Glucocorticoids and blood pressure: a role for the cortisol/cortisone shuttle in the control of vascular tone in man

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1. 11β-Hydroxysteroid dehydrogenase converts cortisol to inactive cortisone in man. In distal renal tubules, this inactivation protects mineralocorticoid receptors from cortisol. Congenital 11β-hydroxysteroid dehydrogenase deficiency and inhibition of 11β-hydroxysteroid dehydrogenase by liquorice or carbenoxolone result in cortisol-dependent hypokalaemia and hypertension.

2. 11β-Hydroxysteroid dehydrogenase is expressed in vascular smooth muscle. Both glucocorticoids and mineralocorticoids potentiate vascular responses to noradrenaline. 11β-Hydroxysteroid dehydrogenase activity may therefore influence vascular tone.

3. Experiments were performed in healthy subjects with and without 7 days of oral administration of 11β-hydroxysteroid dehydrogenase inhibitors (liquorice or carbenoxolone), and in a patient with congenital 11β-hydroxysteroid dehydrogenase deficiency. We measured the following parameters: dermal vasconstriction after topical application of cortisol, forearm blood flow during brachial artery infusion of cortisol or noradrenaline, and blood pressure during systemic infusion of noradrenaline.

4. Cortisol-induced dermal vasconstriction was increased by liquorice (23 ± 6 to 52 ± 7 units; P < 0.04) and in congenital 11β-hydroxysteroid dehydrogenase deficiency (87 units). In congenital 11β-hydroxysteroid dehydrogenase deficiency intra-arterial infusion of cortisol caused vascular constriction (20% reduction in blood flow in the infused arm) and accentuated the response to application of lower-body negative pressure, which stimulates sympathetically mediated vasconstriction (35% reduction). However, intra-arterial infusion of cortisol had no effect in healthy subjects either with or without administration of liquorice.

5. Carbenoxolone potentiated both noradrenaline-induced forearm vasconstriction (P < 0.01) and pressor response (P < 0.001).

6. We conclude that 11β-hydroxysteroid dehydrogenase modulates the access of cortisol to vascular receptors and thereby influences vascular sensitivity to noradrenaline. Complementary to its role in kidney, 11β-hydroxysteroid dehydrogenase could influence blood pressure by this mechanism, which may underlie our observations of impairment of 11β-hydroxysteroid dehydrogenase and increased dermal vascular sensitivity to cortisol in patients with essential hypertension.

INTRODUCTION

The enzyme 11β-hydroxysteroid dehydrogenase (11β-DH; EC 1.1.1.146) catalyses the conversion of the active glucocorticoid cortisol to its inactive metabolite cortisone in man. In the kidney this inactivation protects mineralocorticoid receptors from exposure to cortisol, and thereby allows specific access for aldosterone [1, 2]. In congenital 11β-DH deficiency [the syndrome of ‘apparent mineralocorticoid excess’ (AME)] [3] and after administration of the 11β-DH inhibitors liquorice [4] and carbenoxolone [5], the protective mechanism fails, intra-renal cortisol levels rise and cortisol gains inappropriate access to mineralocorticoid receptors resulting in hypokalaemia and hypertension.

11β-DH is expressed in many organs, including liver, lung, testis, placenta, colon and brain [6], raising the possibility that it modulates the access of cortisol to receptors in many sites. Recently, 11β-DH activity was identified in rat blood vessels [7]. We have localized 11β-DH immunoreactivity and mRNA to rat vascular smooth-muscle cells and have shown that its activity is greater in resistance vessels (mesenteric and caudal arteries) than in aorta [8]. It is therefore appropriately sited to modulate the access of cortisol to vascular steroid receptors.

Although corticosteroids are not directly vasoactive, they influence vascular responses to other agents, particularly noradrenaline. For example, vascular sensitivity to catecholamines is increased by
glucocorticoid administration in vivo or in vitro, and in spontaneous Cushing's syndrome (reviewed in [9]). This effect probably contributes to the pathogenesis of glucocorticoid hypertension [10]. So, if 11β-DH modulates vascular steroid receptor activation, it may influence blood pressure by a complementary mechanism to that described in the kidney [1, 2, 6]. Previous work from our group has shown that the dermal vasoconstriction induced by the topical application of cortisol is markedly potentiated by co-application of glycyrhetinic acid (an 11β-DH inhibitor and the principal active constituent of liquorice) [11]. However, it is not clear where topical glycyrhetinic acid has its effect because immunostaining for 11β-DH in skin is present in both dermal vascular smooth-muscle and epidermis [11].

In the present study we tested the hypothesis that loss of 11β-DH activity in human blood vessels results in increased vascular sensitivity to cortisol and thereby to noradrenaline. We examined the effects of oral 11β-DH inhibitors on vascular responses in healthy subjects, and on the vascular responses of our patient with AME, who remains the only adult case to have been reported so far [3].

METHODS

Subjects

All subjects gave their written informed consent. Local Ethics Committee approval was obtained. Cannulae were inserted under local anaesthesia with 1% (w/v) lignocaine. Studies were performed with the subjects on ad libitum sodium intake. Noradrenaline was measured by a radioenzymic assay as previously described [12]. Blood pressure was measured using a semi-automated sphygmomanometer (A and D UA-751, Takeda) [13]. Mean arterial blood pressure was calculated as: (diastolic blood pressure) + (pulse pressure ÷ 3).

Drug preparations

Liquorice was a kind gift from Geo. Bassett's Ltd, U.K. Carbenoxolone sodium tablets were obtained from Biorex Labs, U.K., and were crushed into 50 mg capsules. The placebo was lactose in identical capsules. For skin vasoconstriction studies, cortisol (as hydrocortisone-21-acetate; Sigma, Poole, Dorset, U.K.) was dissolved in 95% (v/v) ethanol/5% (v/v) H₂O. For brachial artery infusions, cortisol (as hydrocortisone-21-succinate; Solucortef; Upjohn, Crawley, Sussex, U.K.) was dissolved in 154 mmol/l NaCl, and noradrenaline (Levophed; Winthrop Labs, Newcastle-upon Tyne, U.K.) was dissolved in a solution containing 1 mmol/l ascorbic acid and 154 mmol/l NaCl. The ascorbic acid was added to prevent the oxidation of noradrenaline.

Assay of skin vasoconstrictors

This was performed as described previously [11]. The potent synthetic glucocorticoid BDP was used as a positive control, because it is protected from 11β-DH metabolism by its 9α-chloro group. Twelve solutions containing cortisol (0.1, 0.3, 1, 3, 5 and 10 mg/ml) or BDP (0.1, 0.3, 1, 3, 5 and 10 µg/ml) were prepared on the morning of the test. In the afternoon (16.00–17.00 hours), 12 squares of 7 mm × 7 mm were outlined on the volar aspect of the subject’s forearm with silicone grease. The squares had 10 µl of steroid solution applied, with a different solution for each square. The order of application was randomized and double-blind. After evaporation the site was occluded with Saran wrap (Dow, U.K.), which was removed at 08.00 hours the next morning. The intensity of dermal vasoconstriction for each square was assessed 1, 2, 3, 4, 6 and 8 h later by a blinded observer using a visual analogue scale from 0 to 3. The response to each steroid solution was expressed as the sum of scores obtained over time for that square (maximum = 18 units). The response to cortisol and BDP in each subject was represented by the area under the dose-response curve and was designated the ‘blanching score’ for each drug (maximum = 180 units µg ml⁻¹ for BDP and 180 units mg ml⁻¹ for cortisol).

Measurement of forearm blood flow

Before starting the experiments, the subjects rested supine for at least 30 min. Room temperature was maintained at 27 ± 1°C. The left brachial artery was cannulated with a 27-standard-wire-gauge steel cannula (Cooper’s Needle Works, Birmingham, U.K.) Vehicle, noradrenaline or cortisol solutions were infused at a constant rate of 1 ml/min. At least 30 min elapsed between arterial cannulation and the start of experimental recordings. Forearm blood flow was measured in both arms using venous occlusion plethysmography with temperature-compensated indium/gallium-in-silastic strain gauges [14, 15]. During recording periods the hand circulation was excluded by the inflation of wrist cuffs to 200 mmHg and flows were measured for 10 s in every 15 s by repeated inflation of upper-arm cuffs to 40 mmHg. Recording periods lasted for 4 min [when lower-body negative pressure (LBNP) was not required] or 6 min (when LBNP was applied during the second 3 min). The interval between recording periods was at least 6 min. After each recording period the gauges were calibrated on-limb and blood pressure was measured in the right arm. Data were collected and analysed on a Macintosh microcomputer. The mean of the final five measurements from each recording period was used for analysis.

Effects of infusion are represented by the percentage change in forearm blood flow calculated as:

\[ \frac{Q_{flow} - Q_{base}}{Q_{base}} \times 100 \]
where $I$ and $NI$ represent measured blood flows in the infused and non-infused arms, respectively, during periods of drug ($d$) and vehicle ($v$) administration. Using this calculation the non-infused arm acts as a control for non-specific variations in blood flow [16]. Forearm vascular resistance was derived from the equation: 

$$\frac{\text{mean arterial blood pressure}}{\text{flow \ in \ ml\ min}^{-1}\ 100\text{ml}^{-1}}.$$ 

When LBNP was required it was applied, as described previously [15, 17], for the second half of the recording period. Subjects rested supine in a plastic-covered steel cage enclosing the lower limbs and hips and sealed around the waist above the level of the anterior superior iliac spines. Suction was applied using a vacuum pump to produce a constant 20 cmH$_2$O negative pressure (compared with atmospheric). The alteration from atmospheric pressure was both applied and relieved rapidly. This degree of LBNP induces a sympathetically mediated reflex which reduces forearm blood flow without measurable effect on heart rate or blood pressure 2 min after application [15].

**Study 1: effect of 11β-DH inhibitors on vascular sensitivity to cortisol**

**Dermal vascular bed.** Six healthy subjects (three males, three females) aged 22–33 years (mean = 26 years) had skin vasoconstrictor assays performed before and after 7 days oral administration of liquorice (200 g daily).

**Forearm vascular bed.** Six healthy male subjects aged 26–32 years (mean = 29 years) had forearm blood flow measured on two occasions in random order, either with or without 7 days pre-administration of liquorice (orally 200 g daily). Infusions were with vehicle for 12 min, then cortisol at 200 μg/min for 30 min, and finally vehicle again for a 36 min washout period. Recordings were made with and without LBNP during the first 6 min of every 12 min.

**Study 2: vascular sensitivity to cortisol in congenital 11β-DH deficiency**

Our patient with AME was the first adult to be reported, and the 20th case at all ages. He has been described in detail elsewhere [3]. He was aged 25 years at the time of this study. His maintenance therapy was dexamethasone (0.25 mg at 09.00 hours and 0.75 mg at 23.00 hours), frusemide (40 mg at 09.00 hours) and captopril (25 mg every 12 h). His plasma cortisol concentration was undetectable, supine plasma renin activity was 5.4 ng of angiotensin I h$^{-1}$ ml$^{-1}$ (normal range 0.3–1.5 ng of angiotensin I h$^{-1}$ ml$^{-1}$), plasma aldosterone concentration was 380 pmol/l (normal range 30–440 pmol/l) and blood pressure was 127/72 mmHg. His last doses of frusemide, captopril and dexamethasone were 30 h, 16 h and 6 h, respectively, before the experiments. We performed both the skin vasoconstrictor assay and intra-arterial infusion of cortisol as described above.

**Study 3: effect of 11β-DH inhibitors on vascular sensitivity to noradrenaline in the forearm vascular bed and during systemic noradrenaline infusion**

Carbenoxolone was used for inhibition of 11β-DH in this study in part to allow a placebo-controlled double-blind design, in part because it may be a more potent inhibitor of 11β-DH than liquorice (see the Discussion), and in part to avoid the gastrointestinal side effects of liquorice. Six healthy male subjects aged 26–33 years (mean = 30 years) attended on two occasions after 7 days of oral administration of carbenoxolone (100 mg every 8 h) or placebo, in random double-blind order. A 21-gauge cannula was inserted in a right antecubital vein for blood sampling. Intra-arterial infusions were with vehicle for 12 min followed by incremental doses of noradrenaline (12 min each at 10, 20, 40 and 80 ng/min). LBNP was not applied in this study and recordings were made during the last 4 min of each infusion.

Immediately after the intra-arterial study, the cannula was removed. A 21-gauge venous cannula was sited in the left arm and incremental doses of noradrenaline (5 min each at 1, 2, 4 and 8 μg/min) were infused. Blood pressure was recorded in the right arm at 90 s intervals.

For measurement of plasma noradrenaline concentrations, 6 ml of blood was withdrawn from the right arm cannula into lithium–heparin at 4°C: at the beginning of the experiment, during the highest dose of the intra-arterial infusion and during systemic infusion with 2 and 8 μg of noradrenaline/min. Plasma was stored at −70°C until assayed.

**Statistics**

Results are given as means (±SEM). For intra-arterial cortisol infusions, time-points were compared by paired multifactorial analysis of variance. For noradrenaline infusions, dose–response curves were compared by multiple regression with ‘percentage change in flow’ or ‘mean arterial blood pressure’ as the dependent variable and ‘dose of noradrenaline’ and ‘pre-treatment’ (placebo versus carbenoxolone; assigned values of 0 and 1) as controlling variables. Paired two-tail Student’s $t$-tests were used for two-group comparisons.
RESULTS

Dermal vasoconstrictor sensitivity to cortisol

The results are shown in Fig. 1. Oral liquorice potentiated the intensity of vasoconstriction in response to cortisol ($P<0.04$) but not to BDP. Dermal vasoconstriction in our patient with AME was greater after cortisol and less after BDP compared with healthy subjects either with or without administration of liquorice.

Forearm vascular sensitivity to intra-arterial cortisol with or without LBNP

The results are shown in Table 1 and Fig. 2. Resting blood flow, mean arterial blood pressure, derived forearm vascular resistance and degree of vasoconstriction were not affected by liquorice or were not remarkable in the AME patient (Table 1). During cortisol infusions there was no confounding systemic effect, since neither mean arterial blood pressure nor blood flow in the non-infused arm changed significantly. In healthy subjects, either with or without liquorice, cortisol infusion affected neither forearm flow without LBNP (Fig. 2a) nor vasoconstriction in response to LBNP (Fig. 2b). However, in the patient with AME there was vasoconstriction during cortisol infusion, which was exaggerated by LBNP. This was followed, during the washout period, by relative vasodilatation in the absence of LBNP.

Vascular sensitivity to noradrenaline

Results for intra-arterial noradrenaline infusions are shown in Tables 1 and 2 and Fig. 3. Resting blood flow, mean arterial blood pressure and derived forearm vascular resistance at the start of the infusions were not affected by carbenoxolone (Table 1). During infusions noradrenaline had no confounding systemic effect, since neither mean arterial blood pressure nor blood flow in the non-infused arm changed significantly. Furthermore, in neither study did plasma noradrenaline levels rise in the contralateral arm during intra-arterial infusions (Table 2). Carbenoxolone caused potentiation of noradrenaline-induced forearm vasoconstriction ($P<0.01$).

RESULTS for systemic noradrenaline are shown in Table 2 and Fig. 4. After carbenoxolone the levels of noradrenaline in the contralateral arm were significantly lower during infusion with $8 \mu g$ of noradrenaline/min (Table 2). Even so, carbenoxolone potentiated the pressor response to noradrenaline ($P<0.001$).

DISCUSSION

These studies show that (i) cortisol-induced dermal vasoconstriction is increased in AME and after oral administration of liquorice; (ii) cortisol-induced forearm vasoconstriction occurs in AME (when it is potentiated by the sympathetic stimulus of LBNP) but not in healthy subjects either before or after liquorice, and (iii) both the forearm vasoconstriction induced by intra-arterial noradrenaline and the pressor response induced by systemic noradrenaline are potentiated by carbenoxolone. We conclude that $11\beta$-DH modulates the access of cortisol to receptors in blood vessels, and thereby modulates their sensitivity to noradrenaline.

A number of points complicate the interpretation of these data. First, in AME there was cortisol-induced forearm vasoconstriction, which was not reproduced by liquorice. This probably reflects the severity of $11\beta$-DH deficiency in the patient with AME. The half-life of $[1\alpha-{\text{H}}]$cortisol, a measurement of $11\beta$-DH activity, was 42±2min in 19 control subjects was prolonged to 131min in this patient [3] and to 123min after carbenoxolone [5], but only to 85min after liquorice [4].

Secondly, is it possible that the renal effects of $11\beta$-DH inhibition account for these results? For example, increased plasma volume consequent on renal sodium retention might increase vascular sensitivity. However, previous investigators have shown that, although volume expansion due to administration of mineralocorticoids increases forearm vascular sensitivity, volume expansion due to salt loading (with suppressed plasma renin activity and aldosterone) reduces it [18]. Since endogenous mineralocorticoid secretion is suppressed when $11\beta$-DH is inhibited [4, 5], it is unlikely that our findings are secondary to renal sodium retention. Similarly, elevated blood pressure alone might increase vascular sensitivity. However, blood pressure was no different after 7 days of carbenoxolone or liquorice administration. Furthermore, although
Table I. Forearm blood flow and blood pressure at the beginning of each experimental infusion. Values are means ± SEM.

<table>
<thead>
<tr>
<th></th>
<th>Study 1</th>
<th>Study 2</th>
<th>Study 3</th>
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<tbody>
<tr>
<td></td>
<td>Vehicle</td>
<td>Liquorice</td>
<td>AME</td>
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<tr>
<td>Forearm blood flow</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>without LBNP (ml min⁻¹ 100 ml⁻¹)</td>
<td></td>
<td></td>
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<tr>
<td>Infused arm</td>
<td>4.3 ± 0.8</td>
<td>4.5 ± 2.1</td>
<td>3.6</td>
</tr>
<tr>
<td>Non-infused arm</td>
<td>3.2 ± 0.4</td>
<td>3.3 ± 1.0</td>
<td>3.5</td>
</tr>
<tr>
<td>Forearm blood flow</td>
<td></td>
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</tr>
<tr>
<td>with LBNP (ml min⁻¹ 100 ml⁻¹)</td>
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<td></td>
</tr>
<tr>
<td>Infused arm</td>
<td>3.8 ± 0.8</td>
<td>3.3 ± 1.1</td>
<td>3.1</td>
</tr>
<tr>
<td>Non-infused arm</td>
<td>3.4 ± 0.7</td>
<td>2.9 ± 0.7</td>
<td>2.7</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>128 ± 4</td>
<td>124 ± 4</td>
<td>144</td>
</tr>
<tr>
<td>Diastolic</td>
<td>71 ± 1</td>
<td>74 ± 1</td>
<td>104</td>
</tr>
<tr>
<td>Mean arterial</td>
<td>90 ± 3</td>
<td>91 ± 1</td>
<td>117</td>
</tr>
</tbody>
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Fig. 2. Change in forearm blood flow during intra-arterial infusion of cortisol, in six healthy subjects on a control day (■) and after 7 days of oral administration of liquorice (○), and in a patient with AME (□). Recordings were made with (a) and without (b) the application of LBNP. Results are expressed as the percentage change from baseline of the ratio: (flow in the infused arm)/(flow in non-infused arm). Values are means with bars indicating SEM.

Fig. 3. Change in forearm blood flow during intra-arterial infusion of noradrenaline in six healthy subjects after 7 days of oral administration of placebo (■) or carbenoxolone (○). Results are expressed as the percentage change from baseline of the ratio: (flow in the infused arm)/(flow in non-infused arm). Values are means with bars indicating SEM. Comparison of curves was performed by multiple regression: *P < 0.01. Statistical significance (paired Student’s t-test): †P < 0.03.

The patient with AME had a history of hypertension and had higher blood pressure on the day of this study, he had been normotensive on therapy during the 3 years beforehand.

Thirdly, it may be important that both liquorice and carbenoxolone have actions additional to their effect on 11β-DH. They inhibit a number of enzymes which metabolize steroids [19] and prostaglandins [20], and they may act directly on steroid receptors [21] and cell membranes [22]. However, we doubt that these are relevant because we have demonstrated similar abnormal vascular responses in AME, and because previous experiments have shown that plasma concentrations of liquorice derivatives at the doses used in our experiments are not high enough to produce other biochemical effects [4, 23].
Table 2. Plasma noradrenaline levels during noradrenaline infusions in study 3. Values are means ± SEM. Abbreviation: NS, not significant.

<table>
<thead>
<tr>
<th></th>
<th>Plasma noradrenaline level (nmol/l)</th>
<th>Before infusion vs intervention*</th>
<th>Placebo vs carbenoxolone†</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Carbenoxolone</td>
<td>Placebo</td>
</tr>
<tr>
<td>Before infusion</td>
<td>1.17 ± 0.22</td>
<td>1.33 ± 0.28</td>
<td>NS</td>
</tr>
<tr>
<td>Intra-arterial infusion at 80 ng/min</td>
<td>1.48 ± 0.25</td>
<td>1.25 ± 0.23</td>
<td>NS</td>
</tr>
<tr>
<td>Intravenous infusion at 2 µg/min</td>
<td>1.99 ± 0.37</td>
<td>2.23 ± 0.62</td>
<td>NS</td>
</tr>
<tr>
<td>Intravenous infusion at 8 µg/min</td>
<td>6.12 ± 0.79</td>
<td>3.87 ± 0.62</td>
<td>P &lt; 0.01</td>
</tr>
</tbody>
</table>

*Changes within experiments were compared by single-factor analysis of variance (P < 0.001 for both placebo and carbenoxolone) and then by paired Student’s t-tests as shown.
†Comparison between experiments was by paired two-way analysis of variance (P < 0.01 for placebo vs carbenoxolone) and then by paired Student’s t-tests at each dose as shown.

**Mechanism of increased vascular responses**

The present results are consistent with many others in vivo and in vitro in which corticosteroids increased the response to noradrenaline. This effect is common to agonists of both types of classical cytosolic corticosteroid receptor which are expressed in vascular smooth muscle, namely mineralocorticoid and glucocorticoid receptors [9]. Although cortisol is a potential agonist of both receptors, in the kidney mineralocorticoid receptors are protected from cortisol by 11β-DH [1, 2]. However, experiments with specific receptor antagonists have shown that cortisol-induced dermal vasoconstriction is mediated by glucocorticoid receptors [24, 25]. Therefore in vascular tissue it is, at least in part, the access of cortisol to glucocorticoid receptors which is controlled by 11β-DH. This is in keeping with the suggestion that 11β-DH modulates access of cortisol to glucocorticoid receptors in tissues which do not express mineralocorticoid receptors (for example, testis and liver) [6].

In addition it is possible that some effects of steroids are mediated by cell-surface receptors [26]. These would act more rapidly than classical receptors because they are not dependent on gene induction [9]. Activation of surface receptors could account for the rapid vasoconstriction after intrarterial infusion of cortisol in our patient with AME. By contrast, the time course of the dermal response potentiated by liquorice is consistent with gene induction, being maximal at 12–15 h [27].

The mechanism linking steroid receptor activation and the increased response to noradrenaline is uncertain [9]. Although glucocorticoids inhibit extravascular noradrenaline uptake [28] and catechol-0-methyltransferase [29] in vitro, there is no evidence that these effects are important in vivo [30]. In our study, noradrenaline clearance was, if anything, increased by carbenoxolone, as judged by noradrenaline levels during infusions. Perhaps of greater relevance are recent observations that glucocorticoids increase both the number of adrenoceptors [31] and the sensitivity of the phospholipase C/inositol phosphate second messenger cascade [32] in vascular smooth muscle.

**(Relevance to blood pressure regulation)**

The contribution which increased vascular tone makes to the hypertension seen in 11β-DH deficiency is difficult to quantify. After administration of liquorice, there is a dissociation between sodium retention (which occurs in the first few days and reaches equilibrium within 10 days) and elevated blood pressure (which occurs only after chronic administration [33]). Therefore the rise in blood pressure may be independent of renal mineralocorticoid excess. In the present study, despite increased sensitivity to noradrenaline, resting forearm vascular resistance was no different after 7 days of carbenoxolone administration and blood pressure had not risen. This is consistent with findings during the
administration of dexamethasone to rats, when increased vascular sensitivity [34] and pressor response [35] to noradrenaline preceded the rise in blood pressure. Dexamethasone hypertension is not associated with renal mineralocorticoid excess [10].

When the role of 11β-DH in the kidney was described, one of the exciting implications was that it provided a mechanism whereby cortisoldependent hypertension need not be accompanied by elevated plasma cortisol concentrations. This follows because, when cortisol clearance is reduced and intra-renal cortisol concentrations are high, plasma cortisol concentration is maintained in the normal range by feedback suppression of adrenocorticotropic hormone (ACTH) [3, 4]. A large proportion of 'essential' hypertensive patients have been shown to respond to dexamethasone therapy [36, 37], suggesting that they have ACTH- or cortisoldependent hypertension, but abnormal cortisol secretion was not demonstrated. These patients might have 11β-DH deficiency. Recently, we showed that seven out of 20 essential hypertensive patients had prolonged half-lives of [11β-3H]cortisol, indicating 11β-DH deficiency, but they did not have evidence of excessive stimulation of renal mineralocorticoid receptors [38]. However, as a group, the hypertensive patients also had more intense dermal vasoconstriction after topical application of cortisol than control subjects. In the present study we provide evidence for a mechanism which could link 11β-DH deficiency, increased vascular response to cortisol and elevated blood pressure, without invoking renal sodium retention.

In summary, cortisol-induced potentiation of vascular responses to noradrenaline depends not only on the cortisol secretion rate but also on the local metabolism of cortisol by 11β-DH. In adrenocortical regulation of blood pressure, this mechanism may be complementary to the role of the enzyme in the kidney. Deficiency of 11β-DH, either in kidney or in vascular smooth muscle, represents a novel mechanism to be explored in the pathophysiology of essential hypertension.

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