANG II infusion rate. The ANG II-induced increments in plasma aldosterone were similar in the three study procedures (Fig. 1). ANG II-induced increases in diastolic blood pressure at the dose rates of 2, 4 and 10 nmol min$^{-1}$ kg$^{-1}$ were similar under basal conditions (+7 ± 1, +13 ± 2 and +20 ± 2 mmHg), in the presence of mild hypercalcaemia.

![Plasma aldosterone vs. Plasma angiotensin II](image-url)
(±4 ± 1, +15 ± 2 and +22 ± 2 mmHg) or after nifedipine (+6 ± 1, +12 ± 2 and +22 ± 2 mmHg). Heart rate did not change significantly during ANG II infusion in the three study conditions.

Calcium gluconate infused at constant rate during 120 min (procedure B) increased plasma calcium from 2.25 ± 0.02 to 2.5 ± 0.02 mmol/l (P < 0.01), but did not modify blood pressure (from 112/66 ± 12/9 to 114/67 ± 12/9 mmHg), heart rate (from 64 ± 3 to 65 ± 3 beats/min), plasma renin activity (from 1.0 ± 0.2 to 0.7 ± 0.1 pmol h⁻¹ ml⁻¹) or aldosterone (from 310 ± 50 to 291 ± 30 pmol/l) levels.

Discussion

In the present study, neither the basal values of renin or aldosterone nor the responsiveness of plasma aldosterone to ANG II were modified during an acute mild increase in plasma calcium or by short-term administration of the calcium antagonist nifedipine. With the calcium infusion rate used, plasma calcium was increased from 2.25 ± 0.02 to 2.64 ± 0.04 mmol/l. In a previous study from this laboratory [3], acute hypercalcaemia of a more marked degree also failed to alter plasma renin or aldosterone levels.

These observations do not mitigate against a role for calcium in the regulation of renin or aldosterone production. Calcium plays an important role in stimulation–secretion coupling of several endocrine systems [10] and may be required for the biosynthesis of renin and aldosterone [11, 12]. Moreover, it has been suggested that the stimulatory action of ANG II or potassium on aldosterone production may depend upon cellular uptake of calcium [13]. However, such studies in vitro do not imply that in vivo a mild to moderate increase in plasma calcium or the degree of inhibition of transmembrane calcium influx achieved by pharmacological agents should necessarily result in shifts in intracellular calcium concentration or distribution capable of modifying hormone biosynthesis or release. Pharmacological rather than physiological extracellular calcium concentrations have been used in vitro to stimulate aldosterone production [12]. Evidence for aldosterone inhibition by calcium antagonists has been obtained in vitro with lanthanum or verapamil but not nifedipine [13]. In other studies with nifedipine, plasma renin levels were increased acutely after a single dose of the drug in normal or hypertensive subjects [14], but were unaltered after 6 weeks of treatment [15]. The possibility cannot be excluded that acute renin stimulation was mediated by a concomitant decrease in blood pressure or other haemodynamic effects of nifedipine rather than by a calcium-specific mechanism. Such an acute activation of the renin–ANG system may also have contributed to a blunting of ANG II-induced increases in plasma aldosterone during the first 2 h after a single dose of nifedipine [5]. The lack of effect of acute elevation in plasma calcium or short-term calcium inhibition with nifedipine suggest that variations in calcium metabolism occurring under clinical conditions play at most a minor role in modulating renin release and the ANG II-dependent pathway of aldosterone production. Whether calcium may assume a more important role in corticotropin or potassium-mediated aldosterone regulation in man remains to be evaluated.

References

