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Optimization of flow in the collecting duct during the concentrating mode and the diluting mode in a nephron population of two different length with the renin angiotensin system and ADH mechanism

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ABSTRACT

Optimization of Flow in the Collecting Duct during the Concentrating Mode and the Diluting Mode in a Nephron Population of two different length with the Renin Angiotensin System and the ADH mechanism

by

Sivakumar Subramanian

Our present study is to find out how the short and long nephrons are interacting in the human kidney to adjust the flow in the collecting duct to have the maximum flow during the diluting mode and minimum flow during the concentrating mode. The best lengths for the short nephron and long nephron are calculated during the concentrating mode and the diluting mode by using the Newton-Raphson method. If one wants the kidney to perform only the above mentioned functions, a design criteria for an artificial kidney has been proposed. These studies have provided qualitative information regarding the concentrating mechanism and illustrates well the problem involved in attempting to describe accurately the function of an organ like kidney.

OPTIMIZATION OF FLOW IN THE COLLECTING DUCT DURING THE CONCENTRATING MODE AND THE DILUTING MODE IN A NEPHRON POPULATION OF TWO DIFFERENT LENGTH WITH THE RENIN ANGIOTENSIN SYSTEM AND ADH MECHANISM

by

Sivakumar Subramanian

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This thesis is dedicated to my parents

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LIST OF SYMBOLS USED IN THE MODELS

SYMBOL	ABBREVIATION
F^1H20	The rate at which water comes out of the descending limb one nephron.
F^1h20_A	The rate at which water comes out of the descending limb of nephronA
	- two nephron
F^1h20_B	The rate at which water comes out of the descending limb of nephronB
	- two nephron
F^*	The rate at which the salt comes out of the ascending limb of nephron -
	one nephron.
F^*_A	The rate at which the salt comes out of the ascending limb of nephrnA -
	two nephron.
F^*_B	The rate at which the salt comes out of the ascending limb of nephronB
	- two nephron.
Q^0	The input flow for a one nephron.
$Q_A{}^0$	The input flow for a one nephronA.
$Q_B{}^0$	The input flow for a one nephronB.
C^0	The concentration at the top of the descending limb of a nephron.
$C(L_A)$	The concentration at the bottom of nephronA.
$C(L_B)$	The concentration at the bottom of nephronB.
$C^2_A(0)$	The concentration at the top of the ascending limb of nephronA.
$C^2_B(0)$	The concentration at the top of the ascending limb of nephronB.
$Q^2_A(0)$	The flow at the top of the ascending limb of nephronA.
$Q^2_B(0)$	The flow at the top of the ascending limb of nephronB.
Q_{DA}	The flow in the distal convoluted tubuleA.
Q_{DB}	The flow in the distal convoluted tubuleB.
$Q^3(0)$	The flow at the begining of the collectng duct.
$Q^3(LB)$	The flow at length LB in the collecting duct.

CHAPTER 1

INTRODUCTION

1.1 Literature review

In the past few years several investigators have been engaged in the construction and solution of mathematical models of the flow of the flow of water and solute in the kidney.[see, e.g. Stephenson et al. 1974,1976, and 1987]. Models with widely varying degrees of complexity have been considered, but most share the same general features. The system is assumed to consist of a number of components: renal tubules, glomerular and post glomerular capillaries, cortical interstitium (see fig 1 in Stephenson et al. 1976). Lists of relevant literature, along with some commentary, may be found elsewhere (Jacquez et al., 1976; Jamison and Kriz, 1982; Marsh et al., 1980; Moore et al., 1980; Stephenson et al. 1976). In recent years mathematical investigation of concentrating mechanism had tended more toward, large-scale simulation(e.g. Foster et al., 1976; Layton et al., 1986; Jacquez et al., 1976) than toward schematic modelling.

Urine production in the mammalian kidney is a complex dynamic process involving fluid flow, epthelial transport, hormonal regulation and feedback loops. One of those feedback loops, is Tubuloglomerular Feedback(TGF), which helps to regulate the rate of fluid and solute entry into individual nephrons. Much has been learned about TGF in recent years (for review see [16]), and several steady state models for TGF have appeared in [1], [12], [13].

An alternate model , one much closer to the real operation of the kidney is shown by Kuhn and Ramel, 1959. The membrane separating the two limbs now transports solute from the ascending to the descending limb; the membrane is water-impermeable and the solutes in the descending limb are concentrated still further.

Flow rate in the vasarecta is expected to be an important factor in the ability of the medulla to generate hypertonic urine. If the flow rate is increased, countercurrent exchange becomes less efficient, and medullary osmolality drops as solute is lost. Support for this idea came from Thurau and Deetjen. They made use of the observation that medullary circulation is not autoregulated (Kramer et al., 1960) so that elevating arterial blood pressure increases medullary blood flow rate. The structure and concentrating mechanism in the mammalian kidney for various mammals was studied by Bodilscmidt-Nielsen et al and Roberta O' dell et al., 1960 and a close correlation was found between renal medullary thickness and ability to concentrate electrolytes in the urine indicating that the medulla acts as a countercurrent multiplier system. These studies cited provide strong evidence that the distribution of nephrons in the kidney is a significant feature of medullary physiology.

1.2 Introduction

Although the physical characteristics of each component can be studied experimentally in isolation, the complexity of the system precludes the simple translation of these studies into an explanation of the overall kidney function. It is here, as in many other areas of science and engineering, that mathematical modelling and numerical computation is needed. The connectivity of the individual components of the system determines a priori, the structure of the model equations. This structure, intern is used to develop especially efficient and flexible algorithms for the solution of equation.

As part of the quest to understand how countercurrent flow in the tubules of the renal medulla produces highly concentrated urine, many mathematical models have been proposed in the last half-century[25].

The mammalian kidney has the remarkable capability to produce urine that is much more concentrated than blood plasma. For example, the maximum concentration ratios of urine to blood plasma in a human, a rat, and a hopping mouse are about 4, 9, 25 respectively. The capability to produce concentrated urine, along with the capability to also produce dilute urine, enables an animal to maintain its blood plasma osmolality within the narrow range (about 290 to 310 mosm/liter) that provides a suitable environment for its cells.

In our attempt to investigate mathematically the concentrating mechanism of the kidney and its blood plasma osmolality, some new schematic models are developed. we expressed the outputs of the Henle's loop interms of its input. we then succeeded in expressing the input as a function of output of the Henle's loop. That is the nephron actually adjusts Q(0) to achieve a specified sodium concentration $C_2(0)$ at the top of the ascending limb.

Chapter 2 introduces a very simple mathematical model developed by Charles S. Peskin (unpublished manuscript). A single model nephron obeying a number of simplifying assumption is able to bring urine osmolality upto only a factor of e (the Euler constant, e=2.7) over plasma osmolality, regardless of the length of the loop of Henle or type of kinetics specified for pumping sodium chloride from the ascending limb. This model frame work is extended by relaxing the assumption that the water flux in the collecting duct is not negligible compared to the flux coming out of descending limb.

In chapter 3 a model for two nephrons, each similar to the single nephron of chapter 2, but with varying loop of Henle lengths is considered. This two-stage model is found to have a concentrating limit of exp2(theoretically) and maximum flow in the collecting duct during the diluting mode.

In chapter 4, the same two nephron model of chapter 3 is extended as the single nephron model in chapter 1 was extended. This two stage model was

found to have concentrating limit of exp2(theoretically) and minimum flow in the collecting duct during the concentrating mode.

In chapter5 the model framework is extended to represent multinephrons with fixed length. This formulation leads us to solve for optimum flows with fixed number of short and long nephrons with a constraint on the length of the nephron.

In this study, we formulated differential equations for solute and water movement for the counterflow system of the mammalian kidney. Numerical solutions have been obtained by computer calculations.

The work reported here is a sequel to an earlier study (Peskin et al., 1986) which used a similar model framework. The present study confirms that the results previously obtained also hold good for a two nephron model of the loop of Henle.

CHAPTER 2

SINGLE NEPHRON MODEL (CONCENTRATING MODE)

2.1 Introduction

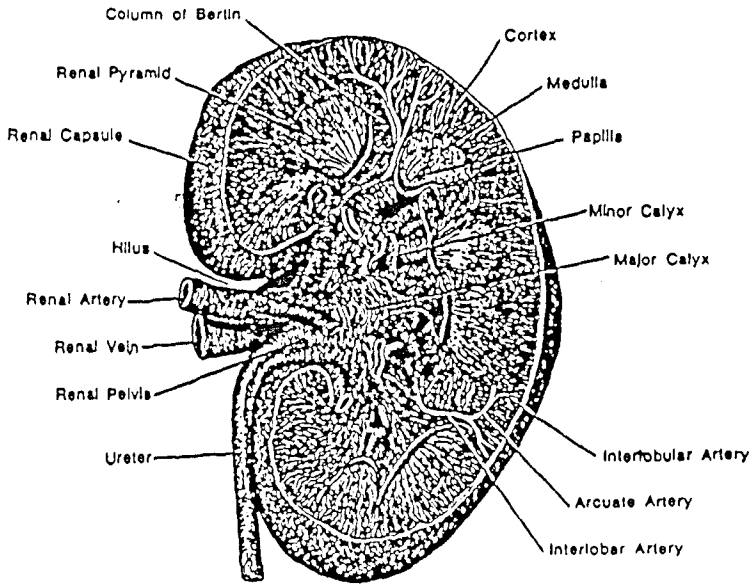
In this section Peskin's mathematical model for a single medullary nephron in the antidiuretic state is introduced. It has been possible to simulate behavior of the whole kidney as a function of solute concentration, and compute concentrations and flows in the various nephron segments. There is no attempt to include all of the phenomena that may contribute to the concentrating mechanism. For example, even though there is experimental evidence that the descending limbs of short-looped nephrons differ in permeability properties from the descending limb of the long looped nephron (Imai et al., 1984;), the model shows that if all the loops turn at the same depth, the concentrating capability is limited by a factor *e* over plasma osmolality. The model equations are derived from the conservation of mass for solute and fluid. Numerical solution have been obtained using computer calculations.

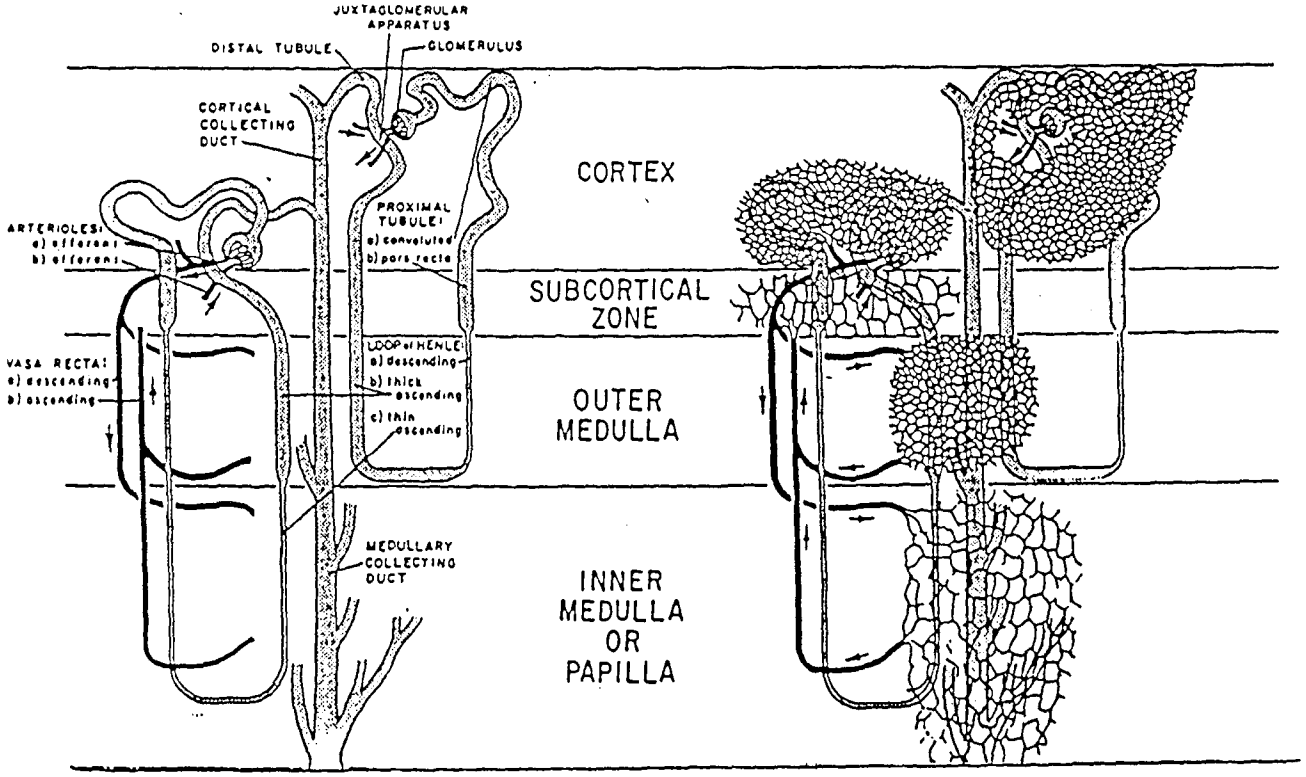
2.2 Model

2.2.1 Assumptions

We shall construct a model of the nephron beginning with the most interesting part of the system, the loop of Henle (see fig(1)). The descending limb of the loop is designated tube 1, the ascending limb as tube 2 and the collecting duct as tube 3. The sodium concentrations and water flows in the tubules are written $C_i(x)$ and $Q_i(x)$, respectively, where i=1,2,3. The external sodium concentration is denoted by c(x). By our sign conventions, the flow is positive in the descending limb and negative in the ascending limb, since x increases downward.

SECTION OF HUMAN KIDNEY





The physiological assumptions of our model of Henle's loop are the following:

1.We assume that the walls of the descending limb are permeable to water but not to sodium. This is a simplification: The walls are also permeable to sodium, but this is not an essential feature of the operation of Henle's loop, and we leave it out. Moreover, we assume that the water permeability is so large that the water flux makes the internal and external sodium concentrations equal. This gives the equations

$$dq_1/dx+f^1h20(x)=0 \quad (1)$$

$$(d/dx)(q_1c_1)=0 \quad (2)$$

$$c_1(x)=c(x) \quad (3)$$

2. We assume that sodium is pumped out of the ascending limb at a fixed rate f^*_{na} per unit length. We also assume that the ascending limb is impermeable to water. This gives

$$dq_2/dx=0 \quad (4)$$

$$(d/dx)(q_2c_2)+f^*_{na} \quad (5)$$

3. At the turn of Henle's loop(x=l) we assume that all of the salt and water leaving the descending limb enter the ascending limb. This gives the boundary conditions

$$c_1(L)=c_2(L) \quad (6)$$

$$q_1(L)=-q_2(L) \quad (7)$$

4. At the collecting duct,we assume that the rate at which the water come out when ADH is present is f^3_{h20}. This gives the equations

$$dq_3/dx = - f^3_{h20} \quad (8)$$

$$d(q_3c_3)/dx = 0 \quad (9)$$

5. Finally, we need an assumption about the peritubular capillaries, which pick up the sodium that is actively pumped out of the ascending limb and the water that passively flows out of the descending limb. First, we assume that the

capillaries pick up this sodium and water locally. That is, we do not allow for any longitudinal flow outside of the tubules and capillaries. Since we are considering a steady state model, it follows that the peritubular capillaries pick up water at the rate $f^1_{h20}(x)$ and sodium at the rate of f^*_{na} per unit length. Here we assume that the interstitial fluid is picked up by a process of filtration analogous to the process that occurs in the glomerular capillaries but running here in the opposite direction. In reverse filtration at the peritubular capillaries, we assume that the sodium is carried passively by the water at its local tissue concentration. This implies a relationship between the flux of sodium and the flow of water:

$$f^*_{na} = c(x)[f^1_{h20}(x)+f^3_{h20}(x)] \quad (10)$$

Solving (2) we get

$$q_1(x)c_1(x) = K; \text{ where } K = q_0c_0 \quad (A)$$

Solving (9), we get

$$q_3(x)c_3(x) = K1; \text{ where } k1 = q_3(0)c_3(0) \quad (B)$$

By the product rule it follows that equation (2) and (9) can be written in the form

$$-(dq_1/dx)\, c = (dc/dx)\, q_1 \quad (11)$$

$$-(dq_3/dx)c = (dc/dx)q_3 \quad (12)$$

Adding (11) + (12) we get

$$dc/dx\,(q_1+q_3) = -(dq_1/dx+dq_3/dx)\, c$$

But, $dq_1/dx = -f^1_{h20}$

$dq_3/dx = -f^3_{h20}$

Therefore

$$dc/dx(q_1+q_3) = -(f^1_{h20}+f^3_{h20})\, c$$

From eqn (10), the above eqn can be written as

$$dc/dx(q_1+q_3) = -f^*_{na} \quad (13)$$

substituting the expression for q1(x) and q3(x) from eqn (a) & (b) and simplifying eqn (13) we get

$dc/dx = (f^*_{na}\, c) / [q_1(0)+q_3(0)]\, c_0$;

which implies that

$c(x) = c0 \exp((f^*_{na}\, x)/[q_1(0)+q_3(0)]\, c_0)$;

and in particular that

$c(l) = c0 \exp((f^*_{na}\, l)/[q_1(0)+q_3(0)]\, c_0)$; (14)

Let $\alpha^* = (f^*_{na} l)/[q_1(0)+q_3(0)]\, c_0$

Therefore eqn (14) becomes

$c(l) = c_0 \exp(\alpha^*)$;

Solving equation (5)

$q_2(x)\, dc_2/dx = -f^*_{na}$ (15)

Where $q_2(x) = q_0 \exp(-\alpha^*)$;

therefore equation (15) becomes

$dc_2/dx = - f^*_{na} \exp(\alpha^*)/q_0$;

Which implies that

$c_2(x) = c_0 \exp(\alpha^*)[1-\alpha] + f^*_{na} \exp(\alpha^*)\, x/c_0$ (16)

Where $\alpha = (f^*_{na} l)/(q_0\, c_0) < 1$;

Note: $f^*_{na}\, l$ is the total rate at which sodium is actively pumped out through the walls of the ascending limb of Henle's loop, while $(q_0 c_0)$ is the rate at which the sodium enters the loop from the proximal tubule. Thus the ratio of these fluxes is always less than 1.

In particular equation (16) can be written as

$c_2(0) = c_0 \exp(\alpha^*)\, [1-\alpha]$ (17)

It is now easy to check that $\exp(\alpha^*)[1-\alpha] < 1$ when α is not equal to zero. Thus, $c_2(0) < c_0$ and the fluid leaving the top of the ascending limb is more dilute than blood plasma.

2.2.2 The Juxtaglomerular Apparatus and the renin angiotensin system

Near the top of the ascending limb of Henle's loop there is a specialized cluster of cells called the juxtaglomerular apparatus. These cells monitor the tubular fluid and secrete a hormone, renin, into the afferent arteriole just before it enters the glomerulus. Renin is converted in the blood to angiotensin, a potent vasoconstrictor, i.e., a substance that stimulates the constriction of blood vessels. Although the details are not certain, it is a plausible hypothesis that the cells of the juxtaglomerular apparatus monitor specifically the sodium concentration at the top of the ascending limb and they secrete enough renin to make glomerular filtration, and pheraps reabsorption from the proximal tubule, proceed at whatever rate is needed to achieve the target concentration at that site.

We will model this feedback mechanism in the simplest possible way: We assume that the inflow $q_1(0)$to the loop of Henle takes on whatever value is needed to satisfy the equation

$$c_2(0) = c^* \tag{18}$$

Where c^* is the target concentration sought by the juxtaglomerular apparatus. Thus we do not model the details of the renin angiotensin system. We assume it is working and we study its effects on the performance of the nephron.

substituting equation (17) in (18), we get

$$a = \exp(\alpha^*)[1-\alpha] \tag{19}$$

Where $a= c^*/c_0 <1$

Here a is regarded as known so equation for α and $q_1(0)$.

From equation (19) we can see that for each a such that $0<a<1$ the solution satisfies $0<\alpha<1$. Thus for small values of a, α is approximately equal to one. we can now rewrite the results with c* as parameter in the following way:

$q_1(0) = (f^*_{na}\, l)/c_0;$

$q_2(0) = q_1(0)\exp(-\alpha^*);$

These results summarize the behavior of the model of Henle's loop as controlled by the juxtaglomerular apparatus.

2.2.3 The Distal tubule and collecting Duct

We now come to the stage in the formation of urine where a decision has to be made whether to excrete a large volume of dilute urine or small volume of concentrated urine. The hormone that determines which possibility will occur is antidiuretic hormone(ADH). When ADH is absent, we assume that the distal tubule and the collecting ducts are simple conduits, impermeable to both salt and water. In these circumstances, the fluid that leaves the top of the ascending limb becomes urine without further modification.

When ADH is present, the situation is more complicated. The effect of ADH is to make the distal tubule and the collecting duct become permeable to water. We assume that this permeability is so great that the equilibrium is achieved at every stage. In the distal convoluted tubule then, enough water is withdrawn to make the sodium concentration equal to that of blood plasma. Then in the collecting duct enough water is withdrawn to equilibrate with c(x) at each x. The sodium flux is given by,

$-c^* q2(0) = c0\ q3(0)$

which can be simplified and written as

$$q3(0) = q0\ a \exp(-\alpha^*) \tag{20}$$

The flow at length l of the collecting duct is given by

$q3(l)\ c(l) = q3(0)\ c0$

which can be simplified and written as

$$q3(l) = q0\ a \exp(-2\alpha^*) \tag{21}$$

Thus, the ADH mechanism cannot be used to regulate the total sodium content of the body. It can be used to regulate the total sodium concentration of the blood plasma by excreting varying amounts of water in response to fluctuations in the plasma concentration of sodium.

CHAPTER 3

TWO NEPHRON MODEL (DILUTING MODE)

3.1 Introduction

According to the countercurrent hypothesis, the loops of Henle act as a countercurrent multiplier system, which creates the increase in osmotic concentration in the kidney tissue from cortex toward the papilla. The final concentration of the urine is supposed to be brought about by passive diffusion of water from the collecting ducts to the interstitium as the urine passes through regions of increasing osmotic pressure. All the experimental evidence obtained so far is consistent with the countercurrent hypothesis (2-6) and in principle there can no longer be much doubt about its validity. However, most mammalian kidneys consist of both long and short-looped nephrons. Whether these two types of nephrons operate in the same manner or if their functions differ is not known.

The model equations are derived from the conservation of mass for solute and fluid. Numerical soloution have been obtained using computer calculations.

3.2 Model

3.2.1 Assumptions

We shall construct a model of two nephrons beginning with the most interesting part of the system, the loop of Henle (see fig(1)). The descending limb of the loop is designated tube 1, the ascending limb as tube 2 and the collecting duct as tube 3. The sodium concentrations and water flows in the tubules are written $C_i(x)$ and $Q_i(x)$, respectively, where i=1,2,3. The external sodium concentration is denoted by c(x). by our sign conventions, the flow is positive in the descending limb and negative in the ascending limb, since x increases downward.

The physiological assumptions of nephron A are:

1.We assume that the walls of the descending limb are permeable to water but not to sodium. This is a simplification: The walls are also permeable to sodium, but this is not an essential feature of the operation of Henle's loop, and we leave it out. Moreover, we assume that the water permeability is so large that the water flux makes the internal and external sodium concentrations equal. This gives the equations

$$dq_{1A}/dx+f^{1A}h20(x)=0 \quad (1)$$

$$(d/dx)(q_{1A}c_{1A})=0 \quad (2)$$

$$c_1(xa)=c(x) \quad (3)$$

2.We assume that sodium is pumped out of the ascending limb at a fixed rate f^{*A}_{na} per unit length. We also assume that the ascending limb is impermeable to water. This gives

$$dq_{2A}/dx=0 \quad (4)$$

$$(d/dx)(q_{2A}c_{2A})+f^{*A}_{na} \quad (5)$$

3.At the turn of Henle's loop(x=la) we assume that all of the salt and water leaving the descending limb enter the ascending limb. This gives the boundary conditions

$$c_1(L_A)=c_2(L_A) \quad (6)$$

$$q_1(L_A)=-q_2(L_A) \quad (7)$$

The physiological assumptions of nephron B are:

1.We assume that the walls of the descending limb are permeable to water but not to sodium. This is a simplification: The walls are also permeable to sodium, but this is not an essential feature of the operation of Henle's loop, and we leave it out. Moreover, we assume that the water permeability is so large that the water flux makes the internal and external sodium concentrations equal. This gives the equations

$$dq_{1B}/dx+f^{1B}h20(x)=0 \quad (8)$$

$(d/dx)(q_{1B}c_{1B})=0$ (9)

$c_1(xb)=c(x)$ (10)

2.We assume that sodium is pumped out of the ascending limb at a fixed rate f^{*B}_{na} per unit length. We also assume that the ascending limb is impermeable to water. This gives

$dq_{2B}/dx=0$ (11)

$(d/dx)(q_{2B}c_{2B})+f^{*B}_{na}$ (12)

3.At the turn of Henle's loop(x=lb) we assume that all of the salt and water leaving the descending limb enter the ascending limb. This gives the boundary conditions $c_1(L_B)=c_2(L_B)$ (13)

$q_1(L_B)=-q_2(L_B)$ (14)

4.Finally, we need an assumption about the peritubular capillaries, which pick up the sodium that is actively pumped out of the ascending limb and the water that passively flows out of the descending limb. First, we assume that the capillaries pick up this sodium and water locally. That is, we do not allow for any longitudinal flow outside of the tubules and capillaries. Since we are considering a steady state model, it follows that the peritubular capillaries pick up water at the rate $f^1_{h20}(x)$ and sodium at the rate of f^*_{na} per unit length from the two nephrons. Here we assume that the interstitial fluid is picked up be a process of filtration analogous to the process that occurs in the glomerular capillaries but running here in the opposite direction. In reverse filtration at the peritubular capillaries, we assume that the sodium is carried passively by the water at its local tissue concentration. This implies a relationship between the flux of sodium and the flow of water:

$f^{*B}_{na}+f^{*A}_{na}=c(x)[f^{1A}_{h20}(x)+f^{1B}_{h20}(x)]$ (15)

in the interval $0 < x < la$ &

$f^{*B}_{na}= c(x)[f^{1B}_{h20}(x)]$ (16)

in the interval la < x < lb .

3.2.2 Soloution in the Cortical region

Descending limb of nephron A and B:solving (2) we get

$q_{1A}(x)c_1(xa) = K$; where $K = q_{A0}c_0$ (A)

Solving (9) we get

$q_{1B}(x)c_1(xb) = K$; where $K = q_{B0}c_0$ (B)

By the product rule it follows that equation (2) & (9) can be written in the form

$- dq_{1A}/dx\ c = dc/dx\ q_{1A}$ (17)

$- dq_{1B}/dx\ c = dc/dx\ q_{1B}$ (18)

Adding (17) + (18) we get

$dc/dx\ (q_{1A}+q_{1B}) = - (dq_{1A}/dx+dq1_B/dx)\ c$

But, $dq_{1A}/dx = - f^{1A}_{h20}$

$dq_{1B}/dx = - f^{1B}_{h20}$

Therefore

$dc/dx(q_{1A}+q_{1B}) = - (f^{1A}_{h20}+f^{1B}_{h20})\ c$

From eqn (15), the above eqn can be written as

$dc/dx(q_{1A}+q_{1B}) = - (f^{*A}_{na}+f^{*B}_{na})$ (19)

substituting the expression for q1(xa),q1(xb) and from eqn (A) & (B) and simplifying eqn (19) we get

$dc/dx = [f^{*A}_{na} + f^{*B}_{na})\ c]/[q_{1A}(0)+q_{1B}(0)]\ c_0$;

which implies that

$c(xa)=c_0\exp(f^{*A}_{na}+f^{*B}_{na})xa)/[q_{1A}(0)+q_{1B}(0)]\ c_0$;

and in particular that

$c(la)=c_0\exp[(f^{*A}_{na}+f^{*B}_{na})la)]/[q_1(0)+q_{1B}(0)]\ c_0$; (20)

Let $\alpha' = (f^{*A}_{na} +f^{*B}_{na})\ la)/[q_1(0)+q_{1B}(0)]\ c_0$ Therefore eqn (20) becomes

$c(la) = c_0\ \exp(\alpha')$;

Ascending limb of nephron A: Solving equation (5)

$$q_2(xa)\, dc_{2A}/dx = -f^{*A}_{na} \qquad (21)$$

Where $q_2(xa) = q_{A0} \exp(-\alpha')$; therefore equation (21) becomes

$$dc_{2A}/dx = - f^{*A}_{na} \exp(\alpha')/q_{A0};$$

Which implies that

$$c_2(xa) = c_0 \exp(\alpha')[1-\alpha A] + f^{*A}_{na} \exp(\alpha')xa/q_{A0} \qquad (22)$$

Where $\alpha A = (f^{*A}_{na}\, la)/(q_{A0}\, c_0) < 1;$

Note: $f^{*}_{na}\, l$ is the total rate at which sodium is actively pumped out through the walls of the ascending limb of Henle's loop, while $q_0\ c_0$ is the rate at which the sodium enters the loop from the proximal tubule. Thus the ratio of these fluxes is always less than 1.

In particular equation (22) can be written as

$$c_{2A}(0) = c_0 \exp(\alpha')*[1-\alpha A] \qquad (23)$$

It is now easy to check that $\exp(\alpha')[1-\alpha A] < 1$ when αA is not equal to zero. Thus, $c_{2A}(0) < c_0$ and the fluid leaving the top of the ascending limb is more dilute than blood plasma.

3.2.3 Soloution in the Medullary region

Descending limb of nephron A and nephron B:In this region the nephron A is absent and only nephron B is present. So

Solving (9) we get

$$q_{1B}(x)c_1(xb) = K; \text{ where } K = q_{B0}c_0 \qquad (B)$$

By the product rule it follows that equation (9) can be written in the form

$$- dq_{1B}/dx\, c = dc/dx\, q_{1B} \qquad (24)$$

But

$$dq_{1B}/dx = - f^{1B}_{h20}$$

Therefore

$dc/dx(q_{1B}) = - (f^{1B}_{h20})\ c$

From eqn (16), the above eqn can be written as

$dc/dx(q_{1B}) = - (f^{*B}_{na})$ (25)

substituting the expression for q1(xb) from eqn (B)and simplifying eqn (25) we get

$dc/dx = [\ f^{*B}_{na}\ c]/[q_{1B}(0)]\ c_0;$

which implies that

$c(xb)=c(la)\exp[f^{*B}_{na}(x-la)]/[(q_{1B}(la))\ c(la)];$

and in particular that

$c(lb)=c_0\exp[(\alpha')+(f^{*B}_{na}(lb-la))/(q_{1B}(0))]c_0$ (26)

Let $\alpha B = (f^{*B}_{na}lb)/(q_{1B}(0)c_0)$ Therefore eqn (26) becomes

$c(lb) = c_0\ \exp[\alpha'+(\alpha Bln)];$

where ln = (lb-la)/lb;

Ascending limb of nephron B: Solving equation (12)

$q_2(xb)\ dc_{2B}/dx = -f^{*AB}_{na}$ (27)

Where $q_2(xb) = q_{B0} * \exp[-\alpha'-(\alpha Bln)]$; therefore equation (27) becomes

$dc_{2B}/dx = - f^{*B}_{na}\ \exp[\alpha'+(\alpha Bln)]/q_{B0};$

Which implies that

$c_2(xB)=l+m;$ (28)

where

$l=c_0\exp[\alpha'+(\alpha Bln)][1-\alpha B]$

$m=f^{*B}_{na}\ \exp[\alpha'+\alpha Bln)])xb/q_{B0}$

$\alpha_B= (f^{*B}_{na}\ lb)/(q_{B0}\ c_0) < 1;$

Note: $f^{*}_{na}\ l$ is the total rate at which sodium is actively pumped out through the walls of the ascending limb of Henle's loop, while $q_0\ c_0$ is the rate at which the sodium enters the loop from the proximal tubule. Thus the ratio of these fluxes is always less than 1.

In particular equation (28) can be written as

$$c_{2B}(0) = c_0 \exp[\alpha' + (\alpha B \ln)] [1-\alpha B] \quad (29)$$

It is now easy to check that $\exp[a' + aB' \ln)][1-aB] < 1$ when αB is not equal to zero. Thus, $c_{2B}(0) < c_0$ and the fluid leaving the top of the ascending limb is more dilute than the blood plasma.

3.2.4 The Juxtaglomerular Apparatus and the renin angiotensin system

Near the top of the ascending limb of Henle's loop there is a specialized cluster of cells called the juxtaglomerular apparatus. These cells monitor the tubular fluid and secrete a hormone, renin, into the afferent arteriole just before it enters the glomerulus. Renin is converted in the blood to angiotensin, a potent vasoconstrictor, i.e., a substance that stimulates the constriction of blood vessels. Although the details are not certain, it is a plausible hypothesis that the cells of the juxtaglomerular apparatus monitor specifically the sodium concentration at the top of the ascending limb and they secrete enough renin to make glomerular filtration, and perhaps reabsorption from the proximal tubule, proceed at whatever rate is needed to achieve the target concentration at that site.

We will model this feedback mechanism in the simplest possible way: We assume that the inflow $q_{1A}(0)$ and $q_{1B}(0)$ to nephron A and nephron B takes on whatever value is needed to satisfy the equation

$$c_{2A}(0) = c^*_A \quad (30)$$

$$c_{2B}(0) = c^*_B \quad (31)$$

Where c^*_A and c^*_B are the target concentration sought by the juxtaglomerular apparatus. Thus we do not model the details of the renin angiotensin system. We assume it is working and we study its effects on the performance of the nephron.

substituting equation (30) in (31), we get

$$aa = \exp(\alpha')[1-\alpha A] \quad (32)$$

$ab = \exp[\alpha'+(\alpha B ln)][1-\alpha B]$ (33)

Where $aa= c^*_A/c_0 <1$

$ab= c^*_B/c_0 <1$

Here aa and ab are regarded as known, so the equation for α' and αB can be solved,hence $q_{1A}(0)$,$q_{1B}(0)$ can also be solved.

From equation (32) and (33) we can see that for each aa and ab such that $0<aa,ab<1$ the solution satisfies $0<\alpha A,\alpha B<1$. Thus for small values of aa and ab, αA and αB are approximately equal to one. We can now rewrite the results with c*A & c*B as parameter in the following way:

$q_{1A}(0) = (f^{*A}_{na} la)/c_0$;

$q_{2A}(0) = q_{1A}(0) \exp(-\alpha')$;

$q_{1B}(0) = (f^{*B}_{na} lb)/c_0$;

$q_{2B}(0) = q_{1B}(0) \exp[-\alpha'-(\alpha B ln)]$;

These results summarize the behavior of the model of Henle's loop as controlled by the juxtaglomerular apparatus.

4.2.5 The Distal tubule and collecting Duct

We now come to the stage in the formation of urine where a decision has to be made whether to excrete a large volume of dilute urine or small volume of concentrated urine. The hormone that determines which possibility will occur is antidiuretic hormone(ADH). When ADH is absent, we assume that the distal tubule and the collecting ducts are simple conduits, impermeable to both salt and water. In these circumstances, the fluid that leaves the top of the ascending limb becomes urine without further modification.

When ADH is present, The situation is more complicated. The effect of ADH is to make the distal tubule and the collecting duct become permeable to water. We assume that this permeability is so great that the equilibrium is achieved at every

stage. In the distal convoluted tubule then, enough water is withdrawn to make the sodium concentration equal to that of blood plasma. Then in the collecting duct enough water is withdrawn to equilibrate with c(x) at each x.

The sodium flux is given by,

$q_{2A}(0)\, c^*_A = c_0\, q_{DA}$ for nephron A and

$q_{2B}(0)\, C^*_B = c_0\, q_{DB}$ for nephron B.

which can be written as

$qDA = q_{2A}(0)\, c^*_A / c_0;$

$qDB = q_{2B}(0)\, c^*_B / c_0;$

Therefore $q_3(0)$ can be written as

$q_3(0) = q_{DA} + q_{DB}$

which implies

$$q_3(0)=[q_{A0}aaexp(-\alpha')]+[q_{B0}abexp\{\alpha'+(\alpha Bln)\}] \quad (34)$$

The flow at length la of the collecting duct is given by

$q3(la)\, c(la) = q3(0)\, c0$

which can be simplified and written as

$$q_3(la)=[q_{A0}aaexp(-2\alpha')]+[q_{B0}abexp\{-2\alpha'-(\alpha Bln)\}] \quad (35)$$

The flow at length lb of the collecting duct is given by

$q3(lb)\, c(lb) = q3(la)\, c(la)$

which can be simplified and written as

$$q_3(lb)=[q_{A0}aaexp(-2\alpha'-\{2\alpha Bln\})]+[q_{B0}abexp\{-2\alpha'2(\alpha Bln)\}] \quad (36)$$

Thus, the ADH mechanism cannot be used to regulate the total sodium content of the body. It can be used to regulate the total sodium concentration of the blood plasma by excreting varying amounts of water in response to fluctuations in the plasma concentration of sodium.

CHAPTER 4

TWO NEPHRON MODEL (CONCENTRATING MODE)

4.1 Introduction

From the single nephron model described in chapter 1, one can note that there is a substantial osmolality gradient, not only in the outer medulla, but also in the inner medulla. The gradient appears equally steep in both medullary regions. Similar results have been obtained in other animal species [2,3]. Significantly, measurements in the human kidney by Berlyne and Hoerni have demonstrated that such gradients are responsible for the concentration of urine in humans, as in animals.

In this model, each nephron obeys the assumption described for the two nephron model in chapter 2 except, the assumption 5 is modified. The model equations are derived from the conservation of mass for solute and fluid. Numerical solution have been obtained using computer calculations.

3.2 Model

3.2.1 Assumptions

We shall construct a model of two nephrons beginning with the most interesting part of the system, the loop of Henle (see fig(1)). The descending limb of the loop is designated tube 1, the ascending limb as tube 2 and the collecting duct as tube 3. The sodium concentrations and water flows in the tubules are written $C_i(x)$ and $Q_i(x)$, respectively, where i=1,2,3. The external sodium concentration is denoted by c(x). By our sign conventions, the flow is positive in the descending limb and negative in the ascending limb, since x increases downward.

The physiological assumptions of nephron A are:

1.We assume that the walls of the descending limb are permeable to water but not to sodium. This is a simplification: The walls are

also permeable to sodium, but this is not an essential feature of the operation of Henle's loop, and we leave it out. Moreover, we assume that the water permeability is so large that the water flux makes the internal and external sodium concentrations equal. This gives the equations

$dq_{1A}/dx+f^{1A}h20(x)=0$ (1)

$(d/dx)(q_{1A}c_{1A})=0$ (2)

$c_1(xa)=c(x)$ (3)

2.We assume that sodium is pumped out of the ascending limb at a fixed rate f^{*A}_{na} per unit length. We also assume that the ascending limb is impermeable to water. This gives

$dq_{2A}/dx=0$ (4)

$(d/dx)(q_{2A}c_{2A})+f^{*A}_{na}$ (5)

3.At the turn of Henle's loop(x=la) we assume that all of the salt and water leaving the descending limb enter the ascending limb. This gives the boundary conditions

$c_1(L_A)=c_2(L_A)$ (6)

$q_1(L_A)=-q_2(L_A)$ (7)

The physiological assumptions of nephron B are:

1.We assume that the walls of the descending limb are permeable to water but not to sodium. This is a simplification: The walls are also permeable to sodium, but this is not an essential feature of the operation of Henle's loop, and we leave it out. Moreover, we assume that the water permeability is so large that the water flux makes the internal and external sodium concentrations equal. This gives the equations

$dq_{1B}/dx+f^{1B}h20(x)=0$ (8)

$(d/dx)(q_{1B}c_{1B})=0$ (9)

$c_1(xb)=c(x)$ (10)

2.We assume that sodium is pumped out of the ascending limb at a fixed rate f^{*B}_{na} per unit length. We also assume that the ascending limb is impermeable to water. This gives

$$dq_{2B}/dx=0 \tag{11}$$

$$(d/dx)(q_{2B}c_{2B})+f^{*B}_{na} \tag{12}$$

3.At the turn of Henle's loop(x=lb) we assume that all of the salt and water leaving the descending limb enter the ascending limb. This gives the boundary conditions

$$c_1(L_B)=c_2(L_B) \tag{13}$$

$$q_1(L_B)=-q_2(L_B) \tag{14}$$

4.At the collecting duct, we assume that the rate at which the water comes out when ADH is present is f^3_{h20}. This give the equations

$$dq_3/dx = -f^3_{h20} \tag{15}$$

$$d(q_3c_3)/dx = 0 \tag{16}$$

5.Finally, we need an assumption about the peritubular capillaries, which pick up the sodium that is actively pumped out of the ascending limb and the water that passively flows out of the descending limb. First, we assume that the capillaries pick up this sodium and water locally. That is, we do not allow for any longitudinal flow outside of the tubules and capillaries. Since we are considering a steady state model, it follows that the peritubular capillaries pick up water at the rate $f^1_{h20}(x)$ and sodium at the rate of f^*_{na} per unit length from the two nephrons. Here we assume that the interstitial fluid is picked up be a process of filtration analogous to the process that occurs in the glomerular capillaries but running here in the opposite direction. In reverse filtration at the peritubular capillaries, we assume that the sodium is carried passively by the water at its local tissue concentration. This implies a relationship between the flux of sodium and the flow of water:

$f^{*B}_{na}+f^{*A}_{na}=c(x)[f^{1A}_{h20}(x)+f^{1B}_{h20}(x)+f^{3}_{h20}(x)]$ (17)

in the interval $0 < x < la$ &

$f^{*B}_{na}= c(x)[f^{1B}_{h20}(x)f^{3}_{h20}(x)]$ (18)

in the interval $la_{=} < x < lb$

3.2.2 Solution in the Cortical region

Descending limb of nephronA and nephronB :solving (2) we get

$q_{1A}(x)\ c_1(xa) = K$; where $K = q_{A0}c_0$ (A)

Solving (9) we get

$q_{1B}(x)\ c_1(xb) = K$; where $K = q_{B0}c_0$ (B)

Solving (16) we get

$q_3(x)\ c_3(x) = K$; where $K = q_{30}c_0$ (C)

By the product rule it follows that equation (2),(9)and (16) can be written in the form

$- dq_{1A}/dx\ c = dc/dx\ q_{1A}$ (19)

$- dq_{1B}/dx\ c = dc/dx\ q_{1B}$ (20)

$- dq_3/dx\ c = dc/dx\ q_3$ (21)

Adding (19) + (20) + (21) we get

$dc/dx\ (q_{1A}+q_{1B}+q_3) = - (dq_{1A}/dx+dq1_B/dx+dq_3/dx)\ c$

But, $dq_{1A}/dx = - f^{1A}_{h20}$

$dq_{1B}/dx = - f^{1B}_{h20}$

$dq_3/dx = - f^{3}_{h20}$

Therefore

$dc/dx(q_{1A}+q_{1B}+q_3) = - (f^{1A}_{h20}+f^{1B}_{h20}+f^{3}_{h20})\ c$

From eqn (17), the above eqn can be written as

$dc/dx(q_{1A}+q_{1B}+q_3) = - (f^{*A}_{na}+f^{*B}_{na})$ (22)

substituting the expression for q1(xa),q1(xb) and q3(x) from eqn (A) (B) & (C) and simplifying eqn (22) we get

$dc/dx = [f^{*A}_{na} + f^{*B}_{na})\ c]/[q_{1A}(0)+q_{1B}(0)+q_3(0)]\ c_0;$

which implies that

$c(xa)=c_0\ \exp(f^{*A}_{na}+f^{*B}_{na})*xa)/[q_{1A}(0)+q_{1B}(0)+q_3(0)]\ c_0;$

and in particular that

$c(la)=c_0\ \exp[(f^{*A}_{na}+f^{*B}_{na})\ la)]/[q_1(0)+q_{1B}(0)+q_3(0)]\ c_0;$ (23)

Let $\alpha' = (f^{*A}_{na} + f^{*B}_{na})\ la)/[q_1(0)+q_{1B}(0)+q_3(0)]c_0$ Therefore eqn (23) becomes

$c(la) = c_0\ \exp(\alpha');$

Ascending limb of nephron A and B:Solving equation (5)

$q_2(xa)\ dc_{2A}/dx = -f^{*A}_{na}$ (24)

Where $q_2(xa) = q_{A0}\ \exp(-\alpha')$; therefore equation (24) becomes

$dc_{2A}/dx = -\ f^{*A}_{na}\ \exp(\alpha')/q_{A0};$

Which implies that

$c_2(xa) = c_0\exp(\alpha')[1-\alpha A] + f^{*A}_{na}\ \exp(\alpha')*xa/q_{A0}$ (25)

Where $\alpha A = (f^{*A}_{na}\ la)/(q_{A0}\ c_0) < 1;$

Note: $f^{*}_{na}\ l$ is the total rate at which sodium is actively pumped out through the walls of the ascending limb of Henle's loop, while $q_0\ c_0$ is the rate at which the sodium enters the loop from the proximal tubule. Thus the ratio of these fluxes is always less than 1.

In particular equation (25) can be written as

$c_{2A}(0) = c_0\ \exp(\alpha')\ [1-\alpha A]$ (26)

It is now easy to check that $\exp(\alpha')[1-\alpha A] < 1$ when αA is not equal to zero. Thus, $c_{2A}(0) < c_0$ and the fluid leaving the top of the ascending limb is more dilute than blood plasma.

3.2.3 Solution in the Medullary region

Descending limb of nephron A and B:In this region the nephron A is absent and only nephron B is present. So Solving (9) we get

$q_{1B}(x)\, c_1(xb) = K$; where $K = q_{B0}c_0$ (B)

$q_3(x)\, c_3(x) = K$; where $K = q_{30}c_0$ (C)

By the product rule it follows that equation (9)and (16) can be written in the form

$-dq_{1B}/dx\ c = dc/dx\ q_{1B}$ (27)

$-dq_3/dx\ c = dc/dx\ q_3$ (28)

$dc/dx\,(q_{1B}+q_3) = -\,(dq1_B/dx+dq3/dx)\ c$

$dq_{1B}/dx = -\,f^{1B}_{h20}$

$dq_3/dx = -\,f^{3}_{h20}$

Therefore

$dc/dx(q_{1B}+q_3) = -\,(f^{1B}_{h20}+f^{3}_{h20}))\ c$

From eqn (16), the above eqn can be written as

$dc/dx(q_{1B}+q_3) = -\,(f^{*B}_{na})$ (29)

substituting the expression for q1(xb) and q3(x) from eqn (B) and simplifying eqn (29) we get

$dc/dx = [\, f^{*B}_{na}\, c]/[q_{1B}(0)+q_3(0)]\ c_0$;

which implies that

$c(xb)=c(la)\exp[f^{*B}_{na}*(x-la)]/[(q_{1B}(la)+q_3(la))\, c(la)]$;

and in particular that

$c(lb)=c_0\ \exp[(\alpha')+(f^{*}Bna(lb-la))/(q_{1B}(0)+q_3(0))]\ c_0$ (30)

Let $\alpha B' = f^{*B}_{na} * lb)/[q_{1B}(0)+q_3(0)] * c_0$ Therefore eqn (30) becomes

$c(lb) = c_0 * \exp[\alpha'+(\alpha B'*ln)]$;

where ln = (lb-la)/lb;

Ascending limb of nephron B: Solving equation (12)

$q_2(xb)\ dc_{2B}/dx = -f^{*AB}_{na}$ (31)

Where $q_2(xb) = q_{B0}\ \exp[-\alpha'-(\alpha B'*\ln)]$; therefore equation (31) becomes

$dc_{2B}/dx = -f^{*B}_{na}\ \exp[\alpha'+(\alpha B'*\ln)]/q_{B0}$;

Which implies that

$c_2(xb)=c_0\exp[\alpha'+(\alpha B'*\ln)][1-\alpha B]+f^{*B}_{na}* \exp[\alpha'+\alpha'*\ln)])*xb/q_{B0}$ (32)

Where $\alpha B = (f^{*B}_{na} * lb)/(q_{B0} * c_0) < 1$;

Note: $f^{*}_{na}\ l$ is the total rate at which sodium is actively pumped out through the walls of the ascending limb of Henle's loop, while $q_0\ c_0$ is the rate at which the sodium enters the loop from the proximal tubule. Thus the ratio of these fluxes is always less than 1.

In particular equation (32) can be written as

$c_{2B}(0) = c_0 \exp[\alpha'+(\alpha B'*\ln)]\ [1-\alpha B]$ (33)

It is now easy to check that $\exp[\alpha'+\alpha'*\ln)][1-\alpha B] < 1$ when αB is not equal to zero. Thus, $c_{2B}(0) < c_0$ and the fluid leaving the top of the ascending limb is more dilute than the blood plasma.

3.2.4 The Juxtaglomerular Apparatus and the renin angiotensin system

Near the top of the ascending limb of Henle's loop there is a specialized cluster of cells called the juxtaglomerular apparatus. These cells monitor the tubular fluid and secrete a hormone, renin, into the afferent arteriole just before it enters the glomerulus. Renin is converted in the blood to angiotensin, a potent vasoconstrictor, i.e., a substance that stimulates the constriction of blood vessels. Although the details are not certain, it is a plausible hypothesis that the cells of the juxtaglomerular apparatus monitor specifically the sodium concentration at the top of the ascending limb and they secrete enough renin to make glomerular filtration, and perhaps reabsorption from the proximal tubule, proceed at whatever rate is needed to achieve the target concentration at that site.

We will model this feedback mechanism in the simplest possible way: We assume that the inflow $q_{1A}(0)$ and $q_{1B}(0)$ to nephron A and nephron B takes on whatever value is needed to satisfy the equation

$$c_{2A}(0) = c^*_A \quad (34)$$

$$c_{2B}(0) = c^*_B \quad (35)$$

Where c^*_A and c^*_B are the target concentration sought by the juxtaglomerular apparatus. Thus we do not model the details of the renin angiotensin system. We assume it is working and we study its effects on the performance of the nephron. substituting equation (34) in (35), we get

$$aa = \exp(\alpha')[1-\alpha A] \quad (36)$$

$$ab = \exp[\alpha'+(\alpha B'*ln)][1-\alpha B] \quad (37)$$

Where $aa = c^*_A n_0 < 1$

$ab = c^*_B n_0 < 1$

Here aa and ab are regarded as known ,so the equation for α' and $\alpha B'$ can be solved,hence $q_{1A}(0)$,$q_{1B}(0)$ can also be solved.

From equation (36) and (37) we can see that for each aa and ab such that $0<aa,ab<1$ the solution satisfies $0<\alpha A,\alpha B<1$. Thus for small values of aa and ab, αA and αB are approximately equal to one. we can now rewrite the results with c*A & c*B as parameter in the following way:

$q_{1A}(0) = (f^{*A}_{na} * la)/c_0;$

$q_{2A}(0) = q_{1A}(0) * \exp(-\alpha');$

$q_{1B}(0) = (f^{*B}_{na} * lb)/c_0;$

$q_{2B}(0) = q_{1B}(0) * \exp[-\alpha'-(\alpha B'*ln)];$

These results summarize the behavior of the model of Henle's loop as controlled by the juxtaglomerular apparatus.

3.2.5 The Distal tubule and collecting Duct

We now come to the stage in the formation of urine where a decision has to be made whether to excrete a large volume of dilute urine or small volume of concentrated urine. The hormone that determines which possibility will occur is antidiuretic hormone(ADH). When ADH is absent, we assume that the distal tubule and the collecting ducts are simple conduits, impermeable to both salt and water. In these circumstances, the fluid that leaves the top of the ascending limb becomes urine without further modification.

When ADH is present, The situation is more complicated. The effect of ADH is to make the distal tubule and the collecting duct become permeable to water. We assume that this permeability is so great that the equilibrium is achieved at every stage. In the distal convoluted tubule then, enough water is withdrawn to make the sodium concentration equal to that of blood plasma. Then in the collecting duct enough water is withdrawn to equilibrate with c(x) at each x.

The sodium flux is given by,

$q_{2A}(0)\, c_A = c_0\, q_{DA}$ for nephron A and

$q_{2B}(0)\, C_B = c_0\, q_{DB}$ for nephron B.

which can be written as

$qDA = q_{2A}(0)\, c_A/c_0;$

$qDB = q_{2B}(0)\, c_B/c_0;$

Therefore $q_3(0)$ can be written as

$q_3(0) = q_{DA} + q_{DB}$

which implies

$$q_3(0)=[q_{A0}aaexp(-\alpha')]+[q_{B0}abexp\{\alpha'+(\alpha B'*ln)\}] \quad (38)$$

The flow at length la of the collecting duct is given by

$q3(la)\, c(la) = q3(0)\, c0$

which can be simplified and written as

$q_3(la)=[q_{A0}aaexp(-2\alpha')]+[q_{B0}abexp\{-2\alpha'-(\alpha B'ln)\}]$ (39)

The flow at length lb of the collecting duct is given by

q3(lb) c(lb) = q3(la) c(la)

which can be simplified and written as

$q_3(lb)=[q_{A0}aaexp(-2\alpha'-\{2\alpha B'ln\})]+[q_{B0}abexp\{-2\alpha'-2(\alpha B'*ln)\}]$ (40)

Thus, the ADH mechanism cannot be used to regulate the total sodium content of the body. It can be used to regulate the total sodium concentration of the blood plasma by excreting varying amounts of water in response to fluctuations in the plasma concentration of sodium.

CHAPTER 5

RESULTS

5.1 Introduction

The maximal concentration that a uniform countercurrent multiplier system can achieve is directly related to the length of the multiplier system. We should therefore expect the ability to concentrate the urine to be closely related to the length of the loops that can act as multiplier system. If only the outer zone of the medulla were active. a thick inner zone should not appreciably increase the concentrating ability. If on the other hand, the entire inner zone also acts as a multiplier system, one should expect the concentrating ability of the animal to be related to the combined thickness of the outer and inner zone of the medulla.

The present study was undertaken primarily to determine the length of short and long looped nephrons that work best in both the concentrating and the diluting modes. To simplify the analysis for the present discussion, we illustrate a short loop and a long loop nephron which represents the entire population of loops and a collecting duct which represents the entire population of collecting ducts.

The model equations are derived from the conservation of mass for solute and fluid. Numerical solution have been obtained using computer calculations.

5.2 Model

The model equations for the two population of nephrons are the following:

$$dq(\Sigma q^{ai})/dx+\Sigma f^{ai}{}_{1h20}(x)=0 \quad (1)$$

$$(d/dx)(\Sigma q^{ai}c)=0 \quad (2)$$

$$d(\Sigma q_2{}^{ai})/dx=0 \quad (3)$$

$$(d/dx)(\Sigma q_2{}^{ai}c_{2A})+\Sigma f^{*ai}{}_{na} \quad (4)$$

$d(\Sigma qbj)/dx+\Sigma f^{bj}{}_{1h20}(x)=0$ (5)

$(d/dx)(\Sigma q_1{}^{bj}c)=0$ (6)

$d\Sigma q_2{}^{bj}/dx=0$ (7)

$(d/dx)(\Sigma q_2{}^{bj}c_2)+\Sigma f^{*bj}{}_{na}=0$ (8)

Due to the following assumptions :

1.$q^{ai}{}_0 = q^a{}_0$ for all the i nephrons of type A

Therefore $\Sigma q^a i = N_A\, q^a{}_0$;

2.$q^{bj}{}_0 = q^b{}_0$ for all the j nephrons of type B

Therefore $\Sigma^{qbj} = N_B\, q^b{}_0$;

3.$f^{*a}i_{na} = F^{*A}$ for all the i nephrons of type A

Therefore $\Sigma f^{ai}{}_{na} = N_A\, F^{*a}$;

4.$f^{*bj}{}_{na} = F^{*B}$ for all the j nephrons of type B

Therefore $\Sigma f^{bj}{}_{na} = N_B\, F^{*b}$;

5.$f^{ai}{}_{1h20}= F^a{}_{1h20}$ for all the i nephrons of type A.

Therfore $\Sigma f^{ai}{}_{1h20} = N_A\, F^a{}_{1h20}$;

6.$f^{bj}{}_{1h20}= F^b{}_{1h20}$ for all the j nephrons of type B.

Therfore $\Sigma f^{bj}{}_{1h20} = N_B\, F^{bj}{}_{h20}$;

The above equations can be rewritten as

$dq(N_A q^{ai})/dx+N_A f^a{}_{1h20}(x)=0$ (1')

$(d/dx)(N_A q^a c)=0$ (2')

$d(N_A q_2{}^a)/dx=0$ (3')

$(d/dx)(N_A q_2{}^a c_{2A})+N_A f^{*a}{}_{na}$ (4')

$d(N_B qb)/dx+N_B f^b{}_{1h20}(x)=0$ (5')

$(d/dx)(N_B q_1{}^b c)=0$ (6')

$d(N_B q_2{}^b)/dx=0$ (7')

$(d/dx)(N_B q_2{}^b c_2)+N_B f^{*b}{}_{na}=0$ (8')

Solving these equations one can obtain :

$c(L_A) = c0 \exp(\alpha')$;

where $\alpha' = (N_A F^{*a} + N_B F^{*b}) LA / (N_A q_{a0} + N_B q_{b0} + Q_{30})$;

$c(L_b) = c0 \exp(\alpha_s')$

where $\alpha_s' = \alpha' + \alpha_b' ln$;

$\alpha b' = (N_B F^{*b} L_B) / (N_B q_{b0} + Q_{30})$;

$ln = (L_B - L_A) / L_B 0$;

$Q_{30} = NAaaq_{a0} \exp(-\alpha') + N_B abq_{b0} \exp(-\alpha_s')$;

$Q_{3(lb)} = \exp(-\alpha_s') Q_{30}$;

5.2.1 Evaluation of the model based on experimental evidence

The parameters used in our model and the experimental values of those are(for humans):

Cortical Thickness/Medullary Thickness = 0.34

Cortical Thickness = 6.0mm

Medullary Thickness = 17.647mm

c0 = 150meq/liter

Number of A-type nephrons = 1720,000

Number of B-type nephrons = 2800,00

Fraction of A-type nephrons = 0.86

Fraction of B-type nephrons = 0.14

Glomerular Filtration rate = 0.125liter/min

The filtrate handled by the kidnney = 0.041667liter/min

The concentration at the top of Ascending limb

of nephron A in the diluting mode = 45

The concentration at the top of Ascending limb

of nephron B in the diluting mode = 45

The concentration at the top of Ascending limb

of nephron A in the Concentrating mode = 10.2

The concentration at the top of Ascending limb

of nephron B in the concentrating mode = 10.2

The rate of soloute reabsorption from the ascending limb of nephrons are calculated the following way:

The percentage of short nephrons is 0.86 and that of long nephrons is 0.14 with a total of two million nephrons in the two kidneys. The load which the kidney handles is one third of the glomerular filtration rate which is equal to 0.041667meq/l. For the kidney to reabsorb most of the salt, the rabsorption capacity must match the salt load (i.e.) $F_* L_T$ = 1/3 GFR4 C0; from which we can calculate the sodium pump rate for the whole kidney.

F_* = (1/3 GFR c0)/L_T meq/mm-min;

= 4.0952e-07 meq/mm-min;

$F_{*A} = F_{*B} = F_*$;

We use Newton Raphson method to calculate the flows from the concentration at the top of the ascending limb. Therefore the initial guess for the for the flow handled by the A-type nephron and the B-type nephron is calculated to be

Q_{A0} = 0.013492318l/min;

Q_{B0} = 0.028174961/min;

It can be seen from the graph that the maximum flow in the diluting mode is achieved at LA = 4.32. It should be emphasized here that the maximum values for urine concentration obtained in our studies are of course approximate only. This may be because the model did not include the effect of urea and the effect of aldosterone. Moreover the variability between the individuals and the

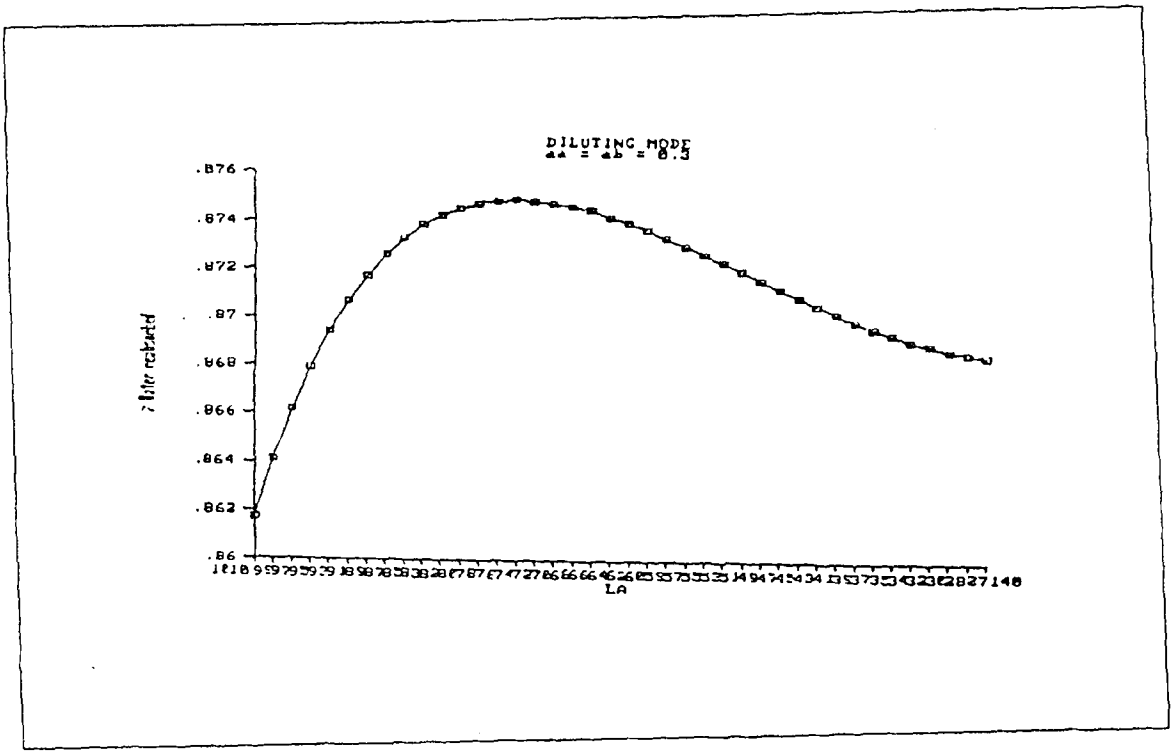


Figure 2 Evaluation based on experimental evidence (Diluting Mode)

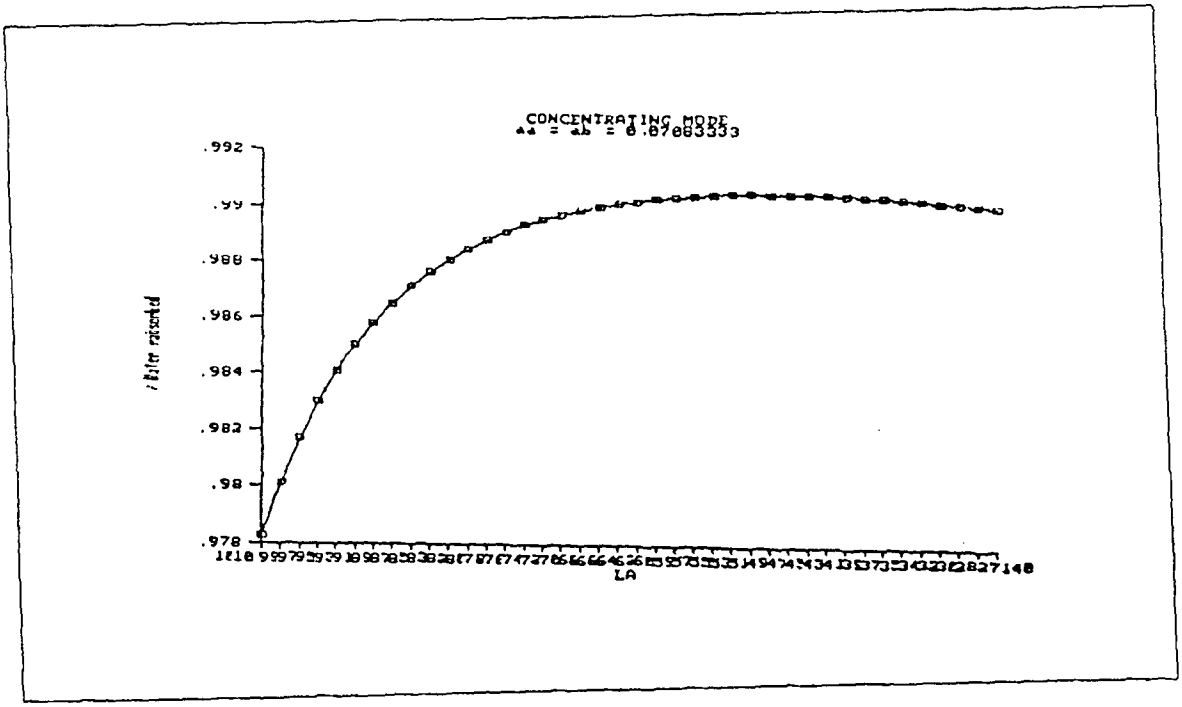


Figure 3 Evaluation based on experimental evidence (Concentrating Mode)

long term effects of diet and environment make it impossible to correlate any sharply defined upper limit for the concentrating ability with experimental values. There is rather good correlation between the percentage of water reabsorbed during the diluting mode and the experimental values. The length for the short nephron and long nephron for maximum flow was found to closely resemble the anatomical length of the short and long nephron. However in the concentrating mode, the length of nephron during the minimum flow conditions is not close to the experimental value (i.e.) during the concentrating mode, the length of nephron A required to minimize the collecting duct flow was 2.985 compared to the experimental value of 6.0mm.

The reasons for the models inability to closely resemble the experimental results are the following:

1.The experimental value of the ratio of cortical to medullary thickness represented the ratio cortical/(cortical+medullary) thickness in the model.

2.The effects of aldosterone was not considered in the model.

3.The influence of urea in the concentrating ability of nephrons was not included in the model.

5.2.2 Design Criteria for an Artificial Kidney

In this case our goal is to find the best parameters of our model to develop an artificial kidney(i.e.) a fixed population of nephrons with two different lengths should work at its best in both the concentrating mode and the diluting mode.

The parameters used in our model and the experimental values of those are(for humans):

Cortical Thickness/Medullary Thickness = 0.1399

Cortical Thickness = 4.16mm

Medullary Thickness = 29.31471mm

c0 = 150meq/liter

Number of A-type nephrons = 1720,000

Number of B-type nephrons = 2800,00

Fraction of A-type nephrons = 0.86

Fraction of B-type nephrons = 0.14

Glomerular Filtration rate = 0.125liter/min

The filtrate handled by the kidney = 0.041667liter/min

The concentration at the top of Ascending limb

of nephron A in the diluting mode = 10.8

The concentration at the top of Ascending limb

of nephron B in the diluting mode = 109.999

The concentration at the top of Ascending limb

of nephron A in the Concentrating mode = 10.2

The concentration at the top of Ascending limb

of nephron B in the concentrating mode = 90.2

The rate of solute reabsorption from the ascending limb of nephrons are calculated the following way:

The percentage of short nephrons is 0.86 and that of long nephrons is 0.14 with a total of two million nephrons in the two kidneys. The load which the kidney handles is one third of the glomerular filtration rate which is equal to 0.041667meq/l. For the kidney to reabsorb most of the salt, the rabsorption capacity must match the salt load (i.e.) $F_* L_T$ = 1/3 GFR4 C0; from which we can calculate the sodium pump rate for the whole kidney.

F_* = (1/3 GFR c0)/LT meq/mm-min;

= 1.425884943e-07 meq/mm-min;

$F_{*A} = F_{*B} = F_*$;

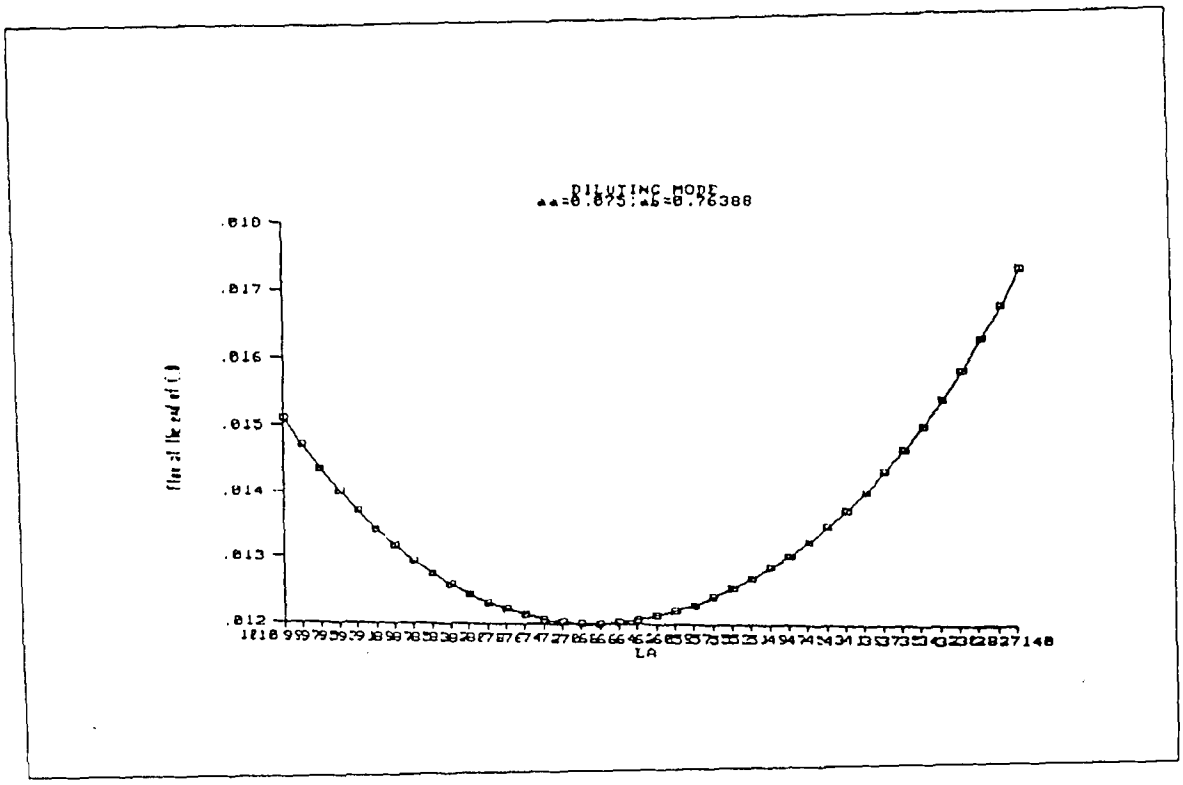


Figure 4 Design criteria for an Artificial Kidney (Diluting Mode)

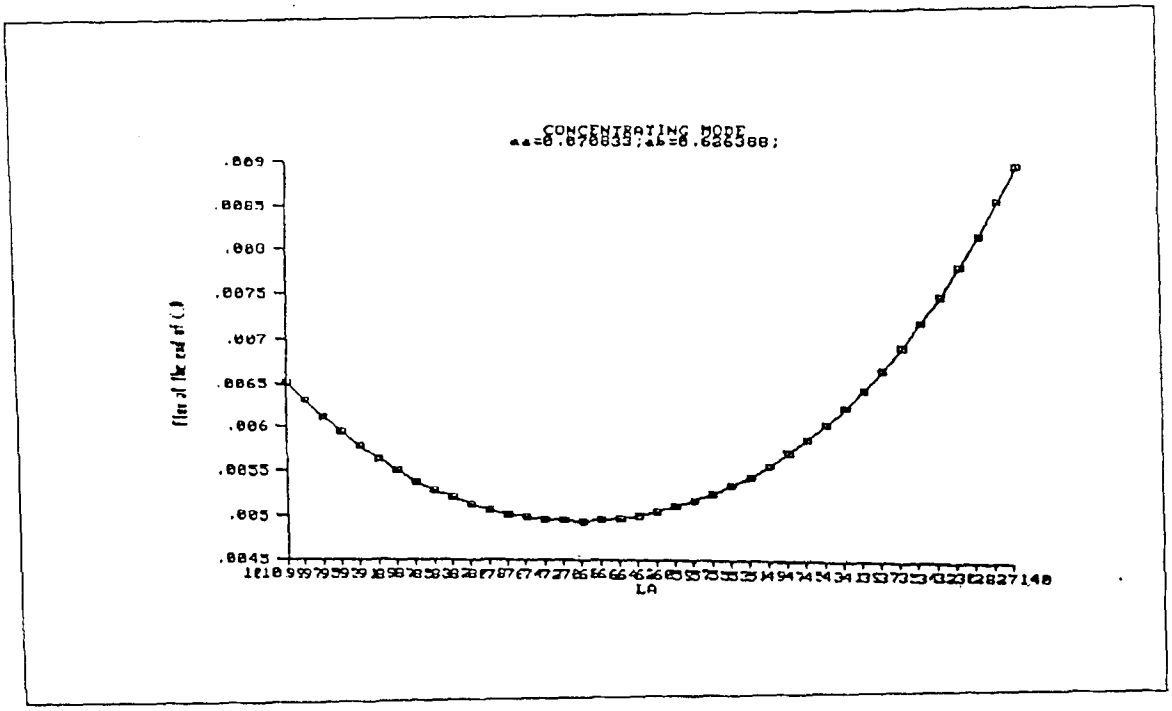


Figure 5 Design criteria for an Artificial Kidney (Concentrating Mode)

We use Newton Raphson method to calculate the flows from the concentration at the top of the ascending limb. Therefore the initial guess for the for the flow handled by the A-type nephron and the B-type nephron is calculated to be

Q_{A0} = 6.984578569e-03l/min;

Q_{B0} = 8.127659021e-03l/min;

From the graphs it can be seen that there is maximum collecting duct flow during the diluting mode and

minimum collecting duct flow during the concentrating mode.It should be noted that the percentage of water reabsorbed in the diluting mode and the concentrating mode are not equal to the experimental results of the real kidney. However this Artificial kidney is designed to work at approximately 77% reabsorption of water in diluting mode and approximately 90% reabsorption of water in the concentrating mode for the above parameters.

CHAPTER 6

CONCLUSIONS

6.1 Discussion

While Peskin's single nephron model can concentrate only upto a factor of *e*, the two nephron model exhibits a cascade effect that permits concentrations consistent with experimental measurements: solute reabsorbed from the ascending limbs of short-looped nephron helps concentrate fluid in the descending limb of long-looped nephron. This effect is particularly transparent 1n chapter 2, 3, & 5, where in chapter 5 a specific distribution of short loops are able to concentrate upto nearly a factor of *e* at the turns of their loops, because the damping effect of the few long loop is small. The long loops are able to concentrate beyond *e* in the region where they extend beyond the short loops.

In kidneys with exclusively short-looped nephrons as well as in those with both types of nephrons, and those with long-looped nephrons only, the sodium concentration showed an increase to about the same value in the zone corresponding to the outer zone of medulla. Thus, it appears that both types of loops function in essentially the same manner. It is quite evident that there is a close correlation between relative thickness of medulla and the kidney's ability to concentrate the urine.

All these models that have been developed have been used to study dynamic phenomena pertinent to tubuloglomerular feedback. In the models, small increases in nephron fluid load induce large relative increases in the salt concentration in cortical thick ascending limb at the macula densa.

We believe that the spectrum of essential hypertension embodies varying proportions of a difference in the delicate interaction between renin secretion and sodium balance. However, a situation could also exist in which there is high plasma renin level, generated from a smaller fractional population of ischemic

nephrons causing the same general effect. Any loss of nephrons would further impair adaptive sodium excretion and would be likely to amplify the hypertension.

We also believe that the system superstructure which leads to the algorithms is surely not unique to kidney modelling. Indeed, the analysis of most large scale engineering and biological systems involves detailed models of individual components which are somehow connected to form a whole functioning unit.

We close by noting that the models explained here were still not quantitatively satisfactory, possibly because of the following reasons: 1. The experimental values of the ratio of cortical to medullary thickness is represenred as the ratio of cortical to cortical plus medullary thickness in the model. 2. The effects of aldosterone were not considered in the model. 3. The influence of urea in the concentrating ability of nephrons was not included in this model. 4. Or because some important aspects of concentrating mechanism has been overlooked. Despite the simplifying assumptions and the limitations of the models presented here, it is believed that they make a strong case for the importance of nephron distribution in the urine concentrating mechanism and illustrates well the problem involved in attempting to describe accurately the function of an organ like kidney.

6.2 Future research

There are numerous directions in which this model of the whole kidney can be extended. The author interprets these findings as indicative of the presence of a potent active sodium-transport system in the ascending limb of henle. On the other hand, similar sodium-transport characteristics have not been described separately in the ascending limb as thin and thick ascending limbs. Direct micropuncture evidence is now available that provides strong support for

existence of active sodium-transport in the ascending thin limb. While the studies provide qualitative information regarding the presence of active sodium transport in the ascending thin limb, they do not permit any quantitative assessment of the capabilities of the pump.

The model can be modified to include the experimental ratio of cortical thickness to medullary thickness which could increase the maximum concentrating ability of the long nephron.

Including the effects of aldosterone, urea, and increased tubular load would help in providing answers for the high blood pressure.

The assumption of single collecting duct can be relaxed and the model can be modified to represent a specific number of collecting ducts starting at different levels of the cortex and medulla.

Another proposal that has not been discussed is pressure-driven water transport out of the vasrecta could cause a single effect for counter current multiplication.

Finally in some cases such as renin-angiotensin system, are well characterized whereas other systems such as renomedullary vasodepressor system are not well defined at present. Work over the next decade will, it is hoped, be directed at determining how the above mentioned characteristics will influence the concentrating mechanism.

APPENDIX

PROGRAM FOR TWO NEPHRON MODEL (DIRECT METHOD)

```
#include <stdio.h>
#include <math.h>


double xa,xb,cxa,cxb,cla,clb,c2xa,c2a0,c2xb,c2b0;
double fstara=4.359e-04,la=3.0,fstarb=1.339e-03,lb=30.0;
double aa,ab,c0,ln;
double alphaa,alphab,alphapri,albpri;
double k,k1,k2,k3,qa0,qb0,q30;
int n;


main()
{
        printf(" model#1 is 2-nephron model assuming the water
        comming out of \n");
        printf(" the collecting duct is negligible compared to
        the water comming \n");
        printf(" out of descending limb of the nephrons.\n
        \n");


        printf(" model#2 is 2-nephron model assuming the water
        comming out of \n");
        printf("the collectingduct isnot negligible compared to
        the water comming \n");
        printf(" out of descending limb of the nephrons.
        \n\n");


        printf("Press 1 to choose model #1 or press 2 for
        model#2 \n");
        scanf("%d",&n);

        printf("Enter the value of xa\n");
        scanf("%G",&xa);
        printf("Enter the value of xb\n");
        scanf("%G",&xb);
        printf("Enter the value of c0\n");
        scanf("%G",&c0);
        printf("Enter the value of qa0\n");
        scanf("%G",&qa0);
        printf("Enter the value of qb0\n");
        scanf("%G",&qb0);

        k1 = (fstara*la+fstarb*la)/c0;
        k = (fstara*la+fstarb*lb)/c0;
        k2 = (fstarb*lb)/c0;
```

```
        printf("k2 = %g\n", k2);
        k3 = (fstara*la)/c0;
        printf("k3 = %g\n", k3);
        if( n==1)
        {q30=0;
        }
        else
                q30= qa0+qb0-k;
        alphapri = k1/(qa0+qb0+q30);
        printf("alphapri = %g\n", alphapri);
        albpri= k2/(qb0+q30);
        printf("albpri = %g\n", albpri);
        alphaa= k3/qa0;
        alphab= k2/qb0;
        ln = (lb-la)/lb;
        if (xb < la )
        {       cxa= c0*exp((alphapri*xa)/la);
                cla= c0*exp(alphapri);
                cxb= c0*exp((alphapri*xb)/la);
                clb= cla;
        }
        else
        {       cxa= c0*exp((alphapri*xa)/la);
                cla= c0*exp(alphapri);
                cxb= cla*exp((albpri*(xb-la))/lb);
                clb= cla*exp(albpri*ln);
        }
        c2xa= (c0*exp(alphapri)*(1.0
        alphaa))+((fstara*exp(alphapri)*xa)/qa0);
        c2xb= (c0*exp(alphapri+(albpri*ln))*(1.0-alphab)) + ((fstarb*
        exp(alphapri+(albpri*ln))*xb)/qb0);
        c2a0= (c0*exp(alphapri)*(1.0-alphaa));
        c2b0= (c0*exp(alphapri+(albpri*ln))*(1.0-alphab));
        aa = c2a0/c0;
        ab = c2b0/c0;
        printf("q30 = %g\n", q30);
        printf("alphapri = %g\n", alphapri);
        printf("albpri = %g\n", albpri);
        printf("alphaa = %g\n", alphaa);
        printf("alphab = %g\n", alphab);
        printf("cxa = %g\n", cxa);
        printf("cxb = %g\n", cxb);
        printf("cla = %g\n", cla);
        printf("clb = %g\n", clb);
        printf("c2xa = %g\n", c2xa);
        printf("c2xb = %g\n", c2xb);
        printf("c2a0 = %g\n", c2a0);
        printf("c2b0 = %g\n", c2b0);
        printf("aa = %g\n", aa);
        printf("ab = %g\n", ab);
        printf("qa0 = %g\n", ((fstara*la)/(alphaa*c0)));
        printf("qb0 = %g\n", ((fstarb*lb)/(alphab*c0)));
}
```

PROGRAM TWO NEPHRON MODEL (CONCENRATING MODE) (INDIRECT METHOD)

```
#include <math.h>
#include <stdio.h>
#define ERROR_TOLERANCE 1.0e-6
/*max allowed  error between JGA  relative. conc. [ aA and aB] of*/
/*solution input flows [ qAo = x(0) and qBo=x(1) ] and target values*/
/*set by JGA  [aatarget = cstara/c0 and abtarget= cstarb/c0]*/
#define MAX_NEWTON_ITT 100
/*MAX_NEWTON_ITT sets the maximum number of iterations of the Newton-
Raphson method*/

#define MAX_COUNTL 100
#define TOTAL_LENGTH 2.0
#define FALSE  0
#define TRUE   1

/* double fstara=4.359e-04,la=3.0,fstarb=1.339e-03,lb=30.0; */
double delta[2], fx[2], j[2][2], x[2],inv[2][2];
double fstara=1.,la,fstarb=0.5,lb,length_inc;
double aatarget,abtarget,temp,detj;
double alphaa,alphab,alphapr,alphabpr,alphas;
double c2a,c2b,c0,cstara,cstarb,carel,cbrel;
double length_ratio,length_factor;
double k,k1,k2,k3,k4;
double d,p,w;
int i,iteration,count_L;
double qazero,qbzero, qtilda,qhat,q3zero,q0total;
double aanow, abnow;
double derivative1,derivative2;
int solution;

main()
{
        solution = FALSE;
        printf("Enter the value of c0\n");
        scanf("%lG",&c0);
        printf("Enter the target JGA value of c*A\n");
        scanf("%lG",&cstara);
        printf("Enter the target JGA value of c*B\n");
        scanf("%lG",&cstarb);
        Length_inc = TOTAL_LENGTH/MAX_COUNTL;
        la=1;
        aatarget = cstara/c0;
        abtarget = cstarb/c0;
        /* x[0] and x[1] are initial guesses of flows in A & B
           nephron, respectively*/
           x[0] = 1.;
           x[1] = 1.;
        /* cstara is set point conc. of JuxtaGlomerular App. in
          Nephron A*/
```

```
/* cstarb is set point conc. of JuxtaGlomerular App. in
   Nephron B*/
/* aatarget and abtarget are set pts. in dimensionless
   form fraction of starting*/
/* serum conc. c0 */

for(count_L = 0;(count_L < MAX_COUNTL/2) &&
(iteration<100); count_L++)
{
        lb = TOTAL_LENGTH -la;
        printf("\n la  %lG \n",la);
        printf("\n lb  %lG \n",lb);
        length_ratio = la/lb;
        length_factor = 1 - length_ratio;
        k = (((fstara*la) + (fstarb*lb)) / c0) ;
        k1 = ((((fstara*la) + (fstarb*la)) * 0.5) / c0) ;
        k2 = (fstarb*lb*0.5) / c0 ;
        k3 = (fstara*la) / c0 ;
        k4 = (fstarb*lb) / c0 ;


        /*******NEWTON RAPHSON**********/


        for(iteration =1; (iteration < MAX_NEWTON_ITT) &&
        (solution == FALSE); iteration++)
{
        /*printf("\n qAo guess %lG \n",x[0]);
        printf(" qBo guess %lG \n",x[1]);*/
        d = x[0]+x[1]-(0.5*k);
        alphapr = k1/d;
        alphabpr = (k2*length_factor)/((0.5*x[0])+x[1]-(0.5*k));
        w = k3*exp(alphapr)/x[0];
        carel =  exp(alphapr) ;
        aanow = carel - w;/* this is present value of
        aA */
        fx[0] = aatarget - aanow;
        /* discrepency in aA = targetvalue of aA -
        presentvalue of aA */
        alphas =alphapr + alphabpr;
        cbrel = exp(alphas) ;
        p = ((k4*exp(alphas))/x[1]);
        abnow = cbrel - p;
        fx[1] = abtarget - abnow;
        /*discrepency in aB = targetvalue of aB -
        presentvalue of aB */
        /*printf(" \n aA now %lG \n",aanow);
        printf(" aA target %lG \n",aatarget);
        printf(" aB now %lG \n",abnow); /* abnow is
        thepresentvalue of aB
        printf(" aB target %lG \n",abtarget);*/
        /*printf(" fx[0] %lG \n",fx[0]);
        printf(" fx[1] %lG \n",fx[1]);
        printf(" \n cA/c0 %lG \n",carel);
```

```
        printf(" cB/c0 %lG \n",cbrel);*/

if((fabs(fx[0])<ERROR_TOLERANCE)&&(fabs(fx[1])<ERROR_TO
LERANCE)) {
solution = TRUE;
printf("\n\nSOLUTION after iteration=%d\n",iteration);
printf(" \n qa0 %lG \n",x[0]);
printf(" qb0 %lG \n",x[1]);
alphaa = fstara*la/(c0*x[0]);
alphab = fstarb*lb/(c0*x[1]);
q3zero = x[0]*(1 - alphaa) + x[1] * (1 -alphab);
q0total = x[0] + x[1];
printf(" flow at JGA %lg \n",q3zero);
printf(" total inflow %lg \n",q0total);
printf(" alpha A %lg \n",alphaa);
printf(" alpha B %lg \n",alphab);
printf(" \n aA now %lG \n",aanow);
printf(" aA target %lG \n",aatarget);
printf(" aB now %lG \n",abnow);
/* abnow is the presentvalue of aB */
printf(" aB target %lG \n",abtarget);
printf(" fx[0] %lG \n",fabs(fx[0]));
printf(" fx[1] %lG \n",fabs(fx[1]));
printf(" \n cA/c0 %lG \n",carel);
printf(" \n cb/c0 %lG \n",cbrel);
}/*end if*/
else{
/*printf("\n \n \n iteration =n",iteration);*/

                        /*Jacobian 2 */

qazero = x[0];
qbzero = x[1];
qtilda = 0.5 *(qazero - k) + qbzero;
qhat = qtilda + 0.5 * qazero;
derivative1 = k1/(qhat*qhat);
derivative2=k2*length_factor/(0.5 *qtilda*qtilda);
j[0][1] = aanow * derivative1;
/*j[0][0]=j[0][1]-aanow* k3/(qazero*(qazerok3));*/
j[0][0] = j[0][1] - carel * k3/(qazero *qazero);
j[1][0] = abnow * (derivative1+derivative2);
j[1][1]=j[1][0]+abnow(derivativek4/(qbzero(qbzero-k4)));
j[1][1]=j[1][0]+abnow*derivative2cbrel*k4/(qbzero*qbzero);
detj = (j[0][0]*j[1][1])-(j[0][1]*j[1][0]);

                        /*Inverse of Jacobian */
inv[0][0] = j[1][1]/detj;
inv[0][1] = (-1.0*j[0][1])/detj;
inv[1][0] = (-1.0*j[1][0])/detj;
inv[1][1] = j[0][0]/detj;
/*printf(" \n inv[0][0] %lG \n",inv[0][0]);
printf(" inv[0][1] %lG \n",inv[0][1]);
printf(" inv[1][0] %lG \n",inv[1][0]);
printf(" inv[1][1] %lG \n",inv[1][1]);*/
```

```
/*delta[0]anddelta[1]arethecalculatedincrementsto thelastguessed
   inputflows*/
delta[0] = -inv[0][0]*fx[0]-inv[0][1]*fx[1];
delta[1] = -inv[1][0]*fx[0]-inv[1][1]*fx[1];
/*printf(" \n delta qAo  %lG \n",delta[0]);
printf(" delta qBo  %lG \n",delta[1]);*/
                    /* new guess of input flow */
x[0] = x[0]+delta[0];
x[1] = x[1]+delta[1];
}/*end else if*/
}/*end for iteration Newton Method*/
if ((iteration >= MAX_NEWTON_ITT) && (solution ==
FALSE))
{
        printf ("Solution is %d\n",solution) ;
        printf("MAX_NEWTON_ITT has been exceeded
        without obtaining asolution %d \n",
        iteration);
}
la -= length_inc;
solution = FALSE;
}/*end for count_L Length increment */
}
```

PROGRAM FOR TWO NEPHRON MODEL(DILUTING MODE) (INDIRECT METHOD)

```
#include <math.h>
#include <stdio.h>

#define ERROR_TOLERANCE 1.0e-6

/*max allowed  error between JGA  relative. conc. [ aA and aB] of     */
/*solution input flows [ qAo = x(0) and qBo=x(1) ] and target values  */
/*set by JGA  [aatarget = cstara/c0 and abtarget= cstarb/c0]
              */
#define MAX_NEWTON_ITT 100

/*MAX_NEWTON_ITT sets the maximum number of iterations of the Newton-
Raphson method*/

#define MAX_COUNTL 100
#define TOTAL_LENGTH 2.0
#define FALSE  0
#define TRUE   1

/* double fstara=4.359e-04,la=3.0,fstarb=1.339e-03,lb=30.0; */
double saltout,saltin,delta[2], fx[2], j[2][2], x[2],inv[2][2];
double qa0,qb0,fstara=1.0,la=1.0,fstarb=1.0,lb=1.0,length_inc;
double and,totalflow,aatarget,abtarget,temp,detj;
double percent,reab,alphaa,alphab,alphapr,alphabpr,alphas;
double q3lb,q3,c2a,c2b,c0,cstara,cstarb,carel,cbrel;
double out,urine,conserve,length_ratio,length_factor;
double k,k1,k2,k3,k4;
double d,p,w;
int i,iteration,count_L;
doubleqazero,qbzero, qtilda,qhat,q3zero,q0total;
doubleaanow, abnow,qt;
doublederivative1,derivative2;

int solution;

main()
{
        solution = FALSE;
        printf("Enter the value of c0\n");
        scanf("%lG",&c0);
        printf("Enter the target JGA value of c*A\n");
        scanf("%lG",&cstara);
        printf("Enter the target JGA value of c*B\n");
        scanf("%lG",&cstarb);

        length_inc = TOTAL_LENGTH/MAX_COUNTL;
        la=1.0;
        aatarget = cstara/c0;
        abtarget = cstarb/c0;
```

```
/* x[0] and x[1] are initial guesses of flows in A & B    nephron,
respectively*/
x[0] = 1.0;
x[1] = 1.0;

/* cstara is set point conc. of JuxtaGlomerular App. in Nephron A*/
/* cstarb is set point conc. of JuxtaGlomerular App. in Nephron B*/
/* aatarget and abtarget are set pts. in dimensionless form fraction of
 starting*/
/*                      serum conc. c0 */

for(count_L=0;(count_L<MAX_COUNTL/2)&&(iteration<100);
count_L++)
{
        lb = TOTAL_LENGTH -la;
        printf("  %lG ",la);
        /*printf("  %lG ",lb);*/
        length_ratio = la/lb;
        length_factor = 1 - length_ratio;

        k1 = (((fstara*la) + (fstarb*la))  / c0) ;
        k2 = (fstarb*lb) / c0 ;
        k3 = (fstara*la) / c0 ;
        k4 = (fstarb*lb) / c0 ;



        /*******NEWTON RAPHSON**********/


        for(iteration=1;(iteration<MAX_NEWTON_ITT)&&
        (solution==FALSE);iteration++)
        {
                /*printf("\n qAo guess %lG \n",x[0]);
                printf(" qBo guess %lG \n",x[1]);*/
                d = x[0]+x[1];
                alphapr = k1/d;
                alphabpr = ((k2*length_factor)/x[1]);
                alphas = alphapr + alphabpr ;
                w = k3*exp(alphapr)/x[0];

                carel =  exp(alphapr) ;
                aanow = carel - w;/*thisispresentvalueofaA */
                fx[0] = aatarget - aanow;
                /*discrepencyinaA=\targetvalueofaApresent
                valueofaA*/
                alphas =alphapr + alphabpr;
                cbrel = exp(alphas) ;
                p = ((k4*exp(alphas))/x[1]);
                abnow = cbrel - p;
                fx[1] = abtarget - abnow;
                /*discrepencyinaB=targetvalueofaBpresentvalue
                of aB */
```

```
/*printf(" \n aA now %lG \n",aanow);
printf(" aA target %lG \n",aatarget);
printf(" aB now %lG \n",abnow); *//* abnow is
the presentvalue of aB*/
/*printf(" aB target %lG \n",abtarget);*/
/*      printf(" fx[0] %lG \n",fx[0]);
printf(" fx[1] %lG \n",fx[1]);*/
/*printf(" \n cA/c0 %lG \n",carel);
printf(" cB/c0 %lG \n",cbrel);*/


if((fabs(fx[0])<ERROR_TOLERANCE)&(fabs(fx[1])<ERROR_
TOLERANCE)){
        solution = TRUE;
        alphaa=k3/x[0];
        alphab=k4/x[1];
        q3=((x[0]*aatarget*exp(-     alphapr))+(x[1]*abtarget
        *exp(-alphas)));
        saltout= (c0*(exp(-alphas)*(x[0]*(1.0-
        alphaa)+x[1]*(1.0-alphab))));
        q3lb=(exp(-alphas)*(x[0]*(1.0-alphaa)+x[1]*(1.0-
        alphab)));
        totalflow = x[0]+x[1];
        saltin = ((x[0]+x[1])*c0);
        and= q3lb*cbrel;
        out= q3lb;
        urine = out/totalflow;
        reab= and/saltin;
        percent=1-reab;
        conserve=1-urine;
        printf("%lG%lG%lG%lG%lG\n",
        conserve,q3,cbrel,totalflow,percent);


        /*printf("\n\nsoloutionafteriteration=%d\n",
         iteration);*/
        /*printf(" \n qb0 =  %lG \n",x[1]);*/
        /*printf(" \n qa0 =  %lG \n",x[0]);*/

}/*end if*/

else
{

        /*printf("\n\n\niteration=%d\n",iteration);*/

        /*Jacobian 2 */

          qazero = x[0];
          qbzero = x[1];
          qt = qazero+qbzero;

          derivative1 = k1/(qt*qt);
```

```
            derivative2 = k2 * length_factor/ (
            qbzero * qbzero);

            j[0][1] = aanow * derivative1;

          /*j[0][0] = j[0][1]-aanow*k3/(qazero* (qazero- k3));*/
          j[0][0] = j[0][1] - carel * k3/(qazero * qazero);
          j[1][0] = abnow * (derivative1 );
          /*j[1][1]=j[1][0]+abnow*(derivative2-
          k4/(qbzero*(qbzero-k4)));*/
          j[1][1]=abnow*(derivative2+derivative1)-
          ((k4*cbrel)/(qbzero*qbzero));
          detj = (j[0][0]*j[1][1]) - (j[0][1]*j[1][0]);

          /*Inverse of Jacobian */
          inv[0][0] = j[1][1]/detj;
          inv[0][1] = (-1.0*j[0][1])/detj;
          inv[1][0] = (-1.0*j[1][0])/detj;
          inv[1][1] = j[0][0]/detj;
          /*printf(" \n j[0][0] %lG \n",j[0][0]);
          printf(" j[0][1] %lG \n",j[0][1]);
          printf(" j[1][0] %lG \n",j[1][0]);
          printf(" j[1][1] %lG \n",j[1][1]);
          */
          /*delta[0]anddelta[1]arethecalculated
          incrementstothelast*/
          /* guessed input flows
                                  */
          delta[0]=inv[0][0]*fx[0]inv[0][1]*fx[1];
          delta[1]=inv[1][0]*fx[0]inv[1][1]*fx[1];
          /*printf("\ndeltaqAo%lG \n",delta[0]);
          printf(" delta qBo  %lG \n",delta[1]);*/
          /* new guess of input flow */
          x[0] = x[0]+delta[0];
          /*printf(" \n qao =   %lG \n",x[0]);
          printf(" \n qbo =  %lG \n",x[1]);*/
          x[1] = x[1]+delta[1];
}/*end else if*/
}/*end for iteration Newton Method*/

if((iteration>=MAX_NEWTON_ITT)&&(solution==FALSE))
{
printf("MAX_NEWTON_ITThasbeenexceededwithout
obtainingasolution%d\n",
iteration);
}
la -= length_inc;
solution = FALSE;
}/*end for count_L Length increment */
}
```

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