Differential effects of extracellular anions on renin secretion from isolated perfused rat kidneys

HOLGER SCHOLZ, KARL-HEINZ GÖTZ, MARLIES HAMANN, AND ARMIN KURTZ
Institut für Physiologie I, Universität Regensburg, 93040 Regensburg, Germany

Scholz, Holger, Karl-Heinz Götz, Marlies Hamann, and Armin Kurtz. Differential effects of extracellular anions on renin secretion from isolated perfused rat kidneys. *Am. J. Physiol.* 267 (*Renal Fluid Electrolyte Physiol.* 36): F1076–F1081, 1994.—We investigated the relevance of anions for the regulation of renin secretion from the kidneys. For this purpose we measured renin release from isolated rat kidneys that were perfused with medium containing either 120 mmol/l (normal) chloride or 95 mmol/l of isethionate, acetate, or nitrate anions in exchange for equimolar amounts of chloride. Lowering the extracellular chloride concentration by either of these maneuvers significantly enhanced renin secretion rates (RSR) at a perfusion pressure of 100 mmHg. Increasing pressure above 100 mmHg inhibited renin release in the presence of isethionate and acetate but not with nitrate anions. The renin stimulatory effects of isethionate and acetate but not that of nitrate anions disappeared in the presence of bumetanide (100 μmol/l), an inhibitor of macula densa chloride transport. Activation of renin secretion by isethionate and acetate was blunted with 100 pmol/l angiotensin II (ANG II), whereas tenfold higher concentrations of ANG II were required to attenuate the effect of nitrate ions. The amount of renin released in the presence of nitrate was fully additive to RSR values obtained with maximally effective doses of isoproterenol. These findings are consistent with the idea that impermeant anions such as isethionate and acetate enhance renin secretion from the kidneys predominantly via the tubular macula densa mechanism. The stimulatory influence of membrane-permeable nitrate anions appears to involve additional pathways and is mediated by a decreased calcium sensitivity of the renin secretory process rather than resulting from an adenosine 3′,5′-cyclic monophosphate-dependent action.

isolated perfused kidney; juxtaglomerular cells; renal artery pressure; intrarenal baroreceptor; macula densa

WITHIN THE KIDNEYS renin is synthesized, stored, and exocytotically released from the juxtaglomerular (JG) cells in the wall of the afferent arterioles (6, 8). Renin secretion in vivo is under the inhibitory influence of the renal artery pressure and the chloride concentration in the tubular fluid, acting through a putative vascular "baroreceptor" and via the macula densa mechanism, respectively (6, 8). In vitro findings indicate a direct role for chloride ions in the cellular regulation of renin release. Thus lowering extracellular chloride concentrations inhibited renin secretion from isolated rat glomeruli (7, 23) and renal cortical slices (7, 14). Consistent with those findings, a patch-clamp study demonstrated calcium-activated chloride channels in the plasma membrane of renal JG cells, suggesting a relevance of transmembrane chloride fluxes for the intracellular control of renin release (9, 10).

Although a role of anions has been well documented for the regulation of renin release at the cellular level (compare Refs. 6 and 8), their relevance for the more integrative organ control of renin secretion is less clear. In particular, is it unknown whether extracellular anions modulate renin release from intact kidneys also via macula densa-independent pathways, as would be expected from the findings from experiments with renal cortical slices and isolated glomeruli preparations (7, 14, 23). As a first experimental approach to this issue, we measured renin release from isolated rat kidneys that were perfused under normal conditions and during inhibited macula densa chloride transport. Since the demand of the renin secretory process appears not specific for chloride but rather depends on permeant extracellular anions (23), we therefore used a perfusate containing various membrane-permeable and impermeant anions in exchange for equimolar amounts of chloride.

Our findings show that renin secretion from the kidneys is differentially modulated with extracellular anions possibly resulting from differences in membrane permeability characteristics. Whereas impermeant anions such as isethionate and acetate activate renin release mainly via the tubular macula densa mechanism, an additional pathway consisting of a decrease in calcium sensitivity of renal JG cells is suggested for the stimulatory effect of membrane-permeable anions.

MATERIALS AND METHODS

Male (250–350 g body wt) Sprague-Dawley rats (Charles River, Sulzfeld, Germany) with free access to normal sodium diet and tap water were used throughout. Kidney perfusion was performed in a recycling system according to the technique of Schurek and Alt (21) with minor modifications as described in detail previously (18, 20). In brief, animals were anesthetized with 150 mg/kg of 5-ethyl-5-(1-methylpropyl)-2-thiobarbituric acid (Inactin; Byk Gulden, Constance, Germany). Volume loss during the preparation was substituted by intermittent injections of 0.9% saline (~2.5 ml total) via a catheter that was inserted into the jugular vein. After the abdominal cavity had been opened by a midline incision, the right kidney was exposed and placed in a thermoregulated metal chamber. The ureter was cannulated with a small polypropylene tube (PP-10) which was connected to a larger polyethylene catheter (PE-50). After intravenous heparin injection (2 U/g; Braun, Melsungen, Germany) the aorta was clamped distal to the right renal artery, and the large vessels branching off the abdominal aorta were ligated. A double-barreled cannula was inserted into the abdominal aorta and placed close to the origin of the right renal artery. After ligation of the aorta proximal to the right renal artery, the aortic clamp was quickly removed, and perfusion was started in situ with an initial flow rate of 8 ml/min. The kidney was excised, and perfusion at constant pressure (100 mmHg) was established. For this purpose, the renal artery pressure was monitored by a strain-gauge transducer (model P23Db; Statham, San Juan, Puerto Rico), and the pressure signal was

used for feedback control of a peristaltic pump. The perfusion circuit was closed by draining the renal venous effluent, via a metal cannula, back into a reservoir (200–220 ml). The basic perfusion medium, which was taken from the thermostated (37°C) reservoir, consisted of a modified Krebs-Henseleit solution containing (in mmol/l) 140 Na^+, 5.0 K^+, 1.25 Ca^{2+}, 2.0 Mg^{2+}, 120 Cl^-, 27.5 HCO_3^-, and 0.7 HPO_4^{2-}. The perfusate was enriched with all physiological amino acids in concentrations between 0.2 and 2.0 mmol/l and contained additionally (in mmol/l) 8.7 glucose, 0.3 pyruvate, 2.0 L-lactate, 1.0 α-ketoglutarate, 1.0 L-malate, 0.15 creatinine, and 6.0 urea, as well as 6 g/100 ml bovine serum albumin, 1 mU/100 ml vasopressin 8-lysine, and freshly washed human red blood cells (10 ± 2% hematocrit). Ampicillin (3 mg/100 ml) and flucloxacillin (3 mg/100 ml) were added to inhibit bacterial growth. To improve the functional preservation of preparations, the perfusate was continuously dialyzed against a 25-fold volume of similar composition but lacking erythrocytes and albumin. For oxygenation of the perfusate, the dialysate was equilibrated with a prewarmed and moistened 96% O_2-4% CO_2 gas mixture. Perfusate flow rates were obtained from the revolutions of the peristaltic pump, which was calibrated before each experiment. Renal perfusion rate and pressure were continuously monitored on a potentiometric recorder (model REC 102; Pharmacia LKB, Bromma, Sweden). Stock solutions of the drugs to be tested were dissolved in freshly prepared dialysate and infused into the arterial limb of the perfusion circuit directly before the kidneys at exactly 1% of the rate of perfusate flow (perfusion apparatus adapted from Fresenius, Oberursel, Germany). For determination of renin activity, aliquots (~0.2 ml) were taken at 2-min intervals from the arterial limb of the circulation and the renal venous effluent, respectively. Samples were centrifuged (4°C) at 1,500 *g* for 15 min in a bench-top centrifuge (model 5413; Eppendorf, Hamburg, Germany), and the supernatants were immediately assayed for renin activity.

Substitution of chloride ions. Replacement of chloride ions in the perfusate was performed by removing the standard dialysate (120 mmol/l chloride) followed by rapid exchange for a similar volume containing 95 mmol/l of either isethionate, acetate, or nitrate anions instead of equimolar amounts of chloride. Extracellular chloride concentrations were decreased by this maneuver from normally 119.8 ± 1.4 to 25.8 ± 1.2 mmol/l.

Measurement of extracellular chloride. Chloride concentrations were measured electrochemically in 0.5-ml aliquots of perfusate using a silver electrode (Chlor-o-Counter; Marius, Utrecht, Netherlands).

Determination of renin activity. Perfusate samples were incubated for 90 min at 37°C with plasma from bilaterally nephrectomized male rats as renin substrate (11). Generated angiotensin I (ANG I) was determined by radioimmunoassay (Sorin Biomedica, Düsseldorf, Germany).

Renin release. Since renin is not inactivated during its passage through isolated perfused rat kidneys (18), renin secretion rates (RSR) could therefore be calculated from the arteriovenous differences of perfusate renin activity and the corresponding renal flow rates.

Agents. Pyruvate was obtained from Boehringer, Mannheim, Germany. Flucloxacillin was from Beecham, Bern, Switzerland. Glutamate, urea, sodium acetate, sodium nitrate, sucrose, and α-ketoglutarate were obtained from Merck, Darmstadt, Germany. L-Malic acid and L-lactate as sodium salts were obtained from Serva, Heidelberg, Germany. L-Amino acids were from Braun (aminoplasmal 5%; pediatric, free of carbon hydrate). Ampicillin, vasopressin 8-lysine, angiotensin II (ANG II), isoproterenol, bumetanide, and bovine serum albumin (fraction V powder) were purchased from Sigma Chemical, Deisenhofen, Germany. Sodium isethionate was from ICN Biochemicals, Cleveland, OH.

Statistics. Experiments were normally performed in such a way that a single kidney preparation first served as control and was then used for the experimental protocol. If not otherwise indicated, a total number of five different kidney preparations was taken for each group. Statistical significance was calculated by use of one-way analysis of variance followed by a Scheffé test. $P < 0.05$ was considered significant. Data are means ± SE.

RESULTS

Isolated rat kidneys were perfused in vitro for 90 min normally. During this time interval perfusate flow remained stable at 15 ± 1 (SE) $ml \cdot min^{-1} \cdot g^{-1}$ ($n = 20$), and corresponding RSR value was 4.5 ± 1.0 ng ANG $I \cdot h^{-1} \cdot min^{-1} \cdot g^{-1}$ ($n = 20$) at a renal artery pressure of 100 mmHg. Functional stability of the preparations is also indicated by our previous findings that the tubular sodium reabsorption in isolated rat kidneys perfused with a medium containing red blood cells was well preserved within 90 min of perfusion (19).

In a first set of experiments we examined the effects of different anions in the perfusate on renal perfusion rates and RSR. For this purpose, 95 mmol/l of extracellular chloride was replaced by equimolar amounts of either membrane-impermeable isethionate and acetate (2, 23) or highly permeant nitrate anions (12, 15, 23). Chloride concentrations in the perfusate were reduced by this maneuver from normally 119.8 ± 1.4 to 25.8 ± 1.2 mmol/l ($n = 20$).

As shown in Fig. 1, substitution of chloride for isethionate and acetate had a biphasic influence on flow rates consisting of a rapid and transient decrease followed by a more prolonged phase of vascular relaxation. Parallel with the recovery of renal flow, RSR increased maximally to 32 ± 5 ($n = 5$) and 25 ± 4 ng ANG $I \cdot h^{-1} \cdot min^{-1} \cdot g^{-1}$ ($n = 5$) in the presence of isethionate and acetate, respectively (Fig. 1). Similar effects on perfusate flow and RSR were obtained when equimolar amounts of sodium chloride were isosmotically substituted with sucrose (Fig. 1). Exchange of chloride for permeable nitrate anions, on the other side, persistently decreased perfusion rates by ~15% and stimulated renin release to 52 ± 8 ng ANG $I \cdot h^{-1} \cdot min^{-1} \cdot g^{-1}$ ($n = 10$; Fig. 1). The effects of low sodium chloride as well as isethionate, acetate, and nitrate on renal flow and RSR were completely reversible after restoring normal (120 mmol/l) chloride concentrations in the perfusate (Fig. 1).

Withdrawal of chloride ions from the perfusion medium is expected to reduce the chloride delivery to the tubular macula densa cells. The resulting decrease of macula densa chloride transport should provide a stimulatory signal for renin release (13, 22). To distinguish between macula densa-related and -independent effects of chloride substitution, we used bumetanide, which is a potent inhibitor of the luminal macula densa Na^+-K^+-$2Cl^-$ cotransport system (17). Bumetanide (100 μmol/l) alone increased urine flow from 53 ± 7 to 321 ± 29 $\mu l \, min^{-1} \cdot g^{-1}$ and also enhanced basal RSR to 28 ± 5 ng

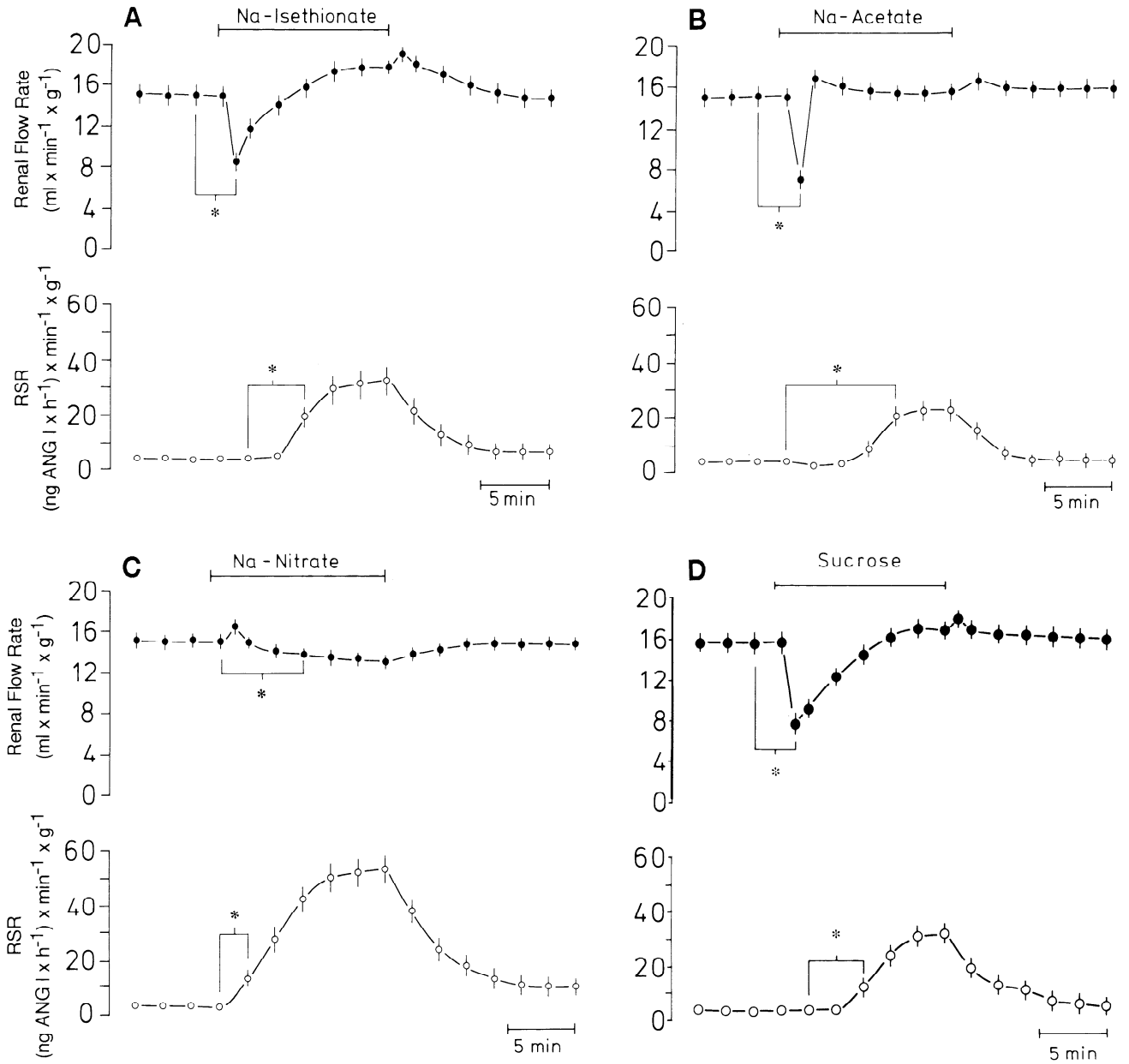

Fig. 1. Renin secretion rates (RSR; ○) and renal flow rates (●) in isolated kidneys that were perfused with medium containing either 120 mmol/l chloride or 95 mmol/l of isethionate (*A*), acetate (*B*), or nitrate anions (*C*) in exchange for equimolar amounts of chloride. In addition, effect of low (25 mmol/l) sodium chloride during isosmotic substitution with sucrose was also examined (*D*). Renal artery pressure was adjusted to 100 mmHg. Values are means ± SE; n = 5 kidney preparations for isethionate, acetate, and low sodium chloride; n = 10 for nitrate experiments. *Significant differences vs. controls ($P < 0.05$).

ANG $I \cdot h^{-1} \cdot min^{-1} \cdot g^{-1}$ (n = 5; Fig. 2). In the presence of bumetanide, isethionate and acetate ions did not further activate renin release (Fig. 2). Bumetanide, however, did not prevent the stimulatory effect of nitrate ions on renin secretion. Instead, RSR in this situation was increased to the maximum value of 57 ± 8 ng ANG $I \cdot h^{-1} \cdot min^{-1} \cdot g^{-1}$ (n = 5) with nitrate (Fig. 2).

In a second series of experiments we aimed to obtain information about possible mechanisms underlying the stimulatory influence of nitrate anions. To examine whether this action was related to intracellular formation of adenosine 3′,5′-cyclic monophosphate (cAMP), which is a stimulatory second messenger for renin secretion (1, 6, 8), we tested the effect of nitrate in the presence of isoproterenol. In a dose-response relationship renin release was enhanced maximally to 460 ± 60 ng ANG $I \cdot h^{-1} \cdot min^{-1} \cdot g^{-1}$ with 1 μmol/l isoproterenol. As shown in Fig. 3, nitrate anions in combination with 1 μmol/l isoproterenol further increased RSR to 870 ± 70 ng ANG $I \cdot h^{-1} \cdot min^{-1} \cdot g^{-1}$ (n = 5).

Next, we examined whether the stimulatory action of nitrate was subject to the typical pressure control of renin release. For this purpose, perfusion pressure was adjusted stepwise from 100 mmHg to 160, 140, 80, and 40 mmHg, respectively. During control conditions (120 mmol/l chloride) renin release was negatively linked to

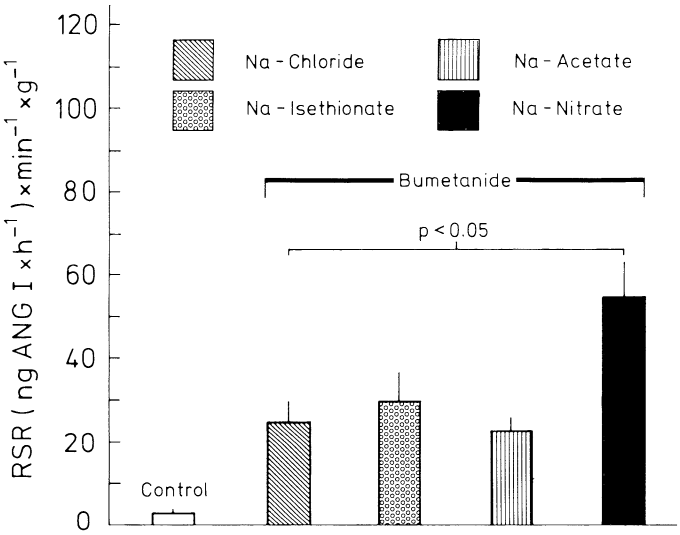

Fig. 2. Effect of bumetanide (100 μmol/l), an inhibitor of macula densa Na^+-K^+-$2Cl^-$ cotransport, on RSR with a perfusate containing either 120 mmol/l chloride or 95 mmol/l of various anions for equimolar amounts of chloride. Values are means ± SE; n = 5 experiments for each protocol. $P < 0.05$ was considered significant.

the renal artery pressure in the range between 40 and 100 mmHg, yielding 53 ± 7 ng ANG $I \cdot h^{-1} \cdot min^{-1} \cdot g^{-1}$ (n = 5) at 40 mmHg (Fig. 4). Increasing pressure above 100 mmHg inhibited RSR to 4.5 ± 1.0 ng ANG $I \cdot h^{-1} \cdot min^{-1} \cdot g^{-1}$ (n = 5; Fig. 4). Substitution of chloride for nitrate anions blunted the characteristic correlation of perfusion pressure and renin release. Thus RSR was not significantly different at 160 and 40 mmHg (45 ± 10 vs. 55 ± 11 ng ANG $I \cdot h^{-1} \cdot min^{-1} \cdot g^{-1}$) with a perfusate containing nitrate ions (Fig. 4). For comparison, replacement of chloride by 95 mmol/l of either isethionate or acetate anions did not principally change the inverse relationship between perfusion pressure and RSR. Adjusting pressure at 160 mmHg reduced renin release to 6.0 ± 1.5 ng ANG $I \cdot h^{-1} \cdot min^{-1} \cdot g^{-1}$ (n = 5) with isethionate and acetate (Fig. 4). Similarly, increasing pressure to 140 and 160 mmHg in the presence of bumetanide (100 μmol/l) inhibited RSR to 14 ± 4 and 11 ± 3 ng ANG $I \cdot h^{-1} \cdot min^{-1} \cdot g^{-1}$, respectively (Fig. 4).

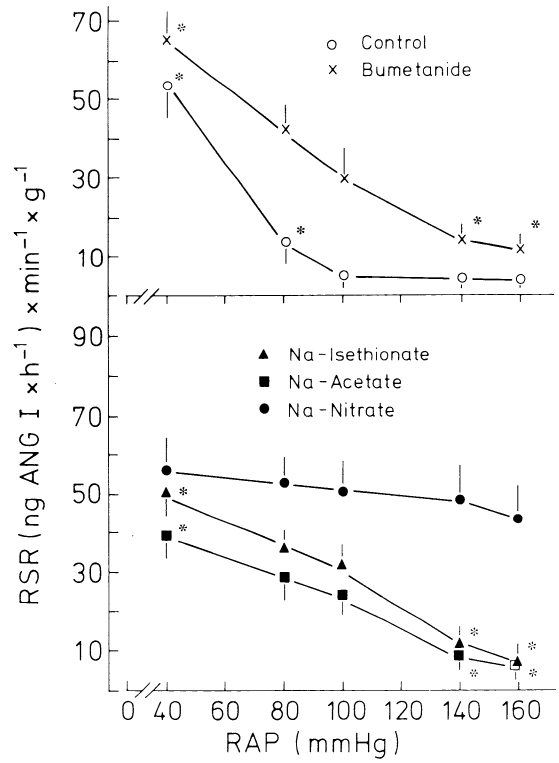

Fig. 4. Pressure-dependent RSR in isolated perfused rat kidneys. Extracellular perfusate contained either 120 mmol/l chloride (with and without 100 μmol/l bumetanide) or 95 mmol/l of various anions for equimolar amounts of chloride. Values are means ± SE; n = 10 kidney preparations for nitrate, and n = 5 for all other conditions. *Significant differences vs. respective RSR at 100 mmHg ($P < 0.05$).

Finally, we examined whether stimulation of renin secretion with nitrate anions may have resulted from a decreased sensitivity of renin release toward inhibitory calcium ions (compare Refs. 6 and 8). As a tool we used ANG II, which has been found to mobilize calcium ions in renal JG cells (10) and which inhibits renin release through a calcium-dependent process (24). In the presence of either bumetanide (100 μmol/l), isethionate, or acetate ions, 100 pmol/l of ANG II reduced RSR approximately to the basal value of 4.5 ng ANG $I \cdot h^{-1} \cdot min^{-1} \cdot g^{-1}$

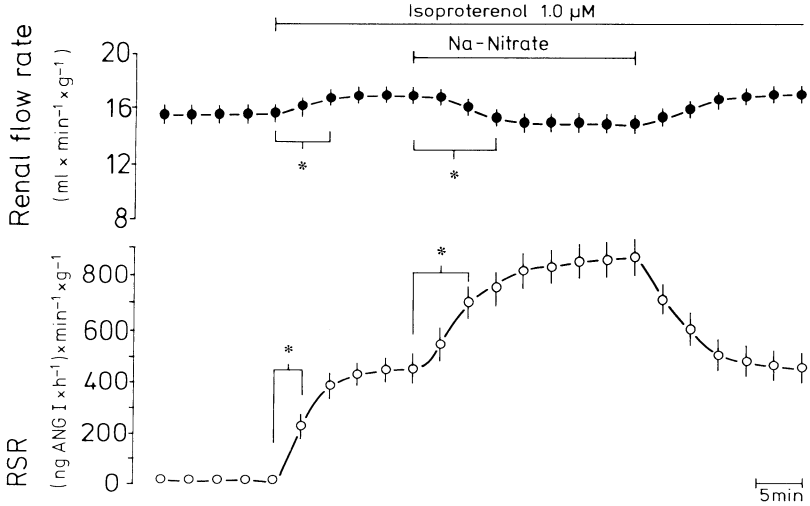

Fig. 3. Influence of nitrate anions (95 mmol/l) in presence of maximally effective doses of isoproterenol (1 μmol/l) on renal flow (●) and RSR (○). Values are means ± SE; n = 5 kidneys preparations. *Significance vs. respective controls ($P < 0.05$).

(n = 5 each; Fig. 5). However, a tenfold higher concentration of ANG II was required to decrease RSR to 12 ± 2 ng ANG I·h^{-1}·min^{-1}·g^{-1} (n = 5) with a perfusate containing nitrate anions (Fig. 5).

DISCUSSION

To investigate the relevance of anions for the intrarenal control of renin secretion, we used a model of isolated perfused rat kidneys, which permits one to modulate the anion composition of extracellular fluid under controlled in vitro conditions (18, 19). Renin release from this preparation is regulated in a way that is very similar to the kidney in vivo. In particular, the tubular macula densa and the vascular baroreceptor control of renin secretion are operating in isolated rat kidneys perfused with a medium containing red blood cells (19, 20, 25).

To obtain first information about the effects of different anions on basal renin release, substantial amounts of chloride in the perfusate were replaced by equimolar quantities of isethionate, acetate, and nitrate analogues, respectively. Lowering the extracellular chloride concentration by either of these maneuvers enhanced RSR values at a pressure of 100 mmHg (Fig. 1). The stimulatory action of nitrate anions is in good agreement with results obtained with intact kidneys (16) and isolated rat glomeruli (23), but isethionate has previously been reported to inhibit renin secretion in isolated glomeruli (23). Moreover, lowering the extracellular chloride concentration decreased renin release also from rat kidney cortical slices (7, 14).

In view of this seeming discrepancy to our results, it should be recalled that withdrawal of chloride ions from the perfusate will reduce the chloride concentration likewise in the tubular fluid passing the macula densa cells. Since renin release from JG cells is negatively linked to the rate of macula densa chloride reabsorption (13, 22), lowering the extracellular chloride concentration would therefore provide a stimulatory signal for renin secretion from isolated kidneys. Indeed, our findings with bumetanide, which is a potent inhibitor of the macula densa Na^+-K^+-$2Cl^-$ cotransport system (17), support a role of the macula densa for the stimulatory effect of isethionate and acetate anions (Fig. 2). Replacing chloride by nitrate ions, however, further enhanced RSR in the presence of bumetanide, suggesting a macula densa-independent mechanism to mediate more than 50% of the renin stimulatory action of nitrate (Fig. 2).

Considering that renal JG cells are equipped with a predominant calcium-activated chloride conductance (9, 10), one can speculate therefore whether differences in membrane permeability characteristics between extracellular anions passing through these channels may have accounted for the differential effects on renin secretion. This possibility is indirectly supported by the results obtained with isolated rat glomeruli, where membrane-permeable anions such as nitrate stimulated renin release, whereas impermeant analogues did not (23). However, we also cannot exclude other possible reasons in this context, for instance, differences in interaction with plasma membrane proteins or with the cytoskeleton (5). Furthermore, with the use of intact kidneys, it is difficult to distinguish whether the renin stimulatory effect of nitrate was due to a direct influence on renal JG cells or whether it was secondary to interaction with other target cells in the kidney.

A more specific influence on the renin secretory process would be supported by the demonstration that nitrate anions preferentially interfered with certain regulatory pathways for renin release. A second series of experiments was therefore addressed to potential mechanisms underlying the stimulatory action of nitrate. Since a rise of cAMP in renal JG cells is thought to activate renin secretion (compare Refs. 6 and 8), we examined adenylate cyclase as a possible target for nitrate anions. Although basal RSR values were stimulated to a peak value with 1 μmol/l isoproterenol, suggesting maximum activation of adenylate cyclase (1), substitution with nitrate anions additionally enhanced renin release (Fig. 3). In conclusion, a cAMP-dependent

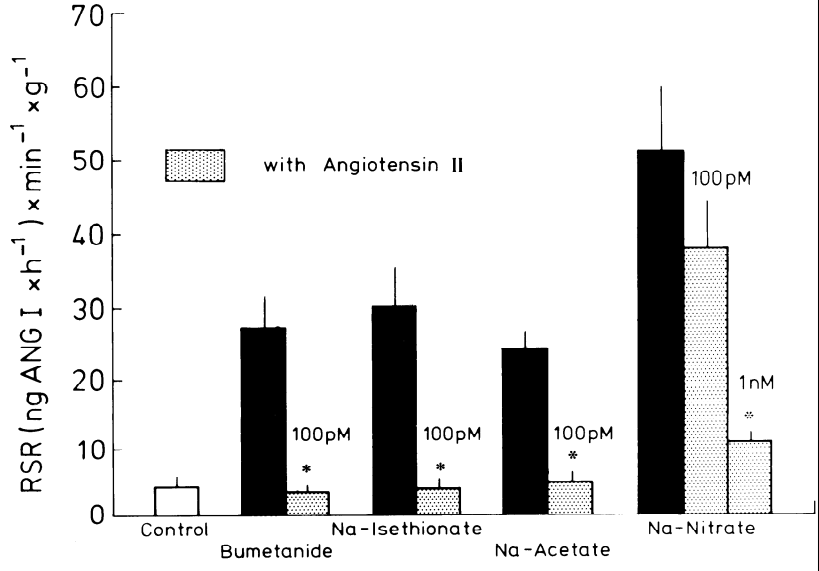

Fig. 5. Effect of ANG II (100 pmol/l, 1 nmol/l) on RSR in isolated kidneys perfused at a pressure of 100 mmHg. Perfusate contained either 120 mmol/l chloride (with and without 100 μmol/l bumetanide) or 95 mmol/l of different nonchloride analogues (see MATERIALS AND METHODS). Values are means ± SE; n = 5 kidney preparations for each protocol. *Significant differences vs. respective controls without ANG II ($P < 0.05$).

mechanism appears less likely for the renin stimulatory action of nitrate.

Substitution of extracellular chloride for nitrate analogues mimicked the rise of RSR in response to lowering the renal artery pressure (Fig. 4). Increasing pressure above 100 mmHg, on the other hand, inhibited RSR in the presence of isethionate and acetate but not with nitrate ions (Fig. 4). Fray suggested intravascular pressure to modulate renin release through enhancing proportionally the rate of transmembrane calcium influx into renal JG cells (3, 4); according to this concept, any manipulation to reduce the calcium sensitivity of JG cells would also affect the pressure control of renin secretion. To test for a similar action of nitrate anions, we used ANG II, which has been shown to mobilize calcium ions in renal JG cells (10) and which inhibits renin release through a calcium-dependent mechanism (24). Notably, tenfold higher concentrations of ANG II were required to reduce RSR in the presence of nitrate compared with isethionate and acetate ions (Fig. 5). One can therefore assume that nitrate anions stimulated renin release from isolated kidneys through decreasing the responsiveness toward inhibitory calcium ions.

Together, our results suggest that renin secretion from isolated perfused rat kidneys is differentially regulated with extracellular anions possibly depending on differences in membrane permeability. In particular, the renin stimulatory action of permeant nitrate ions appears to result from a reduced calcium sensitivity of the renin secretory process rather than being maintained through a cAMP-dependent mechanism. Moreover, our findings are consistent with the concept that the intrarenal perfusion pressure inhibits renin release via a calcium-regulated anion pathway.

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Address for reprint requests: H. Scholz, Institut für Physiologie I, Universität Regensburg, Postfach 101042, 93040 Regensburg, Germany.

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