Angiotensin II production and distribution in the kidney – II. Model-based analysis of experimental data

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Information on the regional concentrations of angiotensin (Ang) II and its type-1 and -2 receptors (AT_1R, AT_2R) in the kidney is still incomplete. Published data on the levels of arterially delivered Ang I and II (Ang Ia, Ang IIa) and intrarenally produced Ang I and II (Ang Ii, Ang IIi) in the renal vein and in whole tissue were analyzed by using a kinetic model of Ang production and distribution in the glomerular and peritubular cortical tissue regions (Glom, Pt). (1) 90% of Ang II is cell-associated, due to its binding to AT_1R and AT_2R; (2) most Ang II in the renal cortex is Ang IIi; (3) Ang IIa is mainly localized in Glom; (4) Ang Ii rather than Ang Ia is a substrate of renal angiotensin-converting enzyme; (5) Ang IIi is localized in Pt and its concentration in interstitial fluid is 5–15 times the Ang II concentration in arterial plasma; and (6) in Glom the interstitial concentration of cell surface-bound AT_1R is above $200K_d$, and in Pt the AT_1R and AT_2R concentrations are above $10K_d$. In conclusion, *endocrine* Ang II mainly acts in Glom, whereas Pt is exposed to *paracrine* Ang II generated by the conversion of intrarenally produced Ang I. High AT_1R concentrations in Glom and Pt favor diffusion-limited binding, so that the apparent binding rate constant at sites closest to the source of Ang II delivery is greatly increased. Results may explain why the kidney is responsive to low levels of *endocrine* Ang II, despite its high content of *paracrine* Ang II.

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Part I of this analysis presents a quantitative model describing the kinetics of the production, distribution, and disposal of Ang II in the kidney.[1] By using this model it is possible to calculate, from Ang I and II measurements in blood and in whole tissue, the Ang I and II concentrations in various tissue compartments as well as the local AT_1 and AT_2 receptor densities. Quantitative information on the concentrations of Ang I and II and on the concentrations of arterially delivered and intrarenally produced Ang I and II in renal venous plasma and in whole tissue is now available, and can be introduced into the model and analyzed. Here, we describe the results of this analysis and its implications.

EXPERIMENTAL DATA

A summary of experimental data introduced into the kinetic model is presented in Tables 1 and 2. The concentrations of arterially delivered Ang I and II (CIa, CIIa) and intrarenally produced Ang I and II (CIi, CIIi) were derived from measurements of intact ^{125}I-Ang I and II and their unlabeled counterparts in blood plasma and in whole renal cortical tissue from pigs receiving systemic infusions of ^{125}I-Ang I.[2] The infusions were administered to animals treated with an angiotensin-converting enzyme (ACE) inhibitor or AT_1 receptor antagonist as well as to untreated controls. Tables 1 and 2 refer to data obtained under steady-state conditions.

The model-based equations for calculating the local Ang I and II concentrations and intrarenal AT_1 and AT_2 receptor densities also contain, as independent variables, a number of physical parameters and kinetic constants. For the values of these variables and for an explanation of the abbreviations and symbols used in the present paper, we refer to part I of the analysis.[1] Results are expressed as mean and s.e.m., and are compared by using two-sided Student's *t*-test for unpaired observations.

MODEL-BASED CALCULATIONS

Distribution of Ang II over various intrarenal compartments

As shown in Figure 1, the calculated concentration of intrarenally produced Ang I in interstitial fluid of the peritubular region (CIi_{IsfPt}) is 10–50 times the plasma concentration of Ang I in the renal artery (CI_{Pa}), depending

Table 1 | Concentrations of arterially delivered Ang I (CIa) and intrarenally produced Ang I (CIi) in the kidney, expressed relative to the concentration in blood plasma

Concentration ratios	Control N=7	Captopril N=5	Eprosartan N=5
Vein/artery (Cla_{Pv}/Cl_{Pa})	0.15±0.05	0.14±0.04	0.07±0.02
Cortex/artery (Cla_T/Cl_{Pa}) (ml/g)	0	0	0
Cortex/vein (Cla_T/Cla_{Pv}) (ml/g)	0	0	0
Vein/artery (Cli_{Pv}/Cl_{Pa})	0.80±0.16	0.78±0.18	1.00±0.28
Cortex/vein (Cli_T/Cli_{Pv}) (ml/g)	18±5	12±4	27±8

Data are mean±s.e.m. and are derived from studies in anesthetized pigs.
Ang I, angiotensin I.

Table 2 | Concentrations of arterially delivered Ang II (CIIa) and intrarenally produced Ang II (CIIi) in the kidney, expressed relative to the concentration in blood plasma

Concentration ratios	Control N=7	Captopril N=5	Eprosartan N=5
Vein/artery ($CIIa_{Pv}/CII_{Pa}$)	0.12±0.02	0.18±0.07	0.09±0.02
Cortex/artery ($CIIa_T/CII_{Pa}$) (ml/g)	4.9±0.6	4.7±0.6	0.38±0.07*
Cortex/vein ($CIIa_T/CIIa_{Pv}$) (ml/g)	47±10	33±6	3.9±0.5*
Vein/artery ($CIIi_{Pv}/CII_{Pa}$)	0.30±0.12	0.23±0.06	0.14±0.03
Cortex/vein ($CIIi_T/CIIi_{Pv}$) (ml/g)	235±41	249±52	132±30*

Data are mean±s.e.m. and are derived from studies in anesthetized pigs.[2]
*$P<0.01$ for differences from control and captopril groups.
Ang II, angiotensin II.

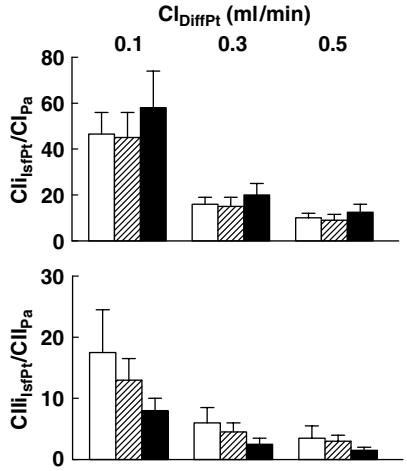

Figure 1 | Bar graphs showing the ratio between the concentration of intrarenally produced Ang I in peritubular interstitial fluid and the plasma concentration of Ang I in the renal artery (Cli_{IsfPt}/Cl_{Pa}), and the ratio between the interstitial fluid concentration of intrarenally produced Ang II and the plasma concentration of Ang II in the renal artery ($CIIi_{Isf}/CIIi_{Pa}$). Calculations were made using data obtained in anesthetized pigs[2] and equations (22)–(24) in Schalekamp and Danser.[1] Cla_{Pv}/Cl_{Pa} in these equations is taken to be equal to 0.15, as measured in control animals (Table 1). Data refer to peritubular transcapillary diffusive Ang I and II clearance rates (Cl_{DiffPt}) of 0.1, 0.3, and 0.5 ml/min per gram of renal cortex.[1] Open bars: control; hatched bars: captopril treatment; closed bars: eprosartan treatment.

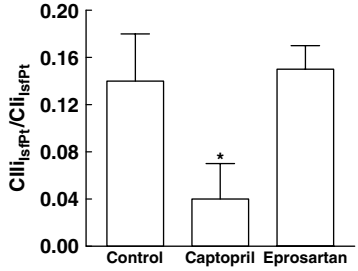

Figure 2 | Effect of ACE inhibition by captopril on the ratio between the calculated concentration, in peritubular interstitial fluid, of intrarenally produced Ang II and the concentration of intrarenally produced Ang I. Calculations were made using data obtained in anesthetized pigs[2] and equations (22)–(24) in Schalekamp and Danser.[1] *$P<0.05$ for differences from control animals and animals treated with the AT_1 receptor antagonist eprosartan.

on the type of treatment of the animals and on the diffusive clearance across the peritubular capillaries (Cl_{DiffPt}), which ranges from 0.1 to 0.5 ml/min per gram of renal cortex.[1] The concentration of intrarenally produced Ang II in peritubular interstitial fluid ($CIIi_{IsfPt}$) is only about 3–15 times the arterial plasma concentration of Ang II (CII_{Pa}).

Very little Ang II in the kidney originates from intrarenal conversion of arterially delivered Ang I.[3–7] On the other hand, the $CIIi_{IsfPt}/CIi_{IsfPt}$ ratio is reduced by 80% after the oral administration of the ACE inhibitor captopril (Figure 2). It appears therefore that the intrarenal Ang II production, at least most of it, depends on conversion of intrarenally produced Ang I by ACE.

Figures 3 and 4 show how arterially delivered (endocrine) Ang II and intrarenally produced (paracrine) Ang II are distributed over the different regions and compartments in the renal cortex. It appears that about 90% of both endocrine and paracrine Ang II is cell-associated.

Regional AT_1 and AT_2 receptor concentrations

The calculated concentrations of cell surface AT_1 and AT_2 receptors in interstitial fluid (CAT_1R_{CsGlom}, CAT_1R_{CsPt}, CAT_2R_{CsPt}) are presented in Figure 5. Results refer to a diffusive clearance rate of Ang II across the peritubular capillaries (Cl_{DiffPt}) ranging from 0.1 to 0.5 ml/min. Figure 5 also shows the concentrations of cell-associated Ang IIa in the glomerular region ($CIIa_{ClGlom}$), expressed as a fraction of the total concentration of Ang IIa in the renal cortex ($CIIa_T$). The model implies that most Ang IIi in the renal cortex is localized in the peritubular compartment. In contrast, at least 70% of Ang IIa appears to be localized in the glomerular compartment. There are no major differences between control and captopril-treated animals.

Results indicate that CAT_1R_{CsGlom} is more than two orders of magnitude higher than the equilibrium dissociation constant, K_d, of the Ang II-AT_1 receptor reaction, and that CAT_1R_{CsPt} and CAT_2R_{CsPt} are at least one order of magnitude higher than K_d.

DISCUSSION

Validity of model-based calculations

Results of these calculations depend on the experimental data presented in Table 1 and 2, as well as on the values of a