Mathematical Models for Two Structures of the Urine Formation of Neonatal Rats

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Introduction

The kidney of a neonatal mammalian can dilute urine as efficiently as the mature kidney. At birth, 1) the total body water is high and at the first week of life, the kidney is excreting this load of water [2]. And 2) infants fed with maternal milk receive a diet with very high water and low protein content [1]. Therefore, under these conditions a healthy infant is capable of maintaining fluid homeostasis. However, such a kidney has limited capability to concentrate the urine. And this could disturb the fluid homeostasis when water intake is restricted or excessive amounts of water are lost, such as occur with diarrhea, vomiting, and fever. In addition, this may place premature infants in greater risk. The factors of this limiting capacity of the immature kidney are not completely understood.

At birth, some mammalians have not completed the kidney maturation process and some animals have not even completed the formation of their nephrons. Our knowledge of the kidney in development, particularly its structure, is limited. Liu an co-workers [5] postulated that the mammalian neonatal structure is similar to the avian one. Their results suggest a uniform organization of the loops of Henle in the renal medulla, see left panel in Figure 1. In a separated study Kim and collaborators [3] suggested a nonuniform structure and that the loops of Henle develop in different generations, see right panel in Figure 1. In this study, by means of mathematical models, we compare the ability of both structures to produce dilute and concentrated urine in neonatal rats.

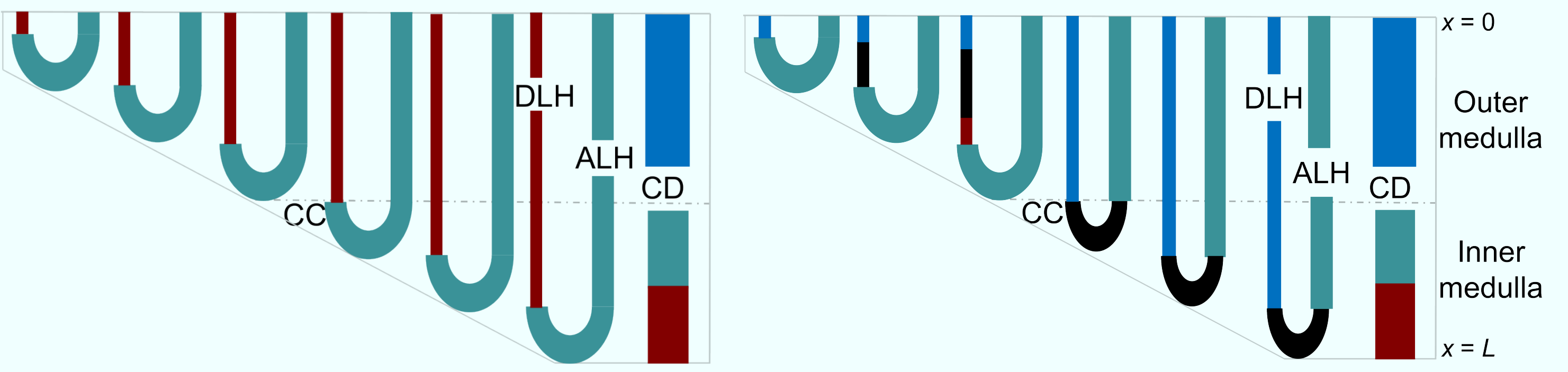

Figure 1: Schematic diagram of the central core model formulation with six representative loops of Henle and a composite collecting duct. On the left a uniform structure as suggested by Liu et al. [5] and on the right a nonuniform structure as it was suggested by Kim et al. [3]. Colors means: blue, water permeable; black, impermeable; red, urea permeable; green, active NaCl transport.

Mathematical model

Model assumptions

- Only juxtamedullary nephrons are represented in the model. In the nonuniform case we considered two generations of nephrons.
- The only solutes represented in the model were NaCl and urea.
- We used a central core (CC) representation [6] to model interactions among the renal tubules in the medulla, see Figure 1.
- A population of loops of Henle was represented by a continuous, monotonically decreasing distribution of tubes, which reach to different levels along the medulla as it was introduced by Layton in [4].

Model equations

Water and solute conservation

$$\frac{\partial}{\partial x}F_{iv} = -J_{iv}$$

$$A_i\frac{\partial}{\partial t}C_{ik} + \frac{\partial}{\partial x}\Big(F_{iv}C_{ik}\Big) = -J_{ik}, \quad i \neq 4,$$

$$A_4\frac{\partial}{\partial t}C_{4k} = -\frac{\partial}{\partial x}\Big(F_{4v}C_{4k}\Big) + D_k\frac{\partial}{\partial x}\left(A_4\frac{\partial}{\partial x}C_{4k}\right) - J_{4k}.$$

Transmural fluxes for water and solutes

$$J_{iv} = -2\pi r_i P_{f,i}\overline{V}_w \sum_k \sigma_{ik}\phi_k\Big(C_{ik} - C_{4k}\Big)$$

$$J_{ik} = 2\pi r_i\left(P_{ik}\Big(C_{ik} - C_{4k}\Big) + \frac{V_{\max,ik}C_{ik}}{K_{m,ik} + C_{ik}}\right).$$

Total transmural line fluxes from DLs or ALs at level x

$$\overline{J}_{ik}(x,t) = J_{ik}(x,L,t)w(L) + \int_x^L J_{ik}(x,y,t)\big(-w'(y)\big)\,\mathrm{d}\,y.$$

In the CC

$$J_{4k} = -\Big(\overline{J}_{1k} + \overline{J}_{2k} + J_{3k}\Big), \quad k = \mathrm{v}, \mathrm{NaCl}, \mathrm{urea}.$$

$i = 1$, DLH; $i = 2$, ALH; $i = 3$, CD; $i = 4$, CC; $k = 1$, NaCl; $k = 2$, urea and $w(y)$ is the fraction of loops reaching to level y.

Parameter computation

$$\begin{aligned} &\underset{\mathbf{z}}{\text{optimize}} \quad FWA\,(\mathbf{z}) \\ &\text{subject to} \quad \mathbf{z}_\ell \leq \mathbf{z} \leq \mathbf{z}_u, \\ &\text{and the model equations are satisfied,} \end{aligned}$$

where FWA is the solute-free water absorption rate, which is given by [7]

$$FWA(\mathbf{z}) = F_{\mathrm{CD,v}}(L;\mathbf{z})\,\big((U/P)(\mathbf{z}) - 1\big)\,.$$

To solve the optimization problem we apply a direction search method (i.e., a method that seeks a maximum in the direction where the derivative of the maximization function increases) to compute a maximum nearby an initial set of parameters. To explore the parameter space aiming to compute a global maximum, we generate a population of initial iterate parameters uniformly distributed and execute the direction search method to convergence starting with each one of the initial parameters. Finally, we select the result (or results) showing the largest model FWA.

Table 1: Fixed parameter values

Parameter	Value
DLH radius, r_1 (μm)	3.6
ALH radius, r_2 (μm)	4.5
CD radius, r_3 (μm)	9.6–12
Outer medullary length, L_{OM} (mm)	2.5
Inner medullary length, L_{IM} (mm)	2.5
Partial molar volume of water, $\overline{V}_w$ (cm^3/mM)	0.018136
Osmotic coefficient of NaCl, ϕ_1 (dimensionless)	1.84
Osmotic coefficient of urea, ϕ_2 (dimensionless)	0.97
Michaelis constant, K_m (mM)	40.0
Plasma osmolality (mosmol/kgH_2O)	248.0
Number of loops of Henle	12,667.0
Number of collecting ducts	2,533.0

Table 2: Baseline and optimal parameters

Parameter	Uniform case			Nonuniform case		
	Baseline value	Maximum value	Minimum value	Baseline value	Maximum value	Minimum value
Water inflow of longest loop of Henle, $F_{v,1}(0)$ (nl/min)						
DLH	2.5	2.00	6.00	2.5	2.00	4.00
Urea concentration at the medulla entrance, $C_{i,2}(0)$ (mM)						
DLH	11.1	7.77	7.77	11.1	7.77	7.77
CD	100	130	70.0	100	130	70.0
Fraction of NaCl flow reaching						
CD	0.667	0.500	0.750	0.667	0.500	0.700
Water permeability, $P_{f,i}$ (μm/s)						
DLH	0	0	0	500	650	650
CD	102.2	132.86	1.00	102.2	132.86	10.0
Urea permeability, $P_{i,2}$ (10^{-5} cm/s)						
DLH	8.00	10.4	10.4	8.00	5.6	5.60
ALH	8.00	5.60	10.4	0	0	0
CD	5.00	3.50	6.50	5.00	3.50	6.50
Na^+ active transport rate, $V_{\max,i}$ (nmol·cm^{-2}·s^{-1})						
ALH	4.00	6.00	1.00	4.00	6.00	1.25
CD	2.00	1.00	6.00	2.00	1.00	6.00
Population distribution exponential decay rate						
Loops of Henle	2.80	1.96	3.64	2.80	2.28	1.96
CD	2.50	3.25	1.75	2.50	1.75	1.75

Results

Table 1 contains the values of the parameters that were kept fixed during the computation. For each model, by using the optimization problem, we computed parameters that yield maximum and minimum model solute free-water absorption rate (FWA), see Table 2. Most parameters were allowed to vary within ±30% from the baseline value. Simulation values for the baseline and each case are shown in Table 3.

Table 3: Model simulation values for the base case and the optimal cases

Description	Uniform case			Nonuniform case		
	Baseline value	Maximum value	Minimum value	Baseline value	Maximum value	Minimum value
U/P	1.41	4.13	0.991	1.21	2.35	0.978
Urine						
Osmolality*	351	1,024	246	300	582	243
[Na^+]**	116	277	96.5	98.7	155	94.8
[urea]**	142	531	70.3	122	306	70.2
Flow†	0.177	0.0290	0.857	0.223	0.0527	0.539
FWA†	0.0734	0.0907	−0.00766	0.0465	0.0709	−0.0118
Bend of longest loop of Henle						
Osmolality*	101	39.8	240	422	651	354
[Na^+]**	40.0	5.20	120	219	343	186
[urea]**	28.6	31.2	19.5	18.9	20.4	11.1
Flow‡	2.50	2.00	6.00	1.47	0.762	2.80

*mOsm/kg H_2O; **mM; †nl/min/nephron; ‡nl/min.

Concluding remarks

- Both models were able to dilute and concentrate the urine.
- For the urine concentration case, the uniform-structure model yields results that are less realistic than the results of the nonuniform-structure model in the sense that the urine osmolality is higher than the one obtained in experiments, ~600 mOsmol/KgH_2O, and the osmolality in the bend of the longest loop of Henle is very low.
- The uniform model employs 4% more active transport in the ALH than the nonuniform model (119 pmol/min for the nonuniform and 124 pmol/min for the uniform) to increase the urine osmolality by 76% above the urine osmolality of the nonuniform model.
- It seems that the central core model for the neonatal rat favors the structure proposed by Kim and collaborators [3] better that the structure proposed by Liu and co-workers [5].

References

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