

Tubuloglomerular feedback: Its physiological and pathophysiological significance

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Tubuloglomerular feedback: Its physiological and pathophysiological significance. The mammalian nephron has a unique structure called juxtaglomerular apparatus (JGA); the primary function of the JGA includes tubuloglomerular feedback. Why is such a structure necessary? Analyses of available data strongly suggest that JGA has evolved to provide a fine tuning of the autoregulation of glomerular hemodynamics and high glomerular filtration rate in the face of very limited salt intake of our terrestrial environment, a function essential to allow a wide range of fluid and electrolyte intake with stable *milieu interieur*. Salt intake in excess is unique only to recent human cultures: salt intake is ordinarily less than 1 to 2 g per 60 kg of body weight in wildlife, including paleolithic humans. Any mutation or alteration of JGA function leading to renal salt conservation or maladaptive to high salt intake will not manifest in a low salt intake and thus would have been beneficial or inconsequential for survival in a natural environment, respectively. Thus, the mutation or alteration will be carried to subsequent generations. However, such altered function will result in essential hypertension or a maladaptation of JGA to high salt intake, which is a unique behavior of human civilizations of recent centuries. The kidney has not adapted to high salt intake through our evolution.

The human kidneys, together weighing 250 g with approximately 2-million nephrons, receive 1 liter/min renal blood flow (RBF), the highest blood flow per gram of organ weight in the body. As the blood flows through glomerular capillaries, the kidney generates a glomerular filtrate of 100 ml/min, of which almost 99% is reabsorbed along the nephron. Characteristic of the kidney function is the high, nonselective filtration and almost complete reabsorption of the filtrate through highly ordered and regulated tubular reabsorption and secretion. Why is such a process necessary? The principal function of the kidney is to maintain homeostasis of our *milieu interieur*—the extracellular fluid (ECF)—despite wide variations of daily fluid and electrolyte intake. Indeed, it is precisely this remarkable kidney function of high filtration and high reabsorption that permits

great flexibility in daily fluid and electrolyte intake: water intake may vary from 0 to 30 liter/day, whereas NaCl and K may vary from 0 to 1,000 mmol/day and 0 to 700 mmol/day, respectively, without causing significant disturbances in the *milieu interieur*. Indeed, a patient with glomerular filtration rate (GFR) of 10% of normal is advised not to ingest too much salt, water, or K, etc., because the consequences are pathological changes in the *milieu interieur*. In this brief overview, the significance of the regulation of renal hemodynamics is discussed. Detailed discussion of the issues outlined here are found in this issue of *Kidney International* and elsewhere [1, 2].

AUTOREGULATION OF RENAL BLOOD FLOW

To maintain high GFR in the face of blood pressure (BP) fluctuations, the kidney must maintain constant RBF and GFR, as summarized in Table 1. This is achieved by RBF autoregulation, a process with two components: the myogenic response of the afferent arteriole (AA) and tubuloglomerular feedback (TGF), located at the juxtaglomerular apparatus (JGA). In response to a change in renal perfusion pressure, the vascular smooth muscle of the AA responds to maintain downstream perfusion pressure so that RBF remains constant: the myogenic response. The last portion of the AA at the entrance to the glomerulus is principally regulated by TGF; this portion contracts or relaxes in response to an increase or decrease in macula densa (MD) Cl^- delivery, respectively [3]. Studies by Holstein-Rathlou and Marsh [4, 5] have shown the presence of approximately 20-second oscillations in distal tubular fluid $[\text{Cl}^-]$ just beyond the MD and of the proximal tubule pressure, a reflection of single nephron GFR (SNGFR), in the same tubule. Further analyses have shown that this oscillation is driven by TGF and is presumably located at the entrance of AA to the glomerulus. The observation indicates that the apparent constancy of SNGFR is maintained by fine tuning of the fluctuating SNGFR by TGF.

Key words: salt, hypertension, renal blood flow, juxtaglomerular apparatus, macula densa, extracellular fluid, afferent arteriole, efferent arteriole.

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Table 1. Principal functions of the kidney

1. To maintain the homeostasis of the *milieu interieur*—the extracellular fluids (ECF)—in the face of diverse and constantly changing inputs of nutrients, fluids, and minerals. The principal input route is oral.
2. To maintain ECF homeostasis, the kidney must excrete quantities of fluid and electrolytes in the urine that are precisely matched to the body inputs. Urine is the only route of regulated excretion of fluid and electrolytes.
3. To achieve this goal, there must be specific sensing mechanisms for specific changes for each constituents of ECF: its volume, toxicity, $[K^+]$, $[Ca^{2+}]$, etc.
4. Regardless of the sensing mechanisms, it is the kidney that responds to these sensing mechanisms to maintain ECF homeostasis.
5. For effective performance of this principal function, high glomerular filtration rate (GFR) and almost 99% tubular reabsorption are essential and guarantee maximal stability of the homeostatic system.
6. Because GFR is high relative to ECF volume, an increase in GFR could represent an immediate threat to life due to a rapid fall in ECF volume.
7. Constancy of high GFR and RPF must be achieved in the face of changes in systemic blood pressure and renal perfusion pressure, i.e., autoregulation.

AUTOREGULATION AND MAINTENANCE OF SNGFR

What is the physiological significance of autoregulation of renal glomerular plasma flow? Let us consider a situation in which salt intake has been extremely low so that systemic BP and renal perfusion pressure fall. Decreased AA resistance (R_A) due to the myogenic response of AA and also due to TGF at the entrance to the glomerulus allows maintenance of glomerular plasma flow. The fall in ECF volume and systemic BP also activates the renin-angiotensin system (RAS). The resulting angiotensin II (Ang II) constricts efferent arterioles, and efferent resistance (R_E) rises, thus maintaining glomerular capillary pressure (P_{GC}) and hence SNGFR. This ensures the wide allowance of the daily intake of fluids and minerals despite a low salt intake [6].

PHYLOGENETIC CONSIDERATION OF THE JUXTAGLOMERULAR APPARATUS

The JGA and TGF probably evolved in the nephron from the amphibia, through reptiles, birds, and mammals [7, 8]. We might thus envision the functional role of the JGA, or TGF, from an evolutionary perspective: simply compare the *milieu interieur* of sea fish (teleosts) with that of the humans. The basic constituents of intracellular and ECFs are the same: thus, ECF is in essence isotonic saline, and K is the major intracellular cation in both teleosts and human. When a seafish ingests its meal, the salt it absorbs has a higher concentration than that of *milieu interieur*, that is, 0.9% saline in ECF versus 3.5% NaCl in sea water. The teleost thus does not need salt, but rather salt-free water. The *milieu interieur* of the teleost is maintained primarily by the gill, and the kidney plays only an ancillary role.

In contrast, for terrestrial animals, there is no guarantee of salt availability, which is, in general, very limited. None-

theless, it is necessary to maintain a high GFR to maintain *milieu interieur* in response to a wide range of fluid and electrolyte intakes. This is why the JGA has appeared from amphibian, and it is likely that JGA must have been an essential component of the nephron in the adaptation to life on land, where a high GFR has to be maintained with a minimal salt intake. It is of note that BP must be higher in terrestrial animals to ensure that the blood can supply oxygen throughout the body in the face of 1.0 G gravity [9]; this helped in the evolution of higher GFR.

RENAL CROSS-TRANSPLANTATION IN RAT MODELS OF HYPERTENSION

In rat models of experimental hypertension, renal cross-transplantation strongly indicates the primary role of the kidney in the genesis of hypertension [10]. Thus, available data clearly indicate that it is the program in the kidney that determines whether hypertension subsequently develops. Similar results have also been obtained in humans. In chronic dialysis patients with end-stage renal failure from severe hypertension, successful kidney transplantation from a normotensive, healthy donor often leads to the disappearance of hypertension [11]. These observations are consistent with the notion that the kidney determines the development of hypertension.

INTRARENAL MECHANISMS RESPONSIBLE FOR ABNORMAL SALT EXCRETION

Numerous reviews and monographs attest to the role of the kidney in the genesis of hypertension. In particular, two recent reviews address the critical role of the kidney. Sealey et al have emphasized the presence of a subset of nephron that secretes inappropriately increased amounts of renin for any given salt intake [12]. Brenner et al hypothesize that smaller numbers of nephrons or effective glomerular filtration surface for any given salt intake are associated with the development of hypertension [13]. This hypothesis is also persuasive.

A hypothesis we would like to advance here is that an abnormal JGA or the resetting of TGF is the renal abnormality responsible for development of hypertension [2]. Available data indicate that there are similarities in the TGF response of spontaneously hypertensive rats (SHR) and control Wistar Kyoto (WKY) rats and that of normal rats with or without Ang II. Thus, for a given salt intake, TGF is more activated in SHR than WKY. This difference is quite similar to those in normal rats with and without Ang II [14, 15]. The data suggest that the TGF of SHR behaves as if it is more sensitive to Ang II for any given salt intake or ECF volume. Thus, the volume expansion following a saline load will inhibit the RAS, and TGF will thus be inhibited; at the same time, distal Cl delivery is increased due to saline load, but TGF inhibition allows GFR to increase. Hence, the saline is effectively excreted in the

urine. In hypertensive subjects, however, this TGF inhibition is incomplete or aberrant so that GFR may not increase but rather fall or remain unchanged in response to increased distal Cl delivery; thus, volume expansion ensues with slower urinary excretion of the loaded saline. This is a characteristic response in hypertensives or even some normotensives with family history of essential hypertension [16, 17]. This series of changes in response to salt loading will eventually lead to hypertension with increased peripheral resistance if the excess salt intake continues. In hypertensives, it is the inability of the kidney to excrete a salt load that must be responsible for the development and maintenance of hypertension [18].

SALT INTAKE IN HUMAN CIVILIZATION

If the previously mentioned hypothesis were correct, one would expect that when salt intake is very low hypertension would not develop, which epidemiological studies verify. In populations with a very low salt intake, such as Papua New Guineans and Yanomamo Indians in the Amazon region, there is no hypertension, and BP does not rise with age [19].

Only humans have acquired the habit of consuming salt in excess [19]. People with a disordered TGF may develop hypertension because they cannot adapt appropriately to the chronic excess salt intake. Nonhuman mammals in their natural environment do not constantly consume excess salt. Salt intake of carnivores could be 20 to 40 mmol/day per 60-kg body wt; that of herbivores will be less than less than 10 mmol/day per 60-kg body wt. Thus, terrestrial mammals in a natural environment are in a state of chronic volume depletion with highly activated RAS.

Analyses of paleolithic nutrition suggest that salt intake in modern human beings (*Homo sapiens sapiens*) was 30 mmol/day at most, with a K intake of 500 to 700 mmol/day [20]. The development of agriculture approximately 10,000 years ago has not changed salt intake, although vegetable foods subsequently came to make up 90% of the diet. Thus, throughout our civilization, salt has been a valuable item and not an item in abundance. Much evidence attests to the importance of salt in our culture and civilization, as reviewed in [19, 21].

CONCLUDING REMARKS: GENETIC AND ENVIRONMENTAL FACTORS OF HYPERTENSION

Our body has evolved through years of evolution via genetic mutations. The kidney and the BP-maintaining system are no exception, so our organism has adapted genetically to the salt depletion of the terrestrial environment. However, "industrialized civilizations" have introduced excessive salt intake, leading to the appearance, in a population subset, of essential hypertension or to a maladaptation to chronic high salt intake. Obviously, there has not been enough time in the recent centuries for our organism to adapt genetically to such excessive salt intake. In fact, some genetic abnormalities responsible for hyper-

Table 2. Principal functions of the kidney and the genesis of hypertension

1. The kidney must maintain a high glomerular filtration rate (GFR), even when extracellular fluid (ECF) volume is low, a prerequisite for stability of the *milieu interieur* when fluid and electrolyte intake vary widely.
2. This stability has been acquired in the transition from high-salt environment of sea water to the terrestrial life, where salt intake is not guaranteed.
3. The juxtaglomerular apparatus (JGA) is critical for this function.
4. Altered function of the JGA or tubuloglomerular feedback may cause essential hypertension and becomes manifest only in chronic high salt intake.
5. High salt intake is a challenge to the structure and function of the kidney; i.e., a critical adaptation necessary in the transition from sea water to terrestrial environment.
6. Hypertension is the price some have to pay for high salt intake in our civilization.

tension, such as the mutation in the distal Na channel leading to increased Na reabsorption (Liddle's syndrome), would have been advantageous for survival with the low salt intake of the natural environment. Such an abnormality has become manifest only in recent (on an evolutionary scale) years because only in this period has high salt intake in our culture emerged as a cause of hypertension. This is the basis for genetic and environmental factors for the genesis of hypertension.

In this view, the three hypotheses on the intrarenal mechanisms of essential hypertension mentioned earlier here may be seen differently. Thus the hypotheses of Sealey et al and Brenner explain why the kidney is unable to excrete salt appropriately, leading to development of hypertension. The hypothesis of abnormal JGA or TGF function explains not only the inability of the kidney to excrete a saline load effectively, but also the cause of an abnormality development. As suggested earlier here, the kidney must have acquired in adapting to the transition from the sea to the land the ability to maintain high GFR in the face of very low salt intake. Thus, high salt intake has never been "expected" at the genetic level in human evolution. Genetic abnormalities associated with hypertension would have been beneficial for survival in the natural environment of low salt intake and thus have been preserved in humans. Only with the recent high salt intake in our culture have they become manifest (Table 2).

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APPENDIX

Abbreviations used in this article are: AA, afferent arteriole; Ang II, angiotensin II; BP, blood pressure; ECF, extracellular fluid; GFR, glomerular filtration rate; JGA, juxtaglomerular apparatus; MC, macula dense; PGC, glomerular capillary pressure; RA, afferent arteriolar resistance; RAS, renin-angiotensin system; RBF, renal blood flow; RE, efferent arteriolar resistance; SNGFR, nephron GRF; TGF, tubuloglomerular feedback.

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