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Effect of glucocorticoids on vascular reactivity to vasoactive hormones in rat isolated kidney: lack of relationship to prostaglandins

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1 The relationship between the effects of glucocorticoids on renal vascular reactivity and prostaglandin synthesis elicited by noradrenaline (NA), angiotensin II (AII), arginine vasopressin (AVP) and bradykinin (Bk) was investigated in the isolated kidney of the rat perfused with Tyrode solution.

2 Administration of NA 0.3–3.0 nmol, AII 0.028–0.28 nmol, AVP 0.027–0.27 nmol and Bk 0.28–2.8 nmol enhanced in a dose-dependent manner the renal output of immunoreactive prostaglandin E_2 (PGE_2) and 6-keto-PGF_{1a}. NA, AII and AVP, but not Bk, produced renal vasoconstriction and increased perfusion pressure.

3 In the presence of dexamethasone (2.6×10^{-5} M) or corticosterone (2.9×10^{-5} M), the effects of NA and AII, in enhancing prostaglandin synthesis and producing renal vasconstriction, were reduced. In contrast, stimulation of prostaglandin synthesis by Bk and AVP and the renal vasoconstriction produced by AVP were not altered by the glucocorticoids. Dexamethasone or corticosterone did not alter the output of prostaglandins elicited by A-23187 or arachidonic acid (AA).

4 Addition of mepacrine (2.1×10^{-5} M) to the perfusion fluid reduced the renal output of prostaglandins elicited by the vasoactive hormones and by A-23187, but not by AA; the vasoconstrictor response to NA and AII, but not to AVP was reduced.

5 In kidneys in which prostaglandin synthesis was inhibited by indomethacin (2.8×10^{-6} M), administration of dexamethasone also reduced the renal vasoconstrictor effect of NA and AII.

6 These data indicate that in Tyrode-perfused rat kidney the glucocorticoids dexamethasone and corticosterone exert a differential effect on the renal vascular reactivity to vasoactive hormones, and that their inhibitory effect on NA and AII-induced renal vasoconstriction appears to be unrelated to prostaglandin synthesis.

Introduction

Glucocorticoids in large doses produce hypertension in the rat and sheep (Knowlton *et al.*, 1952; Krakoff *et al.*, 1975; Scoggins *et al.*, 1978) and enhance the pressor response and vascular reactivity to noradrenaline (NA) and in some species to angiotensin II (AII) (Raab *et al.*, 1950; Kurland & Freeberg, 1951; Mendlowitz *et al.*, 1958; Kalsner, 1969; Schömig, Lüth, Dietz & Gross, 1976). Both NA and AII stimulate prostaglandin synthesis in several tissues including the kidney (Gilmore *et al.*, 1968; McGiff, *et al.*, 1970; 1972; Needleman *et al.*, 1973; Mullane & Moncada, 1980; Shebuski & Aiken, 1980). The ability of prostaglandins, particularly PGE_2 and PGI_2, to reduce vascular reactivity to vasoconstrictor stimuli (Lonigro *et al.*, 1973; Malik *et al.*, 1980; Susić *et al.*, 1981) and the demonstration that glucocorticoids inhibit prostaglandin synthesis in several intact cell systems and perfused organs (Kantrowitz *et al.*, 1975; Tashjian *et al.*, 1975; Lewis & Piper, 1975; Hong & Levine, 1976; Gryglewski, 1976; Herbaczynska-Cedro & Staszewska-Barczak, 1977; Blackwell *et al.*, 1978; Zusman & Keiser, 1980) presumably by stimulating the synthesis of a phospholipase A_2 inhibitor(s) (macrocortin, lipomodulin or renocortin) (Flower & Blackwell, 1979; Hirata *et al.*, 1980; Cloix *et al.*, 1983), has led to the proposal that glucocorticoids enhance vascular reactivity to NA by inhibiting the synthesis of PGE_2 and PGI_2 (Rascher *et al.*, 1980; Axelrod, 1983). However, the finding that in the isolated kidney of the rat *in vitro*,

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prostaglandins do not inhibit but rather potentiate the vasoconstrictor effect of NA and AII (Malik & McGiff, 1975; Armstrong & Lattimer, 1976) raises the possibility that glucocorticoids may reduce vascular reactivity to vasoconstrictor stimuli. To test this hypothesis we have investigated the effect of dexamethasone and corticosterone on the output of prostaglandins and on the vascular reactivity to NA, AII, arginine vasopressin (AVP) and bradykinin (Bk) in the isolated kidney of the rat perfused with Tyrode solution. To distinguish the action of glucocorticoids that are related to inhibition of prostaglandin synthesis from those that are not, we have also examined the effect of dexamethasone on the renal vascular response and on prostaglandin output elicited by vasoactive hormones in the presence of indomethacin, a cyclo-oxygenase inhibitor. A preliminary account of this work has been published (Malik & Cooper, 1983).

Methods

Male Sprague-Dawley rats, weighing 350–400 g, maintained on normal chow, were anaesthetized with ether, and the abdomen was opened by a midline laparotomy. The aorta was ligated proximal and distal to the left renal artery. A catheter was inserted into the renal artery and the kidney was flushed with heparinized saline (100 units ml^{-1}). The kidney was isolated and perfused with Tyrode solution according to the procedure described previously (Malik & McGiff, 1975). The kidney was perfused at a flow rate of 5 ml min^{-1} by means of a Harvard peristaltic pump. Tyrode solution was maintained at 37°C and gassed with a mixture of 95% O_2 and 5% CO_2. The composition of this solution was, in (mmol l^{-1}): NaCl 137, KCl 2.7, $CaCl_2$ 1.8, $MgCl_2$ 1.1, $NaHCO_3$ 12, NaH_2PO_4 0.42 and D(+)-glucose 5.6. Perfusion pressure was measured with a pressure transducer (Statham $P_{23}Db$) and recorded on a physiograph. Since flow rate was maintained constant, changes in perfusion pressure reflect alterations in renal vascular resistance. The kidney was perfused for 35 min before beginning any experimental intervention.

Experimental protocol

All experiments were performed during 35–125 min of perfusion because the basal output of prostaglandins in this period was stable and it was lower before 35 min and higher after 125 min of perfusion. The following three series of experiments were performed.

Series 1 The purpose of this series of experiments was to determine the effect of different doses of noradrenaline (NA), angiotensin II (AII), arginine vasopressin (AVP) and bradykinin (Bk) on the output of prostaglandins and on renal vascular tone. NA 0.3–3 nmol, AII 0.028–0.28 nmol, AVP 0.027–0.27 nmol, Bk 0.28–2.8 nmol or their respective vehicle was injected as a bolus at 15 min intervals in random order into the tubing leading to the catheter inserted into the renal artery. Samples of the renal perfusate were collected for 2 min periods immediately before (basal) and after the administration of various agents or their vehicle. Changes in perfusion pressure were recorded and the output of prostaglandins in the renal perfusate was determined by radioimmunoassay after purification of the samples by the procedure to be described later.

Series 2 This series of experiments was performed to investigate the effect of dexamethasone, corticosterone, mepacrine and indomethacin on the actions of NA, AII, AVP, Bk, A-23187, a calcium ionophore, and arachidonic acid (AA) on prostaglandin output and on vascular tone. Kidneys were perfused with Tyrode solution containing dexamethasone (2.6×10^{-5} M), corticosterone (2.9×10^{-5} M), mepacrine (2.1×10^{-5} M), indomethacin (2.8×10^{-6} M) or their vehicle. NA 1.6 nmol, AII 0.097 nmol, AVP 0.27 nmol, Bk 0.94 nmol, A-23187 9.6 nmol, AA 33 nmol or their respective vehicle was administered, and the samples of renal perfusate for the determination of prostaglandins were collected as described for experimental Series 1. In two additional experiments kidneys were perfused for 4 h with Tyrode solution containing dexamethasone before the administration of vasoactive hormones.

Series 3 This series of experiments was performed to investigate the effect of dexamethasone on the actions of NA and AII on release of prostaglandins and on renal vascular tone in kidneys perfused with Tyrode solution containing indomethacin (2.8×10^{-6} M). NA 1.6 nmol, AII 0.097 nmol or their vehicle was injected into the kidney. Changes in perfusion pressure were recorded, and samples of renal perfusate for prostaglandin determination were collected as described for Series 1 experiments.

Determination of prostaglandins

Prostaglandin E_2 and 6-keto-prostaglandin-$F_{1\alpha}$ in the renal perfusate were measured by radioimmunoassay. Perfusate samples were allowed to thaw at room temperature; 5 ml aliquots were acidified to pH 2.8–3.0 with 2 N HCl and passed through C-18 Sep Paks (Water Associates, Inc., Milford, MA) that were preequilibrated with 0.001 N HCl. The columns were then washed sequentially with 10 ml each of 0.001 N HCl, 15% ethanol, petroleum ether, methyl

formate and methanol. The methyl formate fraction was evaporated to dryness with nitrogen and the residue dissolved in 1 ml of gelatin phosphate buffer (pH 7.4) composed of ($g l^{-1}$) NaN_3 1.0, NaCl 9.0, KH_2PO_4 3.4, K_2HPO_4 13.1 and gelatin 1.0 (Fisher 100 bloom). Aliquots (0.1 ml) of each sample were then added to polypropylene tubes together with 0.1 ml (8000 dpm) of [^{3}H]-PGE_2, or [^{3}H]-6-keto-$PGF_{1\alpha}$ (New England Nuclear, Boston, MA) dissolved in gel buffer and 0.1 ml of the appropriate antisera. The tubes were vortexed and incubated at 0°C for 2 h for PGE_2 assay and 18 h for 6-keto-$PGF_{1\alpha}$ assay. After the incubation period, 1 ml of a charcoal-dextran mixture (2.5 g of charcoal and 0.25 g of dextran l^{-1} of gel buffer) was added to each tube, and 10 min later the tubes were centrifuged. The supernatant was decanted into plastic scintillation vials containing 8 ml of Instagel mixture (Packard, Downers Grove, IL) and the radioactivity measured with a Searle Mark III 6880 Scintillation Counter. The limit of detection of prostaglandins in our assay was 2 pg for PGE_2 and 5 pg for 6-keto-$PGF_{1\alpha}$. The cross reactivity for each antibody was less than 0.5% for other prostaglandins and their metabolites. Extraction blanks varied from 0 to 3 pg per tube. Specific binding ranged from 35 to 45% for each antibody and nonspecific binding ranged from 2 to 3%. The intra-assay and interassay coefficient of variation was 5 and 12% respectively. Recovery of prostaglandins, added to the perfusate before extraction, was 90 to 95% and none of the drugs used in our experiments interfered with the radioimmunoassay.

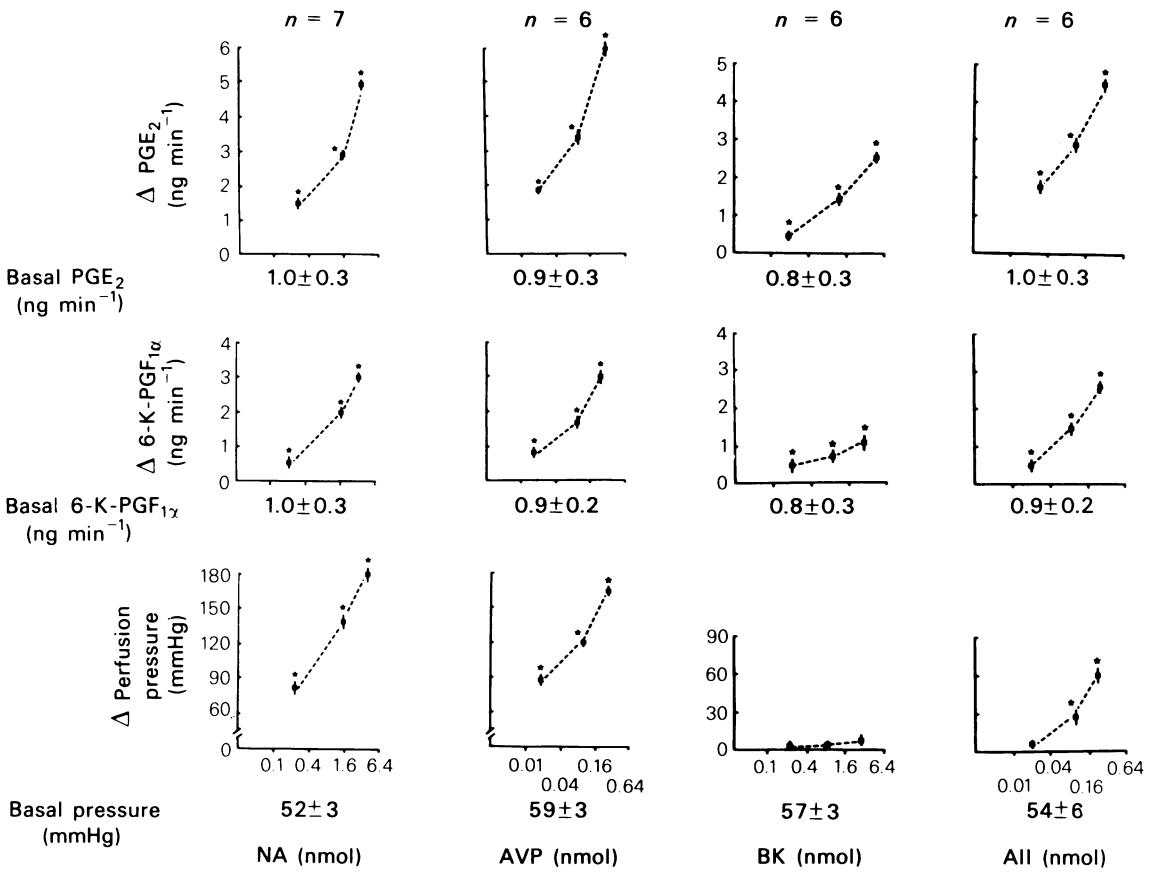

Figure 1 Effect of noradrenaline (NA), arginine vasopressin (AVP) bradykinin (Bk) and angiotensin II (AII) on the output of prostaglandins E_2 (PGE_2, upper panel) and 6-keto-$PGF_{1\alpha}$ (6-K-$PGF_{1\alpha}$) (middle panel) and on the perfusion pressure (bottom panel) in the rat isolated kidney perfused with Tyrode solution. Bars show s.e.mean, * denotes value significantly different from basal ($P<0.05$).

Drugs

The following drugs were used: noradrenaline bitartrate (NA) (Levophed, Winthrop), angiotensin II (AII), dexamethasone acetate, corticosterone, quinacrine hydrochloride (mepacrine) and indomethacin (Sigma Chemical Co.), arginine vasopressin (AVP) (Bachem Inc.), bradykinin diacetate (Bk) (Protein Research Foundation, Minoh-shi), A-23187 (Eli Lilly Co.) and arachidonic acid (AA) (Nu Check Prep. Inc).

AII, AVP and Bk were dissolved in saline and A-23187 in dimethyl sulphoxide (1 mg ml^{-1}) to prepare stock solutions and stored in small aliquots at −20°C. The content of each vial was diluted with saline just before use. NA contained in ampoules was also diluted with saline. Arachidonic acid was dissolved in absolute ethanol (20 mg ml^{-1}) and the clear and colourless solution was divided in 5 µl aliquots and stored at −20°C in small vials protected from light. The content of each vial was diluted before use in 0.1 ml Na_2CO_3 (1 mg ml^{-1}) and 0.9 ml of 0.9% w/v NaCl solution (saline). Solutions of NA, AII, AVP, Bk, A-23187 or AA were injected in a volume of 0.1 ml into the tubing leading to the renal artery. Dexamethasone and corticosterone were dissolved in

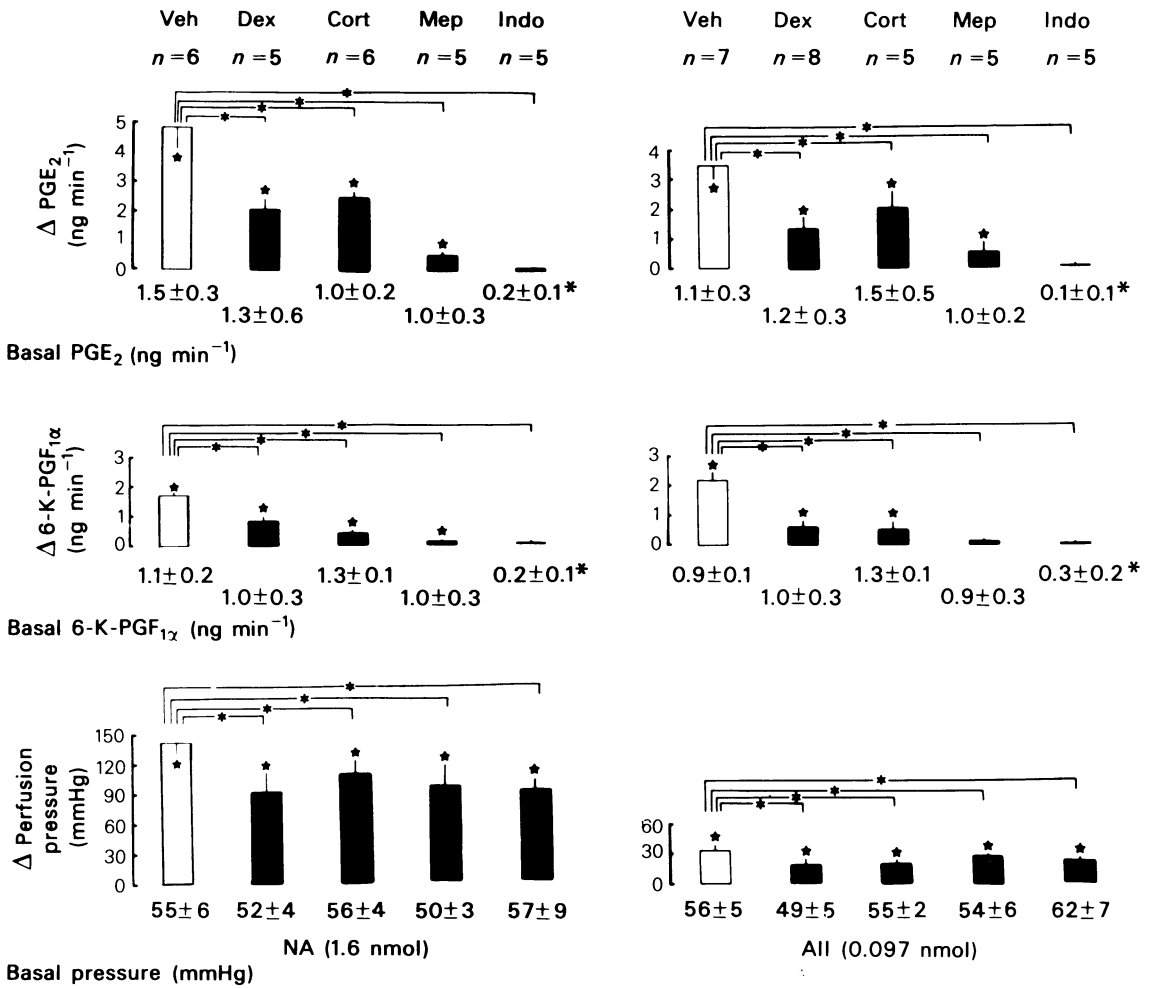

Figure 2 Effects of noradrenaline (NA) and angiotensin II (AII) on the output of prostaglandin E_2 (PGE_2, upper panel) and 6-keto-$PGF_{1\alpha}$ (6-K-$PGF_{1\alpha}$) (middle panel) and on the perfusion pressure (bottom panel) in the rat kidney perfused with Tyrode solution containing dexamethasone (Dex) 2.6×10^{-5} M, corticosterone (Cort) 2.9×10^{-5} M, mepacrine (Mep) 2.1×10^{-5} M, indomethacin (Indo) 2.8×10^{-6} M or their vehicle (Veh). Bars show s.e.mean, * denotes a value significantly different from basal value and * denotes a value significantly different from that obtained during infusion of vehicle ($P < 0.05$).

Tyrode solution (10 mg per 0.5 l) by vigorous stirring for about 1–1.5 h and then added to the perfusion fluid to obtain the final concentration. Indomethacin and mepacrine (10 mg ml^{-1}) were dissolved in Tyrode solution by vigorous shaking and added to the perfusion fluid to obtain the final concentration.

Analysis of data

The basal output and increase in prostaglandin output elicited by various agents is expressed as ng min^{-1} of immunoreactive PGE_2 and 6-keto-$PGF_{1\alpha}$. The basal output of prostaglandins represents the amount of prostaglandins in the samples collected for the 2 min period immediately before the administration of a drug. The increase in the output of prostaglandins elicited by an agent was calculated by subtracting the basal prostaglandin output from that obtained during 2 min periods just after the injection of a drug into the kidney. The results are presented as mean ± s.e.mean. The data were analysed by one-way analysis of variance, and Dunnett's test was used to determine the difference between means and Students' *t* test for unpaired observations. Differences between means were considered significant if the probability (*P*) of the null hypothesis being true was less than 0.05.

Results

Effect of NA, AVP, Bk and AII on the output of prostaglandins and on vascular tone in the isolated kidney (Figure 1)

Administration of NA 0.3–3.0 nmol, AVP 0.027–0.27 nmol, Bk 0.28–2.8 nmol, or AII 0.028–0.28 nmol, into the renal arterial circuit enhanced in a dose-dependent manner the output of immunologically detected PGE_2 and 6-keto-$PGF_{1\alpha}$; the amount of PGE_2 being significantly greater than that of 6-keto-$PGF_{1\alpha}$ ($P<0.05$). In two experiments the amount of immunoreactive $PGF_{2\alpha}$ was also measured. Both the basal (0.2–0.5 ng min^{-1}) as well as the increase elicited by the vasoactive agents (0.4–0.6 ng min^{-1}) was considerably less than that of PGE_2 and 6-keto-$PGF_{1\alpha}$, and it was not measured in subsequent experiments. NA, AII and AVP but not Bk also produced vasoconstriction and a dose-related increase in perfusion pressure. The rise in perfusion pressure elicited by NA peaked in 10–20 s and that elicited by AII and AVP peaked within 30–40 s. The output of prostaglandins elicited by these vasoconstrictor agents as well as by Bk reached maximal level in 2 min and gradually returned to preinjection level within the next 5 min. Injections of the vehicle into the kidney did not alter the output of prostaglandins or perfusion pressure.

Effect of dexamethasone, corticosterone, mepacrine and indomethacin on the actions of NA, AII, AVP, Bk, A-23187 and AA on the output of prostaglandins and on vascular tone (Figures 2, 3, 4 and 5).

In kidneys perfused with Tyrode solution containing either dexamethasone (2.6×10^{-5} M) or corticosterone (2.9×10^{-5} M), injections of NA 1.6 nmol, AII 0.097 nmol, AVP 0.27 nmol, Bk 0.94 nmol, A-23187 9.6 nmol or AA 33 nmol enhanced the output of both PGE_2 and 6-keto-$PGF_{1\alpha}$. However, the output of prostaglandins elicited by NA and AII (Figure 2) but not that caused by AVP (Figure 3), and A-23187 (Figure 4) or AA (Figure 5), was significantly less in the presence of glucocorticoids than that obtained during infusion of their respective vehicle.

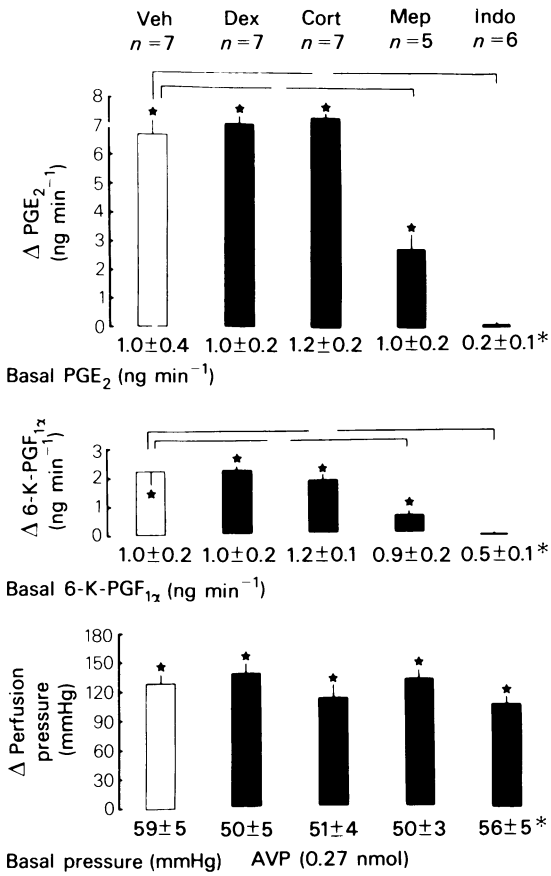

Figure 3 Effect of arginine vasopressin (AVP) on renal output of prostaglandin E_2 (PGE_2, upper panel) and 6-keto-$PGF_{1\alpha}$ (6-K-$PGF_{1\alpha}$) (middle panel) and on the perfusion pressure (bottom panel)in the rat kidney perfused with Tyrode solution containing inhibitors. All details as for Figure 2 (see legend).

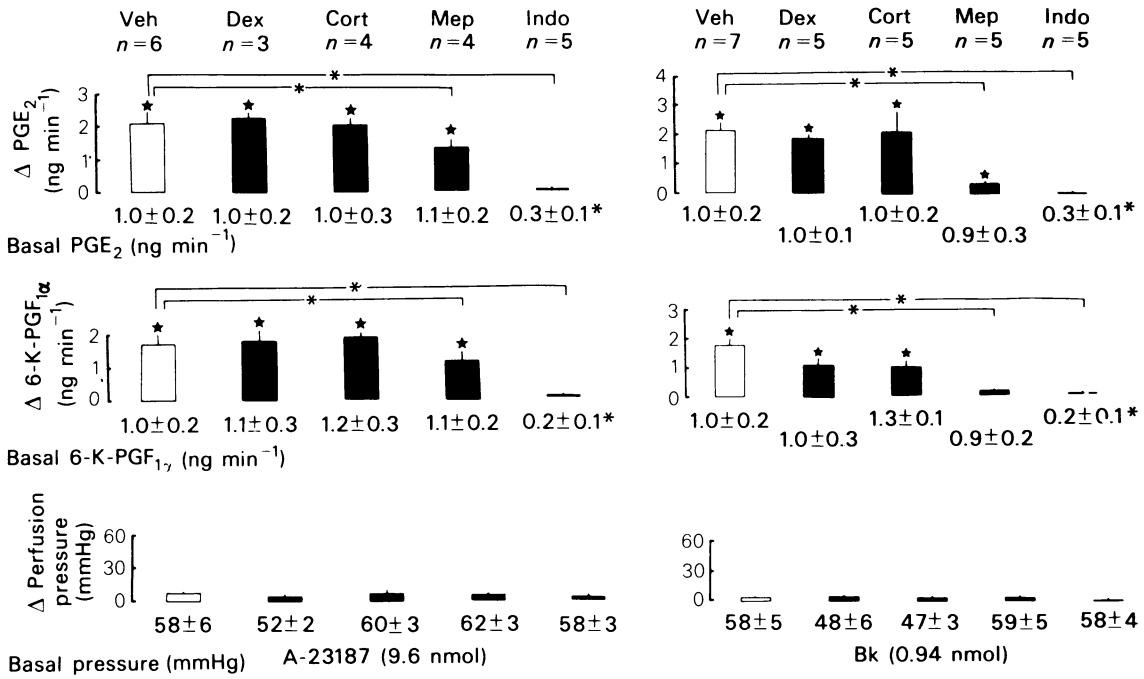

Figure 4 Effect of bradykinin (Bk) and A-23187 on renal output of prostaglandin E_2 (PGE_2, upper panel) and 6-keto-$PGF_{1\alpha}$ (6-K-$PGF_{1\alpha}$, middle panel) and on the perfusion pressure (bottom panel) in the rat kidney perfused in the presence of inhibitors. All other details as for Figure 2 (see legend).

The rise in perfusion pressure elicited by NA and AII, but not that caused by AVP or AA, was also reduced by dexamethasone (28±2% and 29±2%, respectively) and by corticosterone (29±3% and 29±1%, respectively). Similar results were obtained in kidneys perfused with dexamethasone or corticosterone-containing Tyrode solution for up to 4 h. The basal output of prostaglandins and the perfusion pressure were not affected by the glucocorticoids. The effect of lower doses of AVP (0.027 nmol) on prostaglandin output was also unaffected by administration of dexamethasone or corticosterone, as shown in Figure 3 for the higher dose of this peptide. Lower concentrations of dexamethasone or corticosterone (1×10^{-5} M or less) failed to alter the effect of vasoactive hormones on prostaglandin release or perfusion pressure.

In the presence of mepacrine, a phospholipase A_2 inhibitor, the effects of NA, AII, AVP, Bk and A-23187 but not that of AA in enhancing release of PGE_2 and 6-keto-$PGF_{1\alpha}$ were significantly reduced. The rise in perfusion pressure elicited by NA and AII, but not that produced by AVP or AA, was attenuated by mepacrine. The basal output of prostaglandins and the perfusion pressure were not altered in the presence of mepacrine.

In kidneys perfused with indomethacin, a cyclooxygenase inhibitor, the increased prostaglandin output elicited by the vasoactive hormones, A-23187 or AA was abolished; the basal output of prostaglandins was also reduced. The rise in perfusion pressure caused by NA, AII and AA was reduced in the presence of indomethacin.

Effect of dexamethasone on the actions of NA and AII on prostaglandin output and on renal perfusion pressure in the presence of indomethacin (Figure 6)

In kidneys perfused with Tyrode solution containing indomethacin 2.8×10^{-6} M, administration of NA 1.6 nmol and AII 0.097 nmol did not alter the output of prostaglandins but increased renal perfusion pressure. However, the increase in perfusion pressure produced by NA or AII in kidneys perfused with dexamethasone-containing solution was significantly less than in those kidneys perfused with the solution containing its vehicle. The degree of reduction produced by dexamethasone in NA and AII-induced renal vasoconstriction in the presence of indomethacin (31±2% and 30±2%, respectively) was similar to that obtained in the absence of the cyclooxygenase inhibitor ($P>0.05$) (see Figure 3).

Discussion

The present study, which was undertaken to determine the relationship between the effects of glucocorticoids on renal vascular response and prostaglandin synthesis elicited by vasoactive hormones in the isolated kidney of the rat, indicates that (a) glucocorticoids exert a differential effect on renal vascular response to vasoactive hormones and (b) their effect on renal vascular response to vasoconstrictor stimuli appears to be unrelated to prostaglandin synthesis.

In the rat isolated kidney perfused with Tyrode solution, administration of NA and AII produced a dose-related vasoconstriction and enhanced the output of PGE_2 and 6-keto-$PGF_{1\alpha}$. Addition to the perfusion medium of dexamethasone or corticosterone attenuated the effect of NA and AII in enhancing prostaglandin synthesis. However, the vascular response to NA, which is known to be augmented by the glucocorticoids in various tissues (Mendlowitz *et al.*, 1958; Kalsner, 1969; Schömig *et*

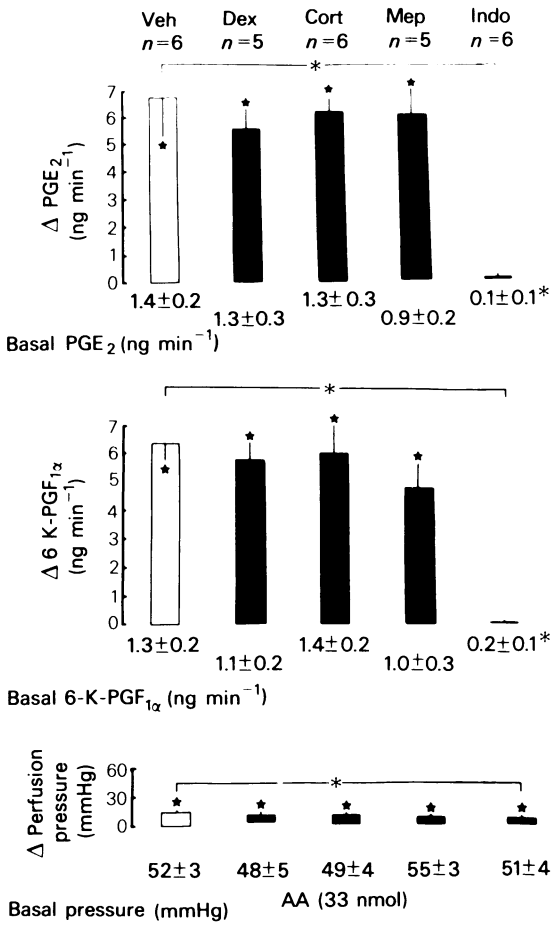

Figure 5 Effect of arachidonic acid (AA) 33 nmol on the output of prostaglandin E_2 (PGE_2, upper panel) and 6-keto-$PGF_{1\alpha}$ (6-K-$PGF_{1\alpha}$, middle panel) and on the perfusion pressure (bottom panel) in the rat kidney perfused with Tyrode solution containing various inhibitors. All other details as for Figure 2 (see legend).

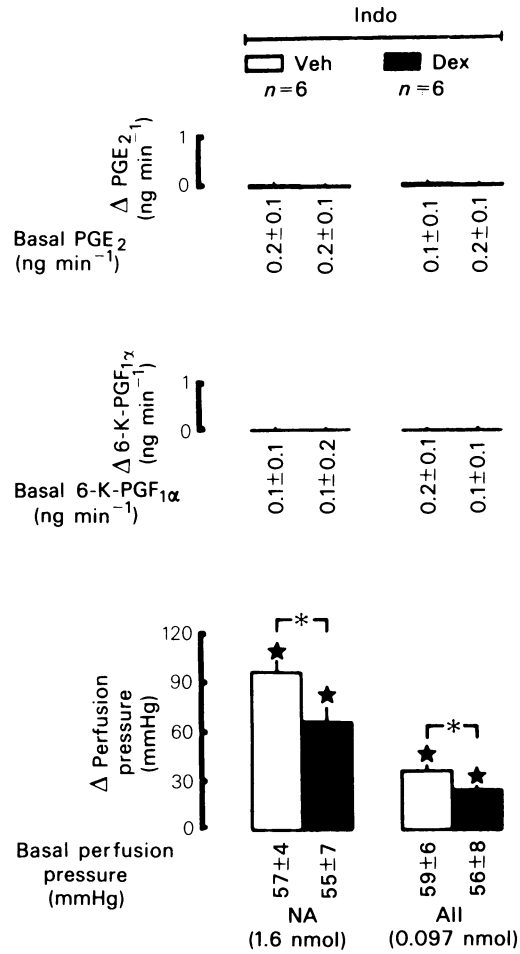

Figure 6 Effect of dexamethasone (Dex 2.6×10^{-5} M) or its vehicle (Veh) on the output of prostaglandin E_2 (PGE_2, upper panel) and 6-keto-$PGF_{1\alpha}$ (6-K-$PGF_{1\alpha}$, middle panel) and on the perfusion pressure (bottom panel) elicited by noradrenaline (NA) and angiotensin II (AII) in the rat kidney in the presence of indomethacin (Indo) 2.8×10^{-6} M. Bars show s.e.mean, ★ denotes values significantly different from basal value and * represents values significantly different from that observed during vehicle infusion ($P < 0.05$).

al., 1976), was reduced in the rat kidney. The inhibition of renal vascular reactivity to NA by glucocorticoids was not specific because they also attenuated the vasoconstrictor response elicited by AII.

Since (a) the renal vasoconstriction and renal output of prostaglandins caused by NA and AII in the present study were also reduced by mepacrine, and (b) the administration of exogenous PGE_2 in Tyrode-perfused rat kidney enhanced the vasoconstrictor response to NA and AII (Malik & McGiff, 1975; Armstrong & Lattimer, 1976), it might appear that the inhibitory effect of dexamethasone and corticosterone on NA and AII-induced renal vasoconstriction is related to inhibition of prostaglandin synthesis. However, this seems unlikely for the following reasons. First, the prostaglandin synthesis elicited by AVP, Bk or A-23187 was not affected by dexamethasone or corticosterone but was inhibited by mepacrine. Second and perhaps most tellingly, dexamethasone reduced the renal vasoconstrictor effect of NA and AII in kidneys in which prostaglandin synthesis elicited by these agents was already abolished by indomethacin, and the magnitude of reduction was similar to that obtained in the absence of the cyclo-oxygenase inhibitor (Figures 2 and 6). Therefore, it appears that the effect of glucocorticoids in attenuating NA and AII-induced renal vasoconstriction is due to a direct action on the vascular smoooth muscle interfering with the interaction of NA and AII with the receptor sites and/or the postreceptor events that in turn reduce the effect of these hormones on prostaglandin synthesis.

Attenuation by glucocorticoids of prostaglandin output elicited by NA or AII was not due to decreased cyclo-oxygenase activity, because both dexamethasone and corticosterone failed to alter the effect of arachidonic acid in increasing the output of PGE_2 and 6-keto-$PGF_{1\alpha}$ and producing renal vasoconstriction. Whether inhibition by glucocorticoids of prostaglandin synthesis elicited by NA and AII but not by AVP, Bk or A-23187 reflects a difference in phospholipase species activated by these agents in the rat kidney is not known. Blackwell *et al.* (1978) and Robinson & Hoult (1980) have reported that glucocorticoids also failed to alter the effect of Bk but not that of other agents such as histamine or antigen challenge in enhancing prostaglandin synthesis in the guinea-pig perfused lung, and they attributed this differential effect of glucocorticoids to two distinct 'types' or 'pools' of phospholipase. However, Zusman & Keiser (1980) have shown that in renomedullary interstitial cells, dexamethasone inhibited prostaglandin synthesis elicited by Bk as well as AII and AVP. Moreover, recently Schleimer *et al.* (1983) have reported that dexamethasone inhibited the release of prostaglandins from human lung fragments but not in purified human lung mast cells. These observations together with our findings suggest that the effect of glucocorticoids on prostaglandin synthesis may also vary in different cell types and tissues. Whether these differences are related to their ability to stimulate the synthesis of phospholipase A_2 inhibitor (Flower & Blackwell, 1979; Hirata *et al.*, 1980; Cloix *et al.*, 1983) or to differences in sensitivity of various hypothetical phospholipase A_2 'pools' (Blackwell *et al.*, 1978; Robinson & Hoult, 1980; Schwartzman *et al.*, 1981) and/or alterations in the interaction of agonists with their receptor sites during treatment with glucocorticoids remains to be determined.

In conclusion, the glucocorticoids dexamethasone and corticosterone exert a differential effect on the renal vascular reactivity to vasoactive hormones in the rat kidney *in vitro*. The inhibitory effect of acute administration of glucocorticoids on renal vasoconstriction elicited by NA and AII appears to be unrelated to prostaglandin synthesis and is probably due to their direct influence on adrenergic and AII receptor interaction and/or associated events. However, the possibility that a reduction in AA products formed through lipoxygenase or mono-oxygenase pathway that could contribute to the inhibitory effect of glucocorticoids on NA and AII-induced renal vasoconstriction remains to be explored. Moreover, in view of the demonstration that PGE_2 can exert an opposite effect *in vitro* and *in vivo* on the rat renal (Malik & McGiff, 1975; Haylor & Towers, 1982; Jackson *et al.*, 1982; Sakr & Dunham, 1982; Inokuchi & Malik, 1982) and mesenteric vasculature (Malik *et al.*, 1976; Jackson & Campbell, 1980), the relationship between the actions of glucocorticoids and prostaglandin synthesis *in vivo* in this species need to be examined.

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