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# Moment Analysis of Drug Disposition in Rat Kidney: Role of Basolateral Membrane Transport in Renal Transepithelial Transport of *p*-Aminohippurate

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**Abstract**—The determining step in transepithelial transport of *p*-aminohippurate (PAH) in renal tubular secretion has been elucidated in the rat isolated perfused kidney. The method was based upon a multiple indicator dilution experiment and non-compartmental moment analysis. Single-pass dilution curves were obtained from venous and urinary effluents after simultaneous intra-arterial injections of Evans blue with albumin, [$^3$H]inulin and [$^{14}$C]PAH. Probenecid was used as a transport inhibitor and dissolved in both perfusate and injection solution. The urinary excretion of PAH decreased depending on the probenecid concentration, while that of inulin was not affected. No correlation was observed between the amount of secretion and the mean residence time of secreted PAH in renal epithelial cells ($\bar{T}_{cell}$). Since $\bar{T}_{cell}$ ought to be affected by the rate of secretion from cells to lumen, it was suggested that the secretion rate was independent of the amount secreted. In contrast, the amount of PAH excreted via tubular secretion showed a linear correlation with the volume of distribution in the kidney and the apparent rate constant for tubular uptake of PAH. Since these kinetic parameters reflect the transport from blood into cells across the basolateral membranes of renal epithelial cells, the present results demonstrated that basolateral membrane transport is a determining step in the transcellular transport of PAH and that the major effect of probenecid is the inhibition of transport from blood into cells.

Organic anions are secreted in the renal proximal tubules via a carrier-mediated active transport system (Weiner 1973; Møller & Sheikh 1983; Grantham & Chonko 1986; Hori et al 1986; McKinny 1988). Tubular secretion is a transcellular transport process including transport from the blood into epithelial cells across basolateral membranes, diffusion in the cytosol and transport from cells to lumen across the brush-border membranes. We have performed isolated membrane vesicle studies to clarify the mechanism of membrane transport (Hori et al 1982, 1985; Inui et al 1986). Since this approach used isolated membrane fractions of the kidney, it is suitable to investigate the nature of the transport carrier itself, but does not provide information on the entire organ. To understand all aspects of the biological mechanism, we needed to conduct kinetic analysis of drug movement in the whole kidney and to integrate the findings obtained from membrane vesicles.

Recently, we developed a method to analyse the transcellular transport of drugs using rat isolated perfused kidney and non-compartmental moment analysis (Hori et al 1987, 1988; Kamiya et al 1990; Tanigawara et al 1990). The method is useful for extracting information on the kinetic features of basolateral and brush-border membrane transport in tubular epithelial cells of the entire kidney. In the present paper, we applied this method to clarify the determining step in the transepithelial transport of *p*-aminohippurate (PAH). Probenecid was used as a transport inhibitor and the relationships between reduced excretion and changes in PAH kinetic parameters are discussed.

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## Materials and Methods

### *Materials*

[$^{14}$C]PAH (46·9 mCi mmol$^{-1}$) and [$^3$H]inulin (3·9 mCi mmol$^{-1}$) were obtained from New England Nuclear (Boston, MA, USA) and Amersham Laboratories (Buckinghamshire, UK), respectively. Bovine serum albumin (BSA) was purchased from Organon Teknika (Boxtel, Holland). All other chemicals were of reagent grade.

### *Experimental procedure*

*Rat isolated perfused kidney experiments.* The right kidney of male Wistar rats, 240–290 g, was isolated by the method of Nishiitsutsuji-Uwo et al (1967) and perfused as a single perfusion as reported previously (Hori et al 1987, 1988; Kamiya et al 1990; Tanigawara et al 1990). Briefly, the perfusate consisted of Krebs-Henseleit bicarbonate buffer, gassed with 95% $O_2$–5% $CO_2$ and containing bovine erythrocytes (haematocrit 11–13%), 5% BSA, 5 mM glucose, 1% mannitol, creatinine and amino acids. The perfusate plasma flow rate was maintained constant in the range of the physiological renal plasma flow rate. After this had stabilized for 20 min, labelled indicators were simultaneously injected into the renal artery. The injection solution contained Evans blue (1·7 mg mL$^{-1}$) and albumin (5%), as a vascular reference, [$^3$H]inulin (40 $\mu$Ci mL$^{-1}$, 53 $\mu$g mL$^{-1}$) as a marker of extracellular space and glomerular filtration and [$^{14}$C]PAH (5·7 $\mu$Ci mL$^{-1}$, 0·1 mM) in Krebs-Henseleit bicarbonate buffer. This concentration of PAH had been shown not to cause saturation of tubular secretion in preliminary experiments. After a bolus injection of 0·05 mL of this solution via the arterial catheter, venous effluents and urine samples were collected up to 15 min as described by Hori et al (1988). The perfusate plasma was separated from

the erythrocytes by centrifugation. Immediately after the experiment, the kidney was excised, weighed for wet weight, then homogenized. Evans blue with albumin, [$^3$H]inulin and [$^{14}$C]PAH concentrations in plasma, urine and homogenate were determined. To reduce the tubular secretion of PAH, 0·1, 1, 2, or 3 mM of probenecid was added to the perfusate and the same concentration of probenecid was also added to the injection solution to avoid perturbation of the steady-state equilibrium.

*Plasma protein binding of PAH.* The plasma protein binding of PAH was determined by the ultrafiltration method using the Micropartition System (MPS-1, Amicon, USA). Briefly, [$^{14}$C]labelled and unlabelled PAH was added to the perfusate to adjust the total plasma concentration to 0·001–0·1 mM in the absence and presence of 3 mM probenecid. After incubation for 5 min, 1 mL of plasma sample was centrifuged at 1500 rev min$^{-1}$ for 10 min at room temperature (ca. 22°C). Adsorption of PAH to the ultrafiltration membrane (YMT, Amicon) had been confirmed to be negligible in a preliminary study.

*Assay.* Radioactivity of each sample was measured using a liquid scintillation counter and the recoveries of the indicators from the perfusate, urine and kidney were calculated. Evans blue and albumin was determined spectrophotometrically (610 nm). The concentration of creatinine in plasma and urine was measured by the alkaline picrate method (Folin & Wu 1919), and the glomerular filtration rate (GFR) of the perfused kidney was estimated by creatinine clearance.

### Data analysis

*Organ availability and clearance.* The drug concentration in plasma was used to analyse the mass transport in the kidney because distribution into erythrocytes was negligible ($<1\%$). The organ availability ($F_v$) was calculated as the ratio of recovery from venous plasma to total recovery from venous plasma plus urine plus kidney homogenate. Although a recent paper suggested the tubular reabsorption of PAH occurs at concentrations higher than 2·1 mM (MacDougall & Wiegmann 1988), secretion was predominant at the concentration examined in this study. Furthermore, HPLC analysis showed that unchanged PAH occupied 95% of the amount excreted in urine, and renal metabolism accounted for about 5% of renal clearance in the present perfused kidney preparation. Therefore, the net extraction in tubules based upon radioactivity data can be regarded mainly as tubular secretion. The tubular secretion intrinsic clearance ($CL_{int}$) was calculated from availability.

$$CL_{int} = Q_v(1 - F_{tu})/F_{tu} \qquad (1)$$

where $Q_v$ is the renal plasma flow, and the availability for the tubular transport process ($F_{tu}$) was evaluated as follows.

$$F_{tu} = F_{v,PAH}/\{1\text{-}f_u(1\text{-}F_{v,inu})\} \qquad (2)$$

where $F_{v,inu}$ and $f_u$ are the organ availability for inulin and plasma unbound fraction of PAH, respectively.

*Mean transit time.* The mean transit time for the renal vein outflow curve ($MTT_v$) was computed by trapezoidal integration according to the following equation (Hori et al 1988).

$$MTT_v = \int_0^T t \cdot C_{out}(t)dt / \int_0^T C_{out}(t)dt \qquad (3)$$

where $C_{out}(t)$ is the venous plasma concentration of indicators at time t and T is the finite time of integration. In a preliminary study, 300 s was suitable as the T value for the venous outflow curves (Hori et al 1988). The distortion of outflow curves due to the catheter was corrected according to the method described previously (Hori et al 1988).

The mean transit time for the urinary outflow curve ($MTT_u$) was calculated during a 15 min period in the same manner.

$$MTT_u = \int_0^{15} t(dA_u/dt)dt/A_u^{0\text{-}15} \qquad (4)$$

where $dA_u/dt$ is the urinary excretion rate and t is the midpoint of the sampling period. $A_u^{0\text{-}15}$ is the total urinary excretion during 15 min.

The secreted PAH fraction was calculated by subtracting the filtered fraction from the fraction excreted in urine. The filtered PAH fraction was computed by multiplying the plasma unbound fraction by the fraction of inulin excreted in urine. The mean time for secreted molecules to be transferred across renal epithelial cells was described in terms of the mean residence time in renal epithelial cell, $\bar{T}_{cell}$ as follows (Hori et al 1988):

$$\bar{T}_{cell} = MTT_{u,s} - MTT_{u,g} \qquad (5)$$

where $MTT_{u,s}$ and $MTT_{u,g}$ are the $MTT_u$ for secreted fraction and filtered fraction, respectively.

*Volume of distribution.* The volume of distribution for non-eliminated drugs (albumin and inulin in tubules, $Vd_{alb}$ and $Vd_{inu}$) can be calculated by a model-independent method:

$$Vd = Q_v \cdot MTT_v \qquad (6)$$

where $MTT_v$ is the MTT of albumin or inulin for the renal vein outflow curve.

The steady-state equivalent volume of distribution for PAH in the kidney was calculated by the following equation (see Appendix).

$$Vd_{PAH} = Q_v \cdot MTT_v + CL_{int} \cdot \bar{T}_{cell} \qquad (7)$$

If we used the plasma measurement data alone, the true volume of distribution cannot be estimated when elimination occurs from a peripheral compartment (DiStefano 1982; Collier 1983; Benet 1985; Veng-Pedersen & Gillespie 1985). The use of both venous and urinary information enables us to evaluate the precise drug distribution in the kidney.

*Influx rate constant.* The outflow fraction per mL was calculated by the fraction of dose that appeared in 1 mL of perfusate plasma effluent at time t. The logarithm of the ratio of the outflow fraction per mL for inulin to that for the transported PAH was plotted against time. The apparent rate constant for tubular uptake of PAH ($k_{1,app}$, influx rate constant) was graphically estimated from the initial slope of this plot (Goresky & Bach 1970; Ito et al 1986).

*Statistics.* The results are expressed as mean ± s.e. Statistical significance was evaluated by one-way analysis of variance and $P < 0·05$ was taken as being significant.

## Results

*Effect of probenecid on the rat isolated perfused kidney preparation*

GFR, urine flow rate, urine pH and plasma flow rate of the isolated perfused kidney were not influenced by the presence of probenecid. The averaged values and s.e. of GFR, urine flow rate, urine pH and plasma flow rate of 19 perfused kidneys were $378 \pm 23$ $\mu$L min$^{-1}$, $70 \pm 9$ $\mu$L min$^{-1}$, $6{\cdot}3 \pm 0{\cdot}0$ and $4{\cdot}9 \pm 0{\cdot}1$ mL min$^{-1}$, respectively. Fig. 1 shows typical examples of venous and urinary outflow curves for Evans blue-albumin, inulin and PAH. Venous outflow curves of Evans blue-albumin showed a similar shape in all kidneys examined, and the dye-albumin was recovered only from venous effluents. The venous and urinary outflow curves of inulin also showed similar patterns regardless of probenecid concentration in the perfusate. The urinary recovery of inulin was not influenced by the presence of probenecid. No differences were observed for $MTT_v$ and Vd in the kidney for Evans blue-albumin or inulin, between the absence and presence of probenecid or among the different concentrations of probenecid, indicating that intravascular and extracellular spaces in the kidney are constant and that the filtration function of the kidney was not affected by probenecid. The mean ± s.e. values of 19 perfused kidneys were as follows: urinary recovery of inulin, $3{\cdot}1 \pm 0{\cdot}2$ (% of dose); $MTT_{v,alb}$, $4{\cdot}0 \pm 0{\cdot}2$ s; $MTT_{v,inu}$, $8{\cdot}4 \pm 0{\cdot}4$ s; $Vd_{alb}$, $0{\cdot}26 \pm 0{\cdot}01$ mL g$^{-1}$; $Vd_{inu}$, $0{\cdot}57 \pm 0{\cdot}03$ mL g$^{-1}$.

*Renal handling of PAH in the absence and presence of probenecid*

Plasma protein binding of PAH was $12{\cdot}9 \pm 0{\cdot}5$% (mean ± s.e. of 10 duplicates) over the range of 0·001–0·1 mM total PAH concentration in plasma, which was not affected by the presence of 3 mM probenecid. The venous and urinary outflow patterns of PAH approached those of inulin with an increase in probenecid concentration (Fig. 1). This tendency

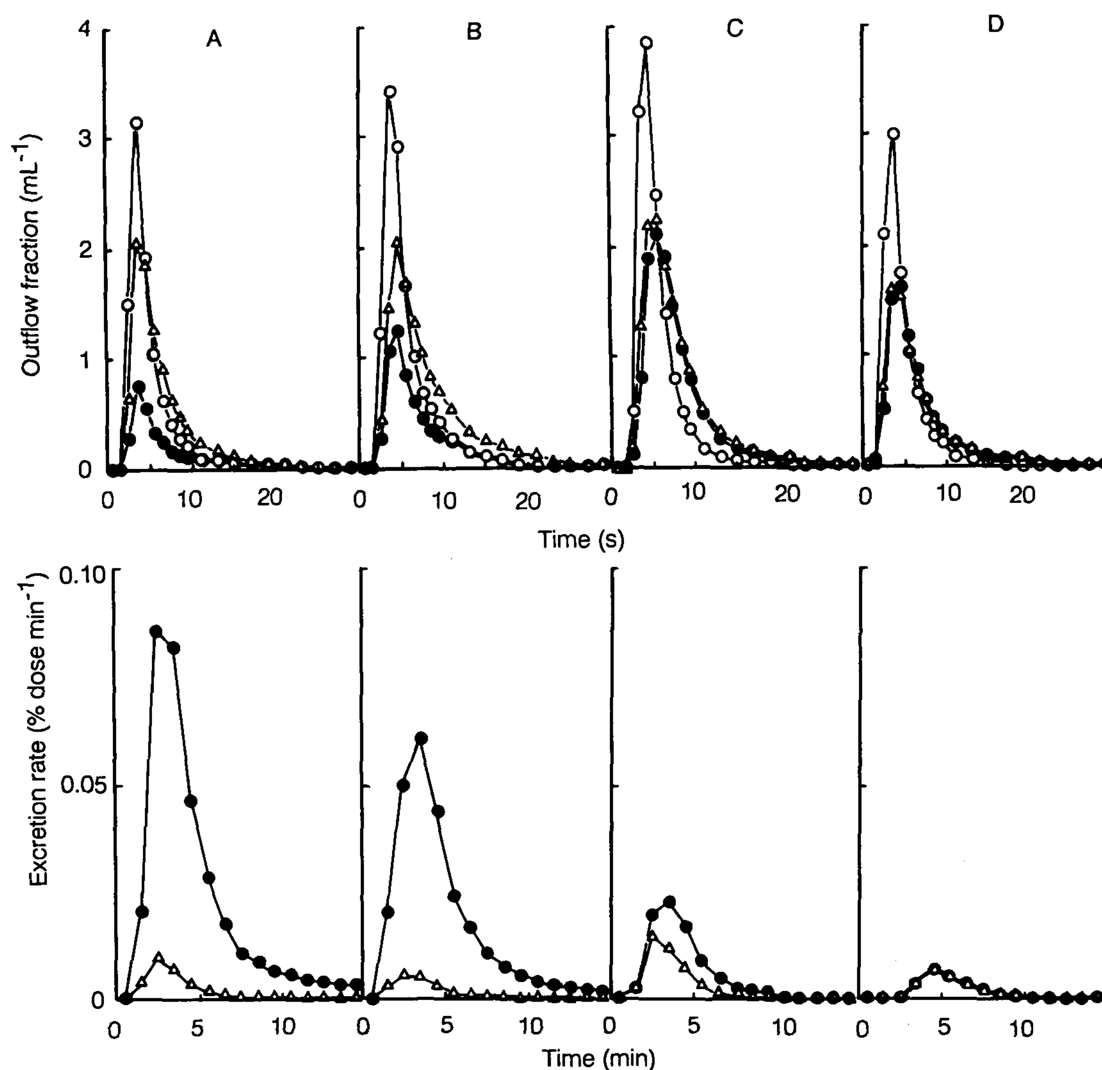


FIG. 1. Renal vein outflow curves and urinary excretion rate vs time curves for Evans blue-albumin (○), [$^3$H]inulin (△), and [$^{14}$C]PAH(●). Renal vein outflow curves are shown in the upper panel and the urinary excretion curves in the lower panel. A represents a control study in the absence of probenecid, B and C probenecid infusion studies (B, 0·1 mM; C, 2 mM) with partial inhibition of PAH secretion accompanied by reduced $Vd_{PAH}$, D a probenecid infusion study (3 mM) with almost complete inhibition accompanied by reduced $Vd_{PAH}$ and prolonged $\bar{T}_{cell}$.

Table 1. Effect of probenecid on the kinetic parameters for tubular transport of *p*-aminohippurate (PAH). Mean transit time for the renal vein outflow curve ($MTT_v$), mean residence time in renal epithelial cells ($\bar{T}_{cell}$), tubular secretion intrinsic clearance ($CL_{int}$) and steady-state equivalent volume of distribution ($Vd_{PAH}$) for PAH were calculated at the different concentrations of probenecid.

| Probenecid (mM) | $MTT_v$ (s) | $\bar{T}_{cell}$ (s) | $CL_{int}$ (mL $min^{-1}$) | $Vd_{PAH}$ (mL $g^{-1}$) | No. of exps[a] |
|---|---|---|---|---|---|
| 0 | 18·3±0·9 | 47±7 | 6·8±0·8 | 5·8±0·8 | 6 |
| 0·1 | 14·4±1·4* | 71±11 | 3·7±1·0* | 4·1±0·6 | 3 |
| 1 | 13·9±1·1* | 66±14 | 1·4±0·1* | 2·5±0·3* | 3 |
| 2 | 11·0±1·2* | 90±6 | 0·4±0·2* | 1·3±0·3* | 3 |
| 3 | 8·5±0·7* | 144±41* | 0·1±0·0* | 0·9±0·1* | 4 |

Each value represents the mean±s.e. [a]Number of experiments using different kidney preparations. * $P<0·05$ compared with control.

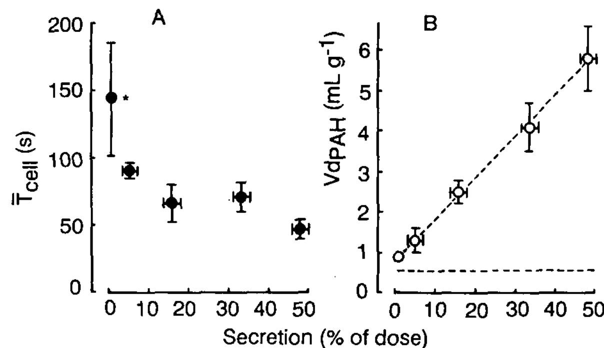


FIG. 2. Relationships between secreted amount and non-compartmental parameters of PAH (A, $\bar{T}_{cell}$; B, $Vd_{PAH}$). Each point represents the mean±s.e. of 3–6 experiments. In panel B, significant correlation was observed between $Vd_{PAH}$ and secreted amount of PAH (r=0·999), and the horizontal dotted line indicates the $Vd_{inu}$ value. * $P<0·05$ compared with control.

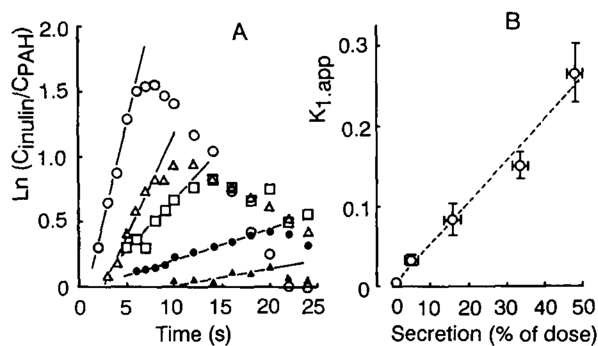


FIG. 3. Estimation of $k_{1,app}$ (tubular uptake rate constant) of PAH from natural logarithm of the ratio (venous outflow fraction per mL for inulin/that for PAH) vs time curves (A) and the relationship between $k_{1,app}$ and the amount of PAH secreted into urine (B). In panel A, $k_{1,app}$ was computed from the initial slope of the plot (solid line). Typical examples are shown for control (○) and for probenecid concentrations of 0·1 (△), 1 (□), 2 (●), and 3 (▲) mM. In panel B, significant correlation was observed between $k_{1,app}$ and the amount of secretion (r=0·991).

was characterized by decreased $CL_{int}$ and decreased $MTT_v$ depending on the probenecid concentration (Table 1).

Fig. 2 shows the relationships between the percent of dose secreted into urine and $\bar{T}_{cell}$ or $Vd_{PAH}$. $\bar{T}_{cell}$ was almost constant at concentrations of probenecid lower than 2 mM, while significantly prolonged $\bar{T}_{cell}$ was observed in the presence of 3 mM probenecid. On the other hand, $Vd_{PAH}$ showed a linear relationship with the amount of PAH secreted into urine.

Fig. 3 shows the natural logarithm of the ratio of the outflow fraction per mL in venous plasma for inulin to that for PAH vs time (A) and the relationship between the apparent rate constant for tubular uptake of PAH ($k_{1,app}$) and the amount of secretion (B). The secreted amount of PAH decreased in association with $k_{1,app}$. As expected from Figs 2 and 3, a good linear relationship was observed between $Vd_{PAH}$ and $k_{1,app}$ (r=0·994).

## Discussion

The amount of PAH secreted was directly correlated with both $k_{1,app}$ and $Vd_{PAH}$. Since $Vd_{PAH}$ is a parameter describing steady-state equivalent volume of distribution in renal tubules, it essentially corresponds to the transport between plasma and cells across basolateral membranes. The parameter $k_{1,app}$ is a unidirectional influx rate constant from plasma to cells. Although a more accurate value of $k_{1,app}$ can be calculated by a computer-assisted non-linear least squares curve-fitting method based on the distributed model (Ito et al 1986), the results obtained depend on the validity of the model. In this study, $Vd_{PAH}$ showed a good correlation with $k_{1,app}$, which implies that a non-compartmental parameter obtained by a simple calculation can be useful for describing transport across basolateral membranes.

In contrast, $\bar{T}_{cell}$ was not correlated with the amount of secretion. For example, $\bar{T}_{cell}$ did not change significantly in the presence of 2 mM probenecid, even though this concentration of probenecid decreased the secretion of PAH by up to 10% of the control value. Since $\bar{T}_{cell}$ is a mean residence time of secreted PAH molecules in epithelial cells, it ought to be affected by the rate of secretion from cells to the lumen. Unchanged $\bar{T}_{cell}$ suggested an unchanged secretion rate.

Accordingly, the present results demonstrated that transport at basolateral membranes is a determining step in tubular PAH secretion, and that the subsequent secretion rate from cells to the lumen was independent of the amount secreted. Similar results were obtained in our recent study concerning PAH transport in perfused kidney isolated from uranyl nitrate-induced acute renal failure rats (Tanigawara et al 1990); the amount of secretion showed a good correlation with $k_{1,app}$ with the progress of renal impairment while $\bar{T}_{cell}$ was not correlated. The previous membrane vesicle

study reported from this laboratory demonstrated carrier-mediated transport of PAH in the basolateral membrane vesicles (Hori et al 1982). Taking into account the previous and present findings, an active transport process can be a determining step for transepithelial movement of PAH from blood to lumen.

In the presence of a high concentration of probenecid, the outflow curves for PAH were almost identical to those for inulin. From a viewpoint of the PAH-probenecid interaction in the tubular transport, it was shown that transport at the basolateral membrane was inhibited depending on the probenecid concentration in perfusate, and that transport at the brush-border membrane was influenced at a high concentration of probenecid. The prolonged $\bar{T}_{cell}$ in the presence of 3 mM probenecid could be explained by the inhibition of transport from cells to the lumen through brush-border membranes, which can cause prolongation of the mean residence time in cells. This is supported by the observation that transport of PAH in the brush-border membrane vesicle was inhibited by probenecid (Hori et al 1982; Steffens et al 1989).

Another possibility is the increased luminal transit time of PAH compared with that of inulin, as discussed with rabbit kidney by Foulkes (1977). However, in a microinjection study with rat kidney by Baines et al (1968), the luminal transit delay was only 9 s and unchanged in the presence of high concentrations of unlabelled PAH. The mean transit time of PAH following microinjection into peritubular capillaries was 75 s longer than that microinjected into proximal tubules. Chinard (1956) first found the transit delay of secreted PAH compared with glomerular substances, and assigned this delay of the order of 70 s to transient accumulation of PAH in the tubule cells during the process of secretion. $\bar{T}_{cell}$ values in Table 1 are of the same order as those reported by Baines et al (1968) and Chinard (1956), therefore it is unlikely that the prolonged $\bar{T}_{cell}$ value was caused by the increased luminal transit time.

Our previous membrane vesicle study reported similar sensitivity of basolateral and brush-border membrane transport against the inhibitory effect of probenecid (Hori et al 1982). In the present study, however, $\bar{T}_{cell}$ was changed without a linear correlation with the probenecid concentration in the perfusate. Although basolateral membrane transport directly depends on the concentration in blood, brush-border membrane transport essentially depends on the concentration in cells or lumen. Therefore, the concentration-independent manner of the inhibitory effect may be explained by the speculation that the intracellular concentration of probenecid might not be linearly correlated with the concentration in perfusate and not high enough to inhibit PAH transport at brush-border membranes, though filtered probenecid was expected to exist in the lumen at around the concentration in plasma multiplied by the unbound fraction. However, it still remains a possibility that basolateral and brush-border membrane transport have different sensitivities for probenecid, as reported by Berner & Kinne (1976).

Decreased $Vd_{PAH}$ with an increase in the concentration of probenecid indicated that basolateral membrane transport is a capacity-limited process. The moment analysis using a deconvolution requires linearity of the system. However, the restriction of linearity does not extend to the input function which may represent a non-linear process (Cutler 1978). When tubular secretion was predominant, $\bar{T}_{cell}$ showed almost constant values (Table 1, Fig. 2), indicating that PAH kinetics after entering the epithelial cells were linear. Therefore, the saturability of basolateral membrane transport corresponds to the non-linearity of the input function but not to the non-linearity of the system. Furthermore, we accomplished the experiment under a plateau concentration of probenecid so as to avoid a non-linear (*in other words*, PAH concentration-dependent or time-dependent) response during a single passage of the radiolabelled tracer injected as a bolus.

In conclusion, the role of the basolateral membrane transport in renal transepithelial transport of PAH was elucidated by non-compartmental kinetic analysis using the rat isolated perfused kidney. The basolateral membrane transport was demonstrated to determine the amount of PAH secretion. The present method will be useful for detailed kinetic analysis of drug disposition in the morphologically intact kidney and applicable to the study of drug interaction in the kidney.

## Appendix

The following derivations show that the steady-state equivalent volume of distribution in the kidney for secreted drugs ($Vd_{kid}$) can be derived by a non-compartmental method in linear systems. Drug elimination in the kidney takes place at the glomerulus and tubules. However, taking into account a very short transit time in the glomerulus (Ito et al 1986), the mean residence time in the kidney indicates the time residing in the tubules, i.e. the volume of distribution in the kidney is consistent with the volume of distribution in the tubules. At steady-state with a constant infusion of the drug from the renal artery, the mass balance equation in the tubules can be written as:

$$C_a \cdot Q_a = C_v \cdot Q_v + \bar{C}_{ss} \cdot CL_{int} \quad (A1)$$

where $C_a$, $C_v$ are the input and output blood concentrations, $Q_a$, $Q_v$ are the input and output blood flow rates, $\bar{C}_{ss}$ is the average blood concentration in the tubules, and $CL_{int}$ is the total drug intrinsic clearance describing tubular secretion. Equation A1 expresses the infusion rate as equal to the sum of the effusion rate to renal vein and the secretion rate to lumen. Since the mean residence times of effused drug and secreted drug are denoted by $MTT_v$ and $\bar{T}_{cell}$, respectively, the total amount in the kidney at steady-state can be written as:

$$A_{ss} = C_v \cdot Q_v \cdot MTT_v + \bar{C}_{ss} \cdot CL_{int} \cdot \bar{T}_{cell} \quad (A2)$$

The steady-state volume of distribution is defined as the ratio of the total amount of drug to the blood concentration at a steady-state of equilibrium between blood and tissue compartments.

$$Vd_{kid} = A_{ss}/\bar{C}_{ss} \quad (A3)$$

Assuming venous equilibrium ($\bar{C}_{ss} \simeq C_v$), $Vd_{kid}$ can be derived as follows.

$$Vd_{kid} = Q_v \cdot MTT_v + CL_{int} \cdot \bar{T}_{cell} \quad (7)$$

## References


Baines, A. D., Gottschalk, C. W., Lassiter, W. E. (1968) Microinjection study of p-aminohippurate excretion by rat kidneys. Am. J. Physiol. 214: 703–709

Benet, L. Z. (1985) Mean residence time in the body versus mean residence time in the central compartment. J. Pharmacokinet. Biopharm. 13: 555–558

Berner, W., Kinne, R. (1976) Transport of p-aminohippuric acid by plasma membrane vesicles isolated from rat kidney cortex. Pflug. Arch. 361: 269–277

Chinard, F. P. (1956) Relative renal excretion patterns of p-aminohippurate (PAH) and glomerular substances. Am. J. Physiol. 185: 413–417

Collier, P. S. (1983) Some considerations on the estimation of steady state apparent volume of distribution and the relationships between volume terms. J. Pharmacokinet. Biopharm. 11: 93–105

Cutler, D. J. (1978) Theory of the mean absorption time, an adjunct to conventional bioavailability studies. J. Pharm. Pharmacol. 30: 476–478

DiStefano, J. J. (1982) Noncompartmental vs compartmental analysis: some bases for choice. Am. J. Physiol. 243: R1–R6

Folin, O., Wu, H. (1919) A system of blood analysis. J. Biol. Chem. 38: 81–110

Foulkes, E. C. (1977) Movement of p-aminohippurate between lumen and cells of renal tubule. Am. J. Physiol. 232: F424–F428

Goresky, C. A., Bach, G. G. (1970) Membrane transport and the hepatic circulation. Ann. N.Y. Acad. Sci. 170: 18–45

Grantham, J. J., Chonko, A. M. (1986) Renal handling of organic anions and cations; metabolism and excretion of uric acid. In: Brenner, B. M., Rector, F. C. (eds) The Kidney. W. B. Saunders, Philadelphia, pp 663–700

Hori, R., Inui, K., Takano, M., Okano, T. (1986) Transport mechanisms of organic ions in rat renal brush border and basolateral membrane vesicles. In: Drioli, E., Nakagaki, M. (eds) Membranes and Membrane Processes, Plenum Press, New York, pp 1–7

Hori, R., Kamiya, A., Saito, Y., Tanigawara, Y. (1987) Kidney perfusion systems in drug disposition studies. In: Breimer, D. D., Speiser, P. (eds) Topics in Pharmaceutical Sciences 1987. Elsevier, Amsterdam, pp 211–219

Hori, R., Takano, M., Okano, T., Kitazawa, S., Inui, K. (1982) Mechanism of p-aminohippurate transport by brush-border and basolateral membrane vesicles isolated from rat kidney cortex. Biochim. Biophys. Acta 692: 97–100

Hori, R., Takano, M., Okano, T., Inui, K. (1985) Transport of p-aminohippurate, tetraethylammonium and D-glucose in renal brush border membranes from rats with acute renal failure. J. Pharmacol. Exp. Ther. 233: 776–781

Hori, R., Tanigawara, Y., Saito, Y., Hayashi, Y., Aiba, T., Okumura, K., Kamiya, A. (1988) Moment analysis of drug disposition in kidney: transcellular transport of p-aminohippurate in the isolated perfused rat kidney. J. Pharm. Sci. 77: 471–476

Inui, K., Takano, M., Okano, T., Hori, R. (1986) Role of chloride on carrier-mediated transport of p-aminohippurate in rat renal basolateral membrane vesicles. Biochim. Biophys. Acta 855: 425–428

Ito, N., Sawada, Y., Sugiyama, Y., Iga, T., Hanano, M. (1986) Kinetic analysis of rat renal tubular transport based on multiple-indicator dilution method. Am. J. Physiol. 251: F103–F114

Kamiya, A., Tanigawara, Y., Saito, Y., Hayashi, Y., Aiba, T., Inui, K., Hori, R. (1990) Moment analysis of drug disposition in kidney. II: Urine pH-dependent tubular secretion of tetraethylammonium in the isolated perfused rat kidney. J. Pharm. Sci. 79: 692–697

MacDougall, M. L., Wiegmann, T. B. (1988) Excretion of para-aminohippurate in the isolated perfused rat kidney: net secretion and net reabsorption. J. Physiol. 397: 459–469

McKinney, T. D. (1988) Renal transport of organic anions and cations. In: Schrier, R. W., Gottschalk, C. W. (eds) Disease of the Kidney. Little, Brown and Company, Boston/Toronto, pp 285–307

Møller, J. V., Sheikh, M. I. (1983) Renal organic anion transport system: pharmacological, physiological, and biochemical aspects. Pharmacol. Rev. 34: 315–358

Nishiitsutsuji-Uwo, J. M., Ross, B. D., Krebs, H. A. (1967) Metabolic activities of the isolated perfused rat kidney. Biochem. J. 103: 852–862

Steffens, T. G., Holohan, P. D., Ross, C. R. (1989) Operational modes of the organic anion exchanger in canine renal brush-border membrane vesicles. Am. J. Physiol. 256: F596–F609

Tanigawara, Y., Saito, Y., Aiba, T., Ohoka, K., Kamiya, A., Hori, R. (1990) Moment analysis of drug disposition in kidney. III: Transport of p-aminohippurate and tetraethylammonium in the perfused kidney isolated from uranyl nitrate-induced acute renal failure rats. J. Pharm. Sci. 79: 249–256

Veng-Pedersen, P., Gillespie, W. (1985) The mean residence time of drugs in the systemic circulation. Ibid. 74: 791–792

Weiner, I. M. (1973) Transport of weak acids and bases. In: Orloff, J., Berliner, R. W. (eds) Renal Physiology, American Physiological Society, Washington, D. C., pp 521–554