Inhibition of prostaglandin and nitric oxide synthesis prevents cortisol-induced renal vasodilatation in sheep

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De Matteo, R., and C. N. May. Inhibition of prostaglandin and nitric oxide synthesis prevents cortisol-induced renal vasodilatation in sheep. Am. J. Physiol. 276 (Regulatory Integrative Comp. Physiol. 45): R1125–R1131, 1999.—Glucocorticoids increase renal blood flow (RBF) and glomerular filtration rate in many species, but the mechanisms involved are unclear. We investigated whether cortisol-induced renal vasodilatation in conscious sheep depends on interactions with prostaglandins or angiotensin II. Intravenous infusion of cortisol (5 mg/h) for 5 h increased renal conductance (RC) by 1.06 ± 0.24 ml·min⁻¹·mmHg⁻¹ more than vehicle. During intrarenal infusion of indomethacin (0.25 mg·kg⁻¹·h⁻¹), the cortisol-induced increase in RC (0.28 ± 0.21 ml·min⁻¹·mmHg⁻¹) was significantly reduced. The cortisol-induced rise in RBF (103 ± 17 ml/min) was not significantly reduced by indomethacin treatment (76 ± 9 ml/min). Combined intrarenal infusion of indomethacin (0.25 mg·kg⁻¹·h⁻¹) with N⁰-nitro-L-arginine (2.0 mg·kg⁻¹·h⁻¹), a nitric oxide synthase inhibitor, abolished the cortisol-induced increases in both RC and RBF. Inhibition of angiotensin II synthesis with intravenous captopril (40 mg/h) blocked the renal vasoconstrictor action of angiotensin I but did not inhibit the cortisol-induced increases in RBF and RC. This study provides evidence that nitric oxide and prostaglandins play a role in cortisol-induced renal vasodilatation but indicates that this response is independent of an interaction with angiotensin.

angiotensin; indomethacin

MAINTENANCE OF NORMAL renal blood flow (RBF) and glomerular filtration rate (GFR) depends on the actions of glucocorticoid hormones. Excess secretion of glucocorticoids causes renal vasodilatation and an increase in GFR, whereas adrenal insufficiency has the opposite effect. Administration of glucocorticoids increases RBF by 30–50% in dogs (18) and sheep (16), but the mechanisms leading to this glucocorticoid-induced renal vasodilatation remain poorly understood.

Micropuncture studies in rats have demonstrated that glucocorticoid-induced increases in glomerular plasma flow depend on reductions in both afferent and efferent arteriolar resistances (2). We have demonstrated that in sheep cortisol-induced renal vasodilatation is due to a direct action on the kidney and that the endothelium-derived relaxing factor nitric oxide plays a role in this response (9). There is evidence that other locally released factors such as prostaglandins can act in concert with nitric oxide to cause vasodilatation (4, 15), but whether prostaglandins play a role in glucocorticoid-induced renal vasodilatation has not been determined.

Prostaglandins regulate pre- and postglomerular tone by relaxing the afferent and efferent arterioles (10), the site at which glucocorticoids act to increase RBF (2). Studies in rats have shown that intrarenal administration of prostaglandin E₂ causes renal vasodilatation and attenuates the vasoconstrictor actions of other agents (7). In vivo studies have indicated that eicosanoid production can increase during glucocorticoid administration (12). These studies indicate that basal release of prostaglandins plays an important role in the control of renal vascular tone and raise the possibility that prostaglandins could mediate glucocorticoid-induced renal vasodilatation.

Another mechanism that could contribute to glucocorticoid-induced renal vasodilatation is a reduction in the vascular responsiveness to endogenous angiotensin. It is well established that angiotensin plays a major role in the regulation of renal hemodynamics, and it has been shown that acute administration of glucocorticoids reduces the vasoconstrictor activity of angiotensin in the isolated perfused rat kidney (8). Although it has been demonstrated that intravenous administration of glucocorticoids increases systemic vascular responsiveness to vasoconstrictor agents, including angiotensin (23), this probably reflects actions at nonrenal sites, because the kidney is the only vascular bed that vasodilates in response to intravenous infusion of cortisol (16).

The present studies were undertaken to examine the role played by prostaglandins and angiotensin in the renal vasodilatation caused by cortisol in conscious sheep. We studied the effect of cortisol in the presence of indomethacin, a blocker of prostaglandin synthesis, and also with a combined infusion of indomethacin and N⁰-nitro-L-arginine (L-NNA), an inhibitor of nitric oxide synthase. In addition, the renal vascular action of cortisol was studied during angiotensin-converting enzyme inhibition with captopril, to exclude any interaction with circulating or locally produced angiotensin.

METHODS

General

Mature merino-cross ewes were used in all experiments and were individually housed in metabolism cages. Access to water was allowed ad libitum, and 800 g of oat chaff was offered daily (containing 90–120 mmol/kg of Na⁺ and 270–380 mmol/kg of K⁺). Sheep were surgically prepared in two stages. In each stage, anesthesia was induced with thiopentone sodium (15 mg/kg) and was maintained with 1.5–2.0% halothane-O₂ mixture. The first stage involved
ovariectomy, uninephrectomy, and construction of external carotid artery loops. Ovariectomy is performed routinely to prevent interference with fluid and electrolyte balance from ovarian reproductive hormones. Three to four weeks later, a transit-time flow probe (4 mm, Transonic Systems) was implanted on the renal artery of the remaining kidney (3) and a Silastic cannula (0.64 mm ID, 1.19 mm OD) was inserted into the renal artery. Cannulas and flow probe leads were protected by a jacket worn by the animal. Animals were allowed 2 wk of recovery after surgery before experiments commenced.

Arterial pressure was measured via a Tygon cannula (1.0 mm ID, 1.5 mm OD), inserted 15 cm into a carotid artery loop, connected to a pressure transducer (TDXIII, Cobe) tied to the wool on the sheep's back. The pressure was corrected to compensate for the height of the transducer above the level of the heart. Heart level was taken as 64% of the distance from the back to the sternum, which is the level of the junction of the left atrium with the left atrial appendage. The signal from the pressure transducer was amplified and calibrated daily against a mercury manometer. Patency of arterial cannulas was maintained by infusing heparinized saline (25 U/ml) at 3 ml/h. Two polyethylene cannulas (1.2 mm ID, 1.7 mm OD) were inserted into the jugular vein for intravenous infusion.

RBF was measured with a transit-time flow probe connected to a transit-time flowmeter (T201CDS, Transonic Systems) either directly or via a four-probe sequential scanner (TM04, Transonic Systems). Mean arterial pressure (MAP), heart rate (HR), RBF, and renal conductance (RC = RBF/MAP) were monitored using a personal computer 486 data-acquisition system with custom-written software (3). After analog-to-digital conversion (DT 2811 board, Data Translation), the data were collected at 100 Hz for 10 s at intervals of 5 min.

Experimental Methods

Effect of intrarenal indomethacin on the renal hemodynamic response to intravenous cortisol. The responses to a 5-h intravenous infusion of cortisol (5 mg/h) were examined during simultaneous intrarenal infusion of indomethacin or saline. After a 1-h control period, indomethacin (0.25 mg·kg⁻¹·h⁻¹) or saline (12 ml/h) was infused directly into the renal artery. After a pretreatment period of 1 h, cortisol (5.0 mg/h) or vehicle (5% glucose containing 4% ethanol, 12 ml/h) was infused intravenously for 5 h, simultaneously with indomethacin or vehicle. During the experiment, RBF, RC, MAP, and HR were recorded every 5 min, and the data were averaged over 1-h time periods.

Effect of intrarenal L-NNA and intrarenal indomethacin on the renal hemodynamic response to intrarenal cortisol. After a 1-h control period, L-NNA (2.0 mg·kg⁻¹·h⁻¹) together with indomethacin (0.25 mg·kg⁻¹·min⁻¹) were infused directly into the renal artery; in control experiments vehicle was infused (normal saline, 12 ml/h). After 3-h pretreatment, a simultaneous intrarenal infusion of either cortisol (1.3 mg/h) or vehicle (dextrose containing 1% ethanol, 12 ml/h) was started. All infusions were stopped after a further 5 h. Every 5 min, RBF, RC, MAP, and HR were monitored and the data were averaged over 1-h time periods. Treatments were given in random order, and 1 wk was allowed between experiments in which L-NNA was administered. We have shown previously that in conscious sheep the renal vasodilator response to intravenous cortisol is mediated by a direct action on the kidney (9) and that the intrarenal dose of cortisol used (1.3 mg/h) causes equivalent increases in RBF and RC to intravenous cortisol (5 mg/h) (9). In addition, we demonstrated that intrarenal infusion of L-NNA (2.0 mg·kg⁻¹·h⁻¹) attenuated, but did not completely inhibit, the increases in RBF and RC in response to cortisol (9).

Effect of intravenous captopril on the renal hemodynamic response to intravenous cortisol. After a 1-h control period, captopril (40 mg/h) or vehicle (normal saline, 12 ml/h) was infused intravenously in six conscious sheep. One hour later, an intravenous infusion of either cortisol (5 mg/h) or vehicle (5% dextrose containing 4% ethanol at 12 ml/h) was started. Both infusions were stopped 5 h later. Every 5 min, RBF, RC, MAP, and HR were recorded and the data were averaged over 1-h time periods.

The dose of captopril used blocked the renal responses to an intrarenal infusion of angiotensin I. Administration of angiotensin I (10 nmol/h for 5 min) caused renal vasoconstriction, as demonstrated by the decreases in RBF (378 ± 30 to 252 ± 60 ml/min, P < 0.05) and RC (5.7 ± 0.4 to 4.3 ± 0.7 ml·min⁻¹·mmHg⁻¹, P < 0.05), and this effect was blocked by pretreatment with intravenous captopril (40 mg/h).

Renal vascular response to cortisol in sheep with elevated arterial pressure. The effect of Intravenous infusion of cortisol (5 mg/h) was studied in four sheep in which mean arterial pressure was increased by intravenous infusion of norepinephrine (24 µg·kg⁻¹·h⁻¹). This dose of norepinephrine caused a similar increase in arterial pressure to that in response to combined treatment with indomethacin and L-NNA.

After a 1-h control period, an intravenous infusion of norepinephrine (24-µg·kg⁻¹·h⁻¹) or vehicle (5% glucose at 6 ml/h) was started. After 1.5 h, cortisol (5 mg/h) or vehicle (5% glucose containing 4% ethanol at 12 ml/h) was started. Infusions were turned off after a further 5 h. Every 5 min, RBF, RC, MAP, and HR were measured, and the data were averaged over 30-min time periods. The treatments were randomized and were given on alternate days.

Statistical Analysis

Data are presented as means ± SE. Statistical analysis was performed in three steps. First, the effect of infusion of the prostaglandin, nitric oxide, or angiotensin synthesis blockers (indomethacin, indomethacin + L-NNA, or captopril, respectively) or vehicle, before the start of the cortisol infusion, on RBF, RC, MAP, and HR was tested for significance by paired t-tests. Second, the effect of infusion of the synthesis blockers, with and without cortisol (5 h), was compared with the pretreatment period (0 h) by paired t-tests. Third, the last 5 h of infusion for each treatment (i.e., from the beginning of the cortisol infusion) were collectively compared using repeated-measures analysis of variance with the Greenhouse-Geisser correction. Analysis of the effect of indomethacin, indomethacin + L-NNA, or captopril on the responses to cortisol compared the response to infusions of the synthesis blockers and cortisol with the responses to vehicle infusion and the interaction between indomethacin, indomethacin + L-NNA, or captopril and cortisol infusions. Similar statistical protocols were used to examine the responses to cortisol in the presence of norepinephrine. Responses were considered significant at the level of P < 0.05.

RESULTS

Effect of Intrarenal Indomethacin on the Renal Hemodynamic Response to Intravenous Cortisol

Infusion of cortisol for 5 h in six conscious sheep increased RBF by 67 ± 9 ml/min (P < 0.05) and RC by 0.88 ± 0.24 ml·min⁻¹·mmHg⁻¹ (P < 0.05), whereas there were no significant changes with infusion of
vehicle (RBF = 9 ± 6 ml/min and RC = 0.25 ± 0.23 ml·min⁻¹·mmHg⁻¹) (Fig. 1, A and B). Both MAP and HR were unchanged during infusion of cortisol or vehicle. Intrarenal infusion of indomethacin reduced RBF from 307 ± 18 to 246 ± 13 ml/min (P < 0.05) and RC from 4.16 ± 0.15 to 3.09 ± 0.15 ml·min⁻¹·mmHg⁻¹ (P < 0.05) over the first hour (Fig. 1). Over the following 5 h of indomethacin infusion, RBF increased by 31 ± 6 ml/min (P < 0.05) and RC by 0.47 ± 0.07 ml·min⁻¹·mmHg⁻¹ (P < 0.05). In the presence of indomethacin, the increase in RC due to cortisol alone (1.06 ± 0.24 ml·min⁻¹·mmHg⁻¹) was significantly less (P < 0.05) than the increase in RC due to cortisol alone (0.28 ± 0.21 ml·min⁻¹·mmHg⁻¹). The increase in RBF due to cortisol was 103 ± 17 ml/min, whereas when cortisol was infused with indomethacin the cortisol-induced increase in RBF, above that with indomethacin, was 76 ± 9 ml/min. Infusion of cortisol did not significantly alter the response of MAP or HR in the presence of indomethacin (Fig. 1, C and D), although MAP tended to remain elevated when indomethacin and cortisol were infused together.

Effect of Intrarenal L-NNA and Intrarenal Indomethacin on the Renal Hemodynamic Response to Intrarenal Cortisol

During the first 3 h of intrarenal infusion of L-NNA and indomethacin, RBF decreased from 344 ± 44 to 234 ± 38 ml/min (P < 0.05) and RC from 4.33 ± 0.62 to 2.52 ± 0.46 ml·min⁻¹·mmHg⁻¹ (P < 0.05) in six sheep (Fig. 2). Over this time MAP increased from 83 ± 3 to 101 ± 3 mmHg (P < 0.05) and HR decreased from 62 ± 3 to 52 ± 4 beats/min (P < 0.05) (Fig. 2). During the next 5 h of infusion of L-NNA and indomethacin, there were no changes in RBF, RC, MAP, or HR.

Intrarenal infusion of cortisol (1.3 mg/h) significantly increased RBF and RC compared with vehicle (P < 0.05) (Fig. 2). As we have shown previously (9), the increases in RBF and RC with intrarenal cortisol (Fig. 2) were similar to those with intravenous cortisol (5 mg/h) (Fig. 1). With intrarenal infusion of cortisol, RBF increased from 393 ± 55 to 470 ± 54 ml/min (P < 0.05) and RC increased from 5.16 ± 0.70 to 6.14 ± 0.78 ml·min⁻¹·mmHg⁻¹. In contrast, during intrarenal infusion of vehicle there was a tendency for RBF (364 ± 61 to 350 ± 56 ml/min) and RC (4.67 ± 0.79 to 4.46 ± 0.77 ml·min⁻¹·mmHg⁻¹) to decrease. The increases in RBF and RC induced by cortisol were abolished when L-NNA and indomethacin were infused together with cortisol. During concomitant infusion of cortisol with L-NNA and indomethacin, RBF started at 231 ± 38 ml/min and was 230 ± 38 ml/min after 5 h. At the start of the simultaneous infusion of cortisol with L-NNA and indomethacin, RC was 2.34 ± 0.36 ml·min⁻¹·mmHg⁻¹ and was unchanged at 2.23 ± 0.39 after 5 h.

Fig. 1. Effects on renal blood flow (RBF; A), renal conductance (RC; B), mean arterial pressure (MAP; C), and heart rate (HR; D) of intravenous vehicle (○), intravenous cortisol (●), intrarenal indomethacin (○), and intrarenal indomethacin + intravenous cortisol (●) in 6 conscious sheep. Treatment with indomethacin started at −1 h, infusion of cortisol started at 0 h, and all infusions finished at 5 h. Statistical analysis was performed in 3 steps. 1) *Significant effect of infusion of indomethacin or vehicle before start of cortisol infusion (−1 vs. 0 h; P < 0.05). 2) #Significant effect of infusion of vehicle and/or cortisol (0 vs. 5 h; P < 0.05). 3) Last 5 h of infusion for each treatment were collectively compared using repeated-measures ANOVA. ‡Significant interaction between indomethacin and cortisol (P < 0.05).
Infusion of cortisol did not alter the response of MAP or HR to the combined infusion of L-NNA and indomethacin (Fig. 2). With all treatments, the changes in MAP and HR for the last 5 h of infusion did not differ from one to the other.

Effect of Intravenous Captopril on the Renal Hemodynamic Response to Intravenous Cortisol

In six sheep, intravenous infusion of captopril (40 mg/h for 1 h) increased RBF from 303 ± 13 to 329 ± 13 ml/min (P < 0.05), increased RC from 3.75 ± 0.18 to 4.30 ± 0.23 ml·min⁻¹·mmHg⁻¹ (P < 0.05), and decreased MAP from 81 ± 4 to 78 ± 5 mmHg (P < 0.05). Over the following 5 h of infusion of captoval there were no changes in RBF, RC, or HR, whereas MAP decreased to 72 ± 4 mmHg (P < 0.05).

Captopril did not inhibit the increases in RBF and RC caused by infusion of cortisol (Fig. 3, A and B). During infusion of cortisol with captopril, RBF increased from 347 ± 33 to 403 ± 18 ml/min (P < 0.05) and RC from 5.0 ± 0.65 to 5.68 ± 0.62 ml·min⁻¹·mmHg⁻¹ (P < 0.05). When cortisol was infused alone, there were similar increases in RBF, from 337 ± 19 to 403 ± 15 ml/min (P < 0.05), and RC, from 4.40 ± 0.28 to 5.21 ± 0.28 ml·min⁻¹·mmHg⁻¹ (P < 0.05). The increases in RBF and RC were not significantly different with the two treatments.

Renal Vascular Response to Cortisol in Sheep With Elevated Arterial Pressure

Intravenous infusion of norepinephrine increased MAP from a control level of 85 ± 2 to 105 ± 5 mmHg after 90 min of infusion (P < 0.05), and MAP remained at this level until the end of the infusion (105 ± 3 mmHg) (Fig. 4). During norepinephrine there was a transient fall in RBF, followed by a return to control levels within 30 min, and RBF stayed at this level for the remainder of the infusion. Norepinephrine reduced RC from 4.6 ± 0.4 to 4.0 ± 0.3 ml·min⁻¹·mmHg⁻¹ within 30 min, after which RC slowly declined throughout the remainder of the infusion to reach 3.7 ± 0.3 ml·min⁻¹·mmHg⁻¹ after 6.5 h of infusion.

Infusion of cortisol increased RBF from 345 ± 17 to 432 ± 24 ml/min (P < 0.05) and RC from 4.2 ± 0.4 to 5.3 ± 0.3 ml·min⁻¹·mmHg⁻¹ (P < 0.05) over 5 h of infusion in four sheep. In the presence of norepinephrine, the cortisol-induced increases in RBF (from 394 ± 46 to 472 ± 46 ml/min) and RC (from 4.0 ± 0.4 to 4.8 ± 0.6 ml·min⁻¹·mmHg⁻¹) were not significantly different from the changes with cortisol alone (Fig. 4). The norepinephrine-induced increase in MAP was not altered by infusion of cortisol.

DISCUSSION

Glucocorticoid hormones have been shown to play an important role in the maintenance of RBF and GFR in several species. Micropuncture studies in rats have demonstrated that these responses depend on glucocorticoid-induced vasodilatation of both the efferent and afferent arterioles (2), but the mechanisms causing this
vasodilatation have not been defined. Recently, we demonstrated that nitric oxide is one factor that plays a role in cortisol-induced renal vasodilatation in sheep (9). The present studies have investigated whether prostaglandins and angiotensin, vasoactive agents that play a central role in the control of renal function, are additional factors that mediate glucocorticoid-induced renal vasodilatation.

The finding that indomethacin inhibited the cortisol-induced increase in renal conductance suggests that prostaglandins are, in addition to nitric oxide, another locally released factor involved in mediating the renal hemodynamic responses to glucocorticoids. The lack of a significant reduction in the cortisol-induced increase in RBF with indomethacin reflects the greater MAP, and therefore greater renal perfusion pressure, in the group treated with indomethacin and cortisol. There is a growing body of evidence that the endothelium-derived mediators, prostaglandins and nitric oxide, are released in response to similar stimuli and act in concert to cause vascular relaxation (4, 15). Our findings that combined treatment with indomethacin and L-NNA abolished the cortisol-induced renal vasodilatation and increase in blood flow suggest that this response is fully accounted for by the release of prostaglandins and nitric oxide. Whether cortisol acts directly to cause release of these endothelium-derived vasodilators or whether this is a secondary response to release of another factor such as bradykinin, which has been shown to cause vasodilatation by release of prostaglandins and nitric oxide (15), requires further study.

A number of other lines of evidence support a role for prostaglandins in the renal response to cortisol. First, there is evidence from in vivo studies that glucocorticoid administration increases renal eicosanoid production (11, 12). Second, prostaglandins have been shown to regulate RBF, GFR, and mesangial function, and renal eicosanoid production has been demonstrated in isolated glomeruli, glomerular epithelia, mesangial cells, medullary collecting tubular cells, and medullary interstitial cells (20, 22, 24). Third, prostaglandins have been shown to cause vasodilatation of the afferent and efferent arterioles (6, 13, 25), the renal vascular site at which glucocorticoids have been shown to act (2). Interestingly, this is also one of the major sites in the kidney at which nitric oxide acts to increase RBF (26).

Treatment with indomethacin, and the combined treatment with indomethacin and L-NNA, increased arterial pressure and caused vasoconstriction of the renal vasculature, which it could be argued induced myogenic autoregulatory responses that interfered with the vasodilator action of cortisol. We do not believe this to be the case because increasing arterial pressure by a similar amount, by infusion of norepinephrine, had no effect on the cortisol-induced increases in RBF and RC. In addition, we have demonstrated previously that the renal vasodilator response to cortisol was not inhibited

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**Fig. 3.** Effects on RBF (A), RC (B), MAP (C), and HR (D) of intravenous vehicle (○), intravenous cortisol (●), intravenous captopril (40 mg/h) (▲), and intravenous captopril + intravenous cortisol (▲) in 6 conscious sheep. Treatment with captopril started at -1 h, infusion of cortisol started at 0 h, and all infusions finished at 5 h. Statistical analysis was performed in 3 steps. 1) *Significant effect of infusion of captopril or vehicle before start of cortisol infusion (-1 vs. 0 h; P < 0.05). 2) #Significant effect of infusion of vehicle, captopril, and/or cortisol (0 vs. 5 h; P < 0.05). 3) Last 5 h of infusion for each treatment were collectively compared using repeated-measures ANOVA. †Significant difference compared with vehicle (P < 0.05).
in kidneys in which the vasculature was preconstricted by an intrarenal infusion of angiotensin II (9). These findings indicate that the inhibition of the renal vasodilator action of cortisol by indomethacin and combined treatment with indomethacin and l-NNA are not non-specific actions secondary to the hypertension and renal vasoconstriction.

The finding that indomethacin treatment caused a large degree of renal vasoconstriction, as shown by the fall in RC, indicates that in sheep basal release of prostaglandins has a tonic vasodilator action on the renal vasculature and that prostaglandins play a role in the maintenance of renal hemodynamics under normal conditions. These results are in agreement with recent studies in humans, which demonstrated that inhibition of prostaglandin synthesis by indomethacin in healthy subjects reduced both RBF and GFR (17, 19). Other studies in dogs and rats have provided little evidence supporting a role for prostaglandins in the regulation of RBF and GFR in the normal, conscious, unstressed animal (1, 5), but this may reflect species differences.

A reduction in sensitivity to the renal vascular actions of angiotensin has been implicated as another mechanism that could contribute to cortisol-induced renal vasodilation. In the isolated perfused rat kidney, dexamethasone or corticosterone diminished the renal vasoconstriction elicited by angiotensin II or norepinephrine (8). However, the majority of evidence examining the pressor responsiveness to vasoconstrictor agents following systemic administration of glucocorticoids indicates that glucocorticoids increase the pressor responsiveness to vasoconstrictor agents (23), although this is not a universal finding (14, 21). It is important to note that the pressor responsiveness in the whole animal may bear little relation to the responses in the kidney, because intravenous infusion of cortisol causes vasodilatation in the kidney but not in the vasculature of the heart, gut, or skeletal muscle (16). The present experiments were designed to examine the renal vascular response to cortisol in the absence of angiotensin II. The finding that captopril treatment did not inhibit the renal vasodilation in response to cortisol indicates that the cortisol-induced renal vasodilatation did not result from a reduction in the vascular responsiveness to angiotensin II. The effective inhibition of angiotensin-converting enzyme by the dose of captopril used was confirmed by showing blockade of the renal vasoconstrictor response to intrarenal infusion of angiotensin I. Treatment with captopril increased RBF and RC, confirming previous studies indicating that endogenous angiotensin II provides a tonic vasoconstrictor influence on the renal vasculature.

These studies have confirmed previous findings in conscious sheep that cortisol causes renal vasodilatation and an increase in RBF. Indomethacin treatment attenuated this response, suggesting that this renal action of cortisol is partly mediated by release of vasodilatory prostaglandins. A combination of indomethacin and l-NNA abolished the response to cortisol, indicating that the locally released endothelial factors,

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**Fig. 4. Effects on RBF (A), RC (B), MAP (C), and HR (D) of intravenous vehicle (○), intravenous cortisol (●), intravenous norepinephrine (24 µg·kg⁻¹·h⁻¹) (▲), and intravenous norepinephrine + intravenous cortisol (■) in 4 conscious sheep. Treatment with norepinephrine started at -1.5 h, infusion of cortisol started at 0 h, and all infusions finished at 5 h. Statistical analysis was performed in 3 steps. 1) *Significant effect of infusion of norepinephrine or vehicle before start of cortisol infusion (-1.5 vs. 0 h; P < 0.05). 2) #Significant effect of infusion of vehicle, norepinephrine, and/or cortisol (0 vs. 5 h; P < 0.05). 3) Last 5 h of infusion for each treatment were collectively compared using repeated-measures ANOVA. †Significant difference compared with vehicle (P < 0.05).**
prostaglandins and nitric oxide, account for the renal vasodilatation in response to cortisol. Induction of a similar increase in MAP and reduction in RC by infusion of norepinephrine did not prevent the renal vasodilator action of cortisol, indicating that the effects of indomethacin and L-NNA were not nonspecific effects secondary to the hypertension and renal vasoconstriction. Captopril did not alter the cortisol-induced vasodilatation, demonstrating that the response was not dependent on an interaction with angiotensin.

Perspectives

It is well established that in the absence of circulating glucocorticoids renal function is reduced, that in adrenal deficiency replacement of glucocorticoids restores renal function, and that in normal animals infusion of glucocorticoids increases RBF and GFR. These findings, in many species, indicate that endogenous glucocorticoids are essential for the maintenance of normal renal function. Recently we provided evidence that the renal vasodilatory response to cortisol in conscious sheep is due to a direct action on the kidney and that nitric oxide plays a role in this response. The present findings, that an inhibitor of prostaglandin synthesis attenuated the renal vascular response to cortisol, suggest that prostaglandins are involved in this response. A complex interrelation between nitric oxide and prostaglandins has been shown to mediate the vasodilator response to other stimuli, and whether cortisol acts directly or via release of another factor to stimulate release of these endothelium-derived vasodilators remains to be determined. Further studies are also required to explain why this vasodilatory response to cortisol is confined to the kidney. This selectivity presumably reflects an action on specific renal sites, such as the afferent and efferent arterioles or the mesangial cells, which have been shown to respond to nitric oxide and prostaglandins.

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REFERENCES


