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Computer analysis of the significance of the effective osmolality for urea across the inner medullary collecting duct in the operation of a single effect for the counter-current multiplication system

Abstract

Background. Although urea and water are transported across separate pathways in the apical membrane of the inner medullary collecting duct (IMCD), the existence of a cellular diffusion barrier as an unstirred layer makes it possible to use coefficients of effective osmotic force ($\sigma^*$) as equivalent to reflection coefficients. The difference in effective osmolality between urea and NaCl across the IMCD becomes a driving force for water if the compositions of solutes are different between tubular lumen and interstitium. Since reported values for $\sigma^*_{\text{urea}}$ are discrepant, we compared the efficiency of a single effect in the counter-current system between an ascending thin limb (ATL) and the IMCD, with the interposition of capillary networks (CNW), between two models with $\sigma^*_{\text{urea}} = 0.7$ (model 1) and $\sigma^*_{\text{urea}} = 1.0$ (model 2).

Methods. The time courses (within 3s) of solute and the water transport profiles among ATL, CNW, and IMCD were simulated with a computer in the absence of flow in each compartment.

Results. In spite of small differences in the profiles of urea and NaCl concentrations between the two models, model 1 displayed a larger volume flux in the IMCD than model 2, resulting in an increase of osmolality in the IMCD and a decrease of osmolality in the ATL. These findings are vital for the operation of the counter-current multiplication system.

Conclusions. The concept of coefficients for effective osmotic force can be applied to the counter-current model between the IMCD and the ATL with the interposition of CNW. The model of $\sigma^*_{\text{urea}} = 0.7$ is more efficient than that of $\sigma^*_{\text{urea}} = 1.0$.

Key words Urine concentration · Inner medullary collecting duct · Henle’s loop · Urea permeability · Counter-current multiplication

Introduction

An accumulation of urea in the renal medulla plays a critical role in the formation of concentrated urine. The models of the counter-current multiplication system by a passive mechanism in the inner medulla, proposed by Kokko and Rector, as well as by Stephenson, provided a strong theoretical approach to understanding the role of urea in the urine concentrating mechanism. However, the proposed model has not been accepted, because it does not fit micropuncture data showing that a considerable amount of urea enters the descending thin limb (DTL), and that both urea and NaCl exit from the lumen of the ascending thin limb (ATL). In addition, the segments of the DTL are heterogeneous between long-loop and short-loop nephrons as well as among species, so that it is unreasonable to predict that urea entry to the DTL is minimal. The computer simulation reported by Taniguchi et al. also did not support the entry of urea into the ATL.

Based on these criticisms, we proposed a new passive counter-current multiplication model, which allows both NaCl and urea to exit from the ATL. The model predicts complicated counter- and parallel-flow systems among the ATL, CNW, and IMCD. The initial driving force of this system is the effective osmolality caused by the differences in the apparent reflection coefficient between urea and NaCl in the IMCD. In support of this model, we reported that in a microperfused hamster IMCD, the apparent reflection coefficient for urea was about 0.7 in the presence of vasopressin, and that partial equi-osmolar replacement of urea in a bath with NaCl caused a marked net water flux in the absence of a nominal osmotic pressure gradient across the tubule.

However, the proposed model was criticized by Chou et al., who showed that the reflection coefficient of the rat IMCD for urea was not different from unity.
Hamada and Imai\textsuperscript{13} carried out a computer analysis to show that cellular constraints to the diffusion (a cellular unstirred layer) of urea may reduce the osmotic gradient across the apical membrane of the IMCD, even if we set the reflection coefficients for urea in both apical and basolateral membranes at unity. Thus, it is reasonable to assume that the effective osmolality across the IMCD is lower for urea than for NaCl. Therefore, we formulated this phenomenon by using the concept of an apparent reflection coefficient. Since this terminology might be confused with the classical terminology, we will change this terminology to the “effective osmotic force coefficient ($\sigma^*$)” in this article. Under this terminology, we can mathematically treat the urea and water transport across the tubular epithelial wall as if both urea and water are transported across a route in a single membrane with a frictional coefficient of $\sigma_{\text{urea}*} = 0.7$.

This study was designed to demonstrate that the model using $\sigma_{\text{urea}*} = 0.7$ (model 1) is more efficient than that using $\sigma_{\text{urea}*} = 1.0$ (model 2) in the operation of the proposed three-compartment model, where the ATL and the IMCD compose the counter-current system with the interposition of CNW. Because it is impossible to test this issue by experiments, we carried out a computer simulation under the simplest conditions.

Methods

Hamada and Imai\textsuperscript{13} reported that an intracellular unstirred layer (a cellular constraint to diffusion) apparently reduced the osmotic driving force of urea across the apical cell membrane. In this case, the effective osmotic driving force across a renal tubular wall is less than the value estimated by a nominal osmotic gradient. Thus, it is necessary to multiply the nominal (physicochemical) osmotic gradient by a factor that is less than unity. Such a factor is similar to the reflection coefficient if one assumes the tubular wall to be a single membrane. In this study, we define such an apparent reflection coefficient as an effective osmotic force coefficient ($\sigma^*$).

Using the following mathematical model, we carried out a computer simulation to compare the transport profile among three compartments representing the ATL, a CNW, and the IMCD at two different effective osmotic force coefficients for urea ($\sigma_{\text{urea}*}$), i.e., 0.7 (model 1) and 1.0 (model 2).

The properties of the ATL, CNW, and IMCD compartments are assumed to be as follows. The ATL and IMCD compartments have a cylindrical shape and are 10$\mu$m in radius and 10$\mu$m in height. Both the ATL and IMCD compartments are interposed by a CNW compartment, and therefore there is no direct contact between the ATL and IMCD compartments. All the transport processes are performed across the circumferential areas of the ATL and IMCD. These transport areas are fixed at a constant size. The initial volume of the CNW compartment is the same as that of the other two compartments.

The flux across the membrane ($n = 1$ or 2 for the membrane of the ATL or IMCD compartment, respectively) is expressed as $J^{(m)}$. The volume and solute-S concentrations in the $n$-th compartments ($n = 1, 2, 3$ for ATL, IMCD, or CNW, respectively) are expressed as $V^{(n)}$ and $[S]^{(n)}$, respectively. The mass balances for the ATL or IMCD compartments ($n = 1$ or 2) can be expressed as

$$\frac{dV^{(n)}}{dt} = -J_{V}^{(m)}$$

(1)

$$\frac{d([S]^{(n)}V^{(n)})}{dt} = J_{S}^{(m)}$$

(2)

where $J_{V}^{(m)}$ and $J_{S}^{(m)}$ are the volumetric and solute-S flux across the $m$-th membrane, respectively. The mass balance for the CNW compartment ($n = 3$) can be expressed as

$$\frac{dV^{(3)}}{dt} = \sum_{m} J_{V}^{(m)}$$

(3)

$$\frac{d([S]^{(3)}V^{(3)})}{dt} = -\sum_{m} J_{S}^{(m)}$$

(4)

The differential of $[S]^{(n)}$ in the ATL or IMCD compartment ($n = 1$ or 2) can be obtained from Eqs. 1 and 2 as Eq. 5, and that in the CNW compartment ($n = 3$) can be obtained from Eqs. 3 and 4 as Eq. 6.

$$\frac{d[S]^{(n)}}{dt} = J_{S}^{(m)} + [S]^{(n)}J_{V}^{(m)}$$

$$\frac{d[S]^{(3)}}{dt} = -\sum_{m} J_{S}^{(m)} - [S]^{(3)}J_{V}^{(m)}$$

(5)

(6)

Volumetric and solute fluxes can be expressed as

$$J_{V}^{(m)} = L_{p}^{(m)}RTA^{(m)}\sum \sigma_{s}^{*} \Delta [S]^{(m)}$$

(7)

$$J_{S}^{(m)} = P_{s}^{(m)}A^{(m)}\Delta [S]^{(m)} - P_{s}^{(m)}A^{(m)}[S]_{\text{mean}}^{(m)}RTF_{T}^{(m)}$$

(8)

where $R$ and $T$ are the gas constant and absolute temperature (310 K), respectively, $L_{p}^{(m)}$ is the hydraulic conductivity in the $m$-th membrane, $P_{s}^{(m)}$ is the permeability coefficient for the solute, $A^{(m)}$ is the membrane area, $\Delta [S]^{(m)}$ is the concentration difference of the solute relative to the concentration in the CNW compartment, $\sigma_{s}^{(m)}$ is the apparent reflection coefficient for the solute, $[S]_{\text{mean}}^{(m)}$ is the mean intramembrane concentration, and $V_{T}^{(m)}$ is the transmembrane voltage relative to the potential in the CNW compartment. $[S]_{\text{mean}}^{(m)}$ can be expressed as

$$[S]_{\text{mean}}^{(m)} = \frac{\Delta [S]^{(m)}}{\ln([S]^{(m)}/[S]^{(3)})}$$

(9)