Relation Between Sodium Intake, Renal Function, and the Regulation of Arterial Pressure

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The long-term regulation of arterial pressure requires the maintenance of a balance between sodium and water intake and sodium and water excretion. Normal salt and water balance leads to stable body fluid volumes and the maintenance of normal renal function is critical to establishing extracellular fluid volume homeostasis. This review focuses on the role of the kidney in the long-term control of salt and water balance with particular emphasis on the relations between sodium intake, the renin-angiotensin-aldosterone system, renal sympathetic nerve activity, and the regulation of arterial pressure via renal sodium and water excretion. The accumulation of evidence in recent years demonstrates that low level elevation of renin release, circulating angiotensin II or aldosterone, or activation of renal sympathetic outflow may alter renal function such that normal natriuretic and diuretic responses to arterial pressure are significantly impeded. Under these circumstances, the maintenance of normal sodium and water excretion requires a significant elevation of arterial pressure. Thus, compromised renal function leads to elevation of arterial pressure to maintain adequate sodium and water balance during periods of increased sodium intake. The resultant chronic elevation of arterial pressure then becomes a compromise that is used by the kidneys to maintain normal extracellular body fluid volumes. (Hypertension 1991;17[suppl I]:I-91-I-96)

The regulation of the extracellular fluid volume encompasses the continuous, ongoing maintenance of normal sodium and water balance as a relation between sodium intake and excretion. As humans, we exist as intermittent sodium and water consumers, leaving the bulk of the task of regulating our constant expansion of extracellular fluid volumes to the renal excretory processes. There are many factors that influence renal sodium excretion and thereby participate in this regulatory process. These factors can be subdivided into extrinsic and intrinsic mechanisms. Extrinsic mechanisms include the production of angiotensin II (Ang II) and aldosterone, the release of atrial natriuretic factor, and the alterations of renal sympathetic outflow; some intrinsic mechanisms are the regulation of glomerular filtration rate, renal hemodynamics, intrarenal physical forces controlling tubular reabsorption, and intrarenal hormonal systems such as kinins, Ang II, and prostaglandins.

Renal Function and Arterial Pressure

A close correlation between normal kidney function and blood pressure control has been demonstrated in several experimental forms of hypertension including the spontaneously hypertensive rat (SHR) and the Dahl salt-sensitive (DS) rat. The spontaneously hypertensive strain of rats develops elevated arterial pressure spontaneously with age, and in some strains this hypertension is exacerbated with elevated sodium chloride intake. Kawabe et al have shown that in this strain, replacement at an early age of the SHR kidneys by transplantation with kidneys from age-matched normotensive control rats results in a substantial diminution of the blood pressure. This same response has been shown in other genetic models of hypertension including the Milan hypertensive strain and the DS rat. Thus, a direct correlation has been documented between renal function and arterial pressure in several genetic models of hypertension, and in some strains a critical interaction exists between sodium intake and the magnitude of the hypertension.

The complex relations between the natriuretic responses to increased arterial pressure in the SHR...
Angiotensin II and Renal Function in Blood Pressure Control

One of the factors that may be responsible for limiting the ability of the kidney to respond normally to arterial pressure is the renin-angiotensin-aldosterone axis. In conscious dogs with normal renal function, elevation of sodium intake results in little or no change in arterial pressure because urinary sodium excretion is rapidly elevated to maintain normal sodium and extracellular fluid volume balance and thereby prevent further volume-mediated elevations of arterial pressure. Hall et al\(^8\) have demonstrated that Ang II blockade with converting enzyme inhibition (SQ 14,225) markedly shifts the pressure-natriuresis relation toward lower arterial pressures. This leftward shift in the pressure-natriuresis curve is particularly pronounced during states of low sodium intake due to the large activation of renin release and subsequent Ang II production in response to sodium depletion. Conversely, low level infusion of Ang II (5.0 ng/kg/min i.v.), which does not alter arterial pressure alone, shifts the renal pressure-natriuresis and -diuresis curves toward higher perfusion pressures necessary to achieve similar rates of urinary sodium excretion.\(^7\)

The shift in the renal pressure-natriuresis and -diuresis curves toward higher pressures may result from direct tubular antinatriuretic effects of Ang II. Antinatriuresis during chronic Ang II infusion may be a result of activation of aldosterone release from the adrenal glomerulosa. Distal tubular elevation of sodium reabsorption would then result in a net decrease in overall sodium excretion for any given step change in systemic arterial pressure. In addition, pressure natriuresis may be blunted by Ang II at more proximal nephron sites. Specific Ang II receptors have been identified on proximal tubular cells\(^9\) and intrarenal Ang II has been shown to increase sodium-hydrogen exchange.\(^10\) Intrarenal Ang II then may directly decrease net sodium excretion by increasing total sodium chloride/bicarbonate reabsorption. Thus, the overall influence of Ang II on urinary sodium excretion during step increases in arterial pressure is to limit the natriuretic capacity of the kidney by elevating tubular sodium reabsorption at proximal and distal nephron sites. Normal renal natriuretic and diuretic responses to elevated arterial pressure are essential to the maintenance of body fluid volumes and consequently of arterial pressure homeostasis during low level infusion of circulating hormones such as Ang II, aldosterone, and arginine vasopressin. When renal excretory function is allowed to respond normally to changes in arterial pressure, low level infusions of Ang II or aldosterone do not markedly alter arterial pressure. In contrast, when renal perfusion pressure is held constant at a normal arterial pressure of approximately 100 mm Hg, low level infusion of either Ang II\(^8\) or aldosterone\(^12\) produces overt and, in some cases, malignant hypertension. This hypertension is associated with continual sodium and water retention and expansion of the extracellular fluid volume. Thus, small alterations in extrinsic circulating hormonal factors do not produce hypertension.
under normal conditions; however, in the presence of compromised renal function, such that the kidneys do not respond normally to transient elevations of arterial pressure, low level activation of the renin-angiotensin-aldosterone axis produces sodium and water retention and the development of severe arterial hypertension.

Renal Sympathetic Nerves, Renal Function, and Arterial Pressure

From the previous discussion, a large body of evidence indicates that alteration of renal function by some intrinsic or extrinsic mechanism is required for the chronic elevation of arterial pressure. There are multiple routes by which elevation of renal sympathetic nerve activity may function as the mediator of this alteration in renal function, including stimulation of renin release, elevation of intrarenal or circulating Ang II, redistribution of intrarenal blood flow or glomerular filtration rate, and activation of renal tubular sodium reabsorption. Ultimately, the kidney must function to maintain extracellular fluid volume constant via regulation of urinary sodium excretion. Thus, important interactions must exist between the relative rates of sodium intake, sodium excretion, level of renal sympathetic nerve activity, and arterial pressure.

Renal sympathetic nerve activity may alter urinary sodium and water excretion by activating sodium reabsorption by at least two specific mechanisms. First, release of neuroadrenergic transmitter at the juxtaglomerular granular cells increases the release of renin via β1-adrenergic receptor activation. This adrenergic stimulation of renin release will consequently increase circulating Ang II and aldosterone and subsequently decrease urinary sodium excretion by the mechanisms previously discussed. Second, renal sympathetic outflow also directly stimulates renal tubular sodium reabsorption at the proximal convoluted tubule or at the thick ascending limb of the loop of Henle. Direct sympathetic innervation of these tubular structures has been identified, and the adrenergic receptor mediating these responses has been described by several investigators as α1. Recent evidence indicates that α-adrenergic receptor activation of renal tubular structures increases sodium reabsorption by activation of sodium-hydrogen exchange, eliciting net increases in renal sodium bicarbonate reabsorption. It is important to note that direct neurogenic activation of tubular sodium reabsorption will concomitantly decrease the distal delivery of sodium chloride, leading to further activation of renin release via the macula densa. Thus, renal sympathetic nerve activity may have an important influence on the net renal excretion of sodium and water. Under these conditions of elevated renal sympathetic nerve activity, the renal pressure–natriuresis relation can be significantly shifted toward higher pressures, thereby requiring elevated arterial pressure to achieve adequate sodium excretion.

Important interactions likely exist between renal sympathetic outflow, renal function, and the ability of the kidney to excrete salt and water. We have evaluated the influence of increasing and decreasing sodium intake on the renal hemodynamic and renin secretion responses to direct electrical stimulation of the renal nerves. In that study, sodium depletion enhanced and sodium loading suppressed the renin secretion responses to 0.5, 1.0, and 2.0 Hz renal nerve stimulation. These changes in the responses to neural activation of renin secretion likely resulted from an interaction between direct neurotransmitter stimulation of β1-adrenergic receptors and alterations in tubular sodium chloride delivery out of the proximal nephrons to the distal macula densa mechanism for renin release. These results indicated that important interactions exist between sodium chloride intake and the neural control of renin secretion; however, the data also suggested that these responses in normal kidneys would be protective against expansion of the extracellular fluid volume (i.e., sodium-depleted states lead to exacerbated renin responses and the reverse is also true).

In contrast, renal hemodynamic responses to renal nerve stimulation demonstrated markedly different results. Figure 2 documents that elevation of sodium intake rendered the renal vasculature more responsive to renal nerve stimulation. In sodium-depleted anesthetized dogs, renal nerve stimulation did not elicit renal vasoconstriction at 0.5 or 1.0 Hz, whereas dogs placed on a high sodium intake significantly decreased renal blood flow even at 0.5 Hz renal nerve stimulation. These data demonstrated that elevation of sodium intake enhanced the renal vascular responses to renal sympathetic outflow either by increasing the release of sympathetic neurotransmitter in the kidney or by increasing the renal vascular responsiveness to intrarenal norepinephrine. Recent evidence also suggests that elevation of renal perfusion pressure interacts with vascular smooth muscle to enhance the renal vascular responsiveness to norepinephrine. Thus, important interactions between sodium chloride intake, renal perfusion pressure, and the level of renal sympathetic outflow may result in subtle alterations in renal function, which lead to expansion of the extracellular fluid volume and consequently to elevation of arterial pressure.

Recent evidence from this laboratory indicates that the renal sympathetic nerves also have an important influence on the regulation of sodium balance by precisely regulating the rate of decreasing urinary sodium excretion after a step decrease in sodium intake. In six conscious dogs, renal sympathetic efferent nerve activity was continuously monitored, and urinary sodium excretion was simultaneously measured at hourly intervals. Dogs were placed on a high sodium intake by intravenous infusion (5.0 meq/hr) for 7 days. Renal nerve recording electrodes were then implanted, and after recovery, control high sodium intake measurements were made, at which time dogs were switched to a low sodium intake (0.2
meq/hr). Measurements were then continued for an additional 30 hours during low sodium intake. As shown in Figure 3, urinary sodium excretion decreased by approximately 3 meq/hr within 12 hours (from a total intake of 5 meq/hr) after sodium intake was decreased. This reduction in sodium excretion was associated with a significant increase in renal sympathetic nerve activity over the same time interval (Figure 3). Subsequent bilateral renal denervation markedly increased the time interval over which dogs achieved sodium balance such that similar decreases in urinary sodium excretion did not occur until 20 hours after reduction of sodium intake. Plasma renin activity and plasma aldosterone concentrations were not significantly altered at 6 and 24 hours after the step decrease in sodium intake. These results have been interpreted to suggest that the renal nerves may function as an important rapid controller of sodium excretion when sodium intake is altered. Clearly, there exist numerous mechanisms for the maintenance of normal sodium balance when sodium intake changes. The rate at which sodium balance is achieved, however, may primarily be controlled by the renal nerves by induction of rapid alterations in tubular sodium transport. Thus, functional aberrations in the regulation of efferent renal sympathetic outflow could potentially cause transient but significant expansion of the extracellular fluid volume after step changes in sodium intake. These continual expansions and contractions of body fluid volumes could potentially result in a chronic resetting of the renal pressure–natriuresis and –diuresis curves and thereby produce prolonged elevation of arterial pressure.

Sodium and Water Retention as a Function of Hypertension

The hypothesis that sodium and water retention precedes the onset of arterial hypertension has been extensively investigated. For the purposes of the present discussion, recent studies will be presented, which indicate that minimal changes in blood volume are required to elicit significant changes in arterial pressure. In conscious areflexic rats, Hinojosa-Laborde et al recently reported that elevation of blood volume by as little as 5% can significantly increase arterial pressure. This significant finding suggested that a very low level elevation of body fluid volume can indeed elevate arterial pressure by increasing cardiac output. It is critical to note, however, that for blood volume increases to lead to chronic elevation of arterial pressure, baroreceptor reflex control of arterial pressure must either be completely reset or impairment of low or high pressure baroreceptor...
Renal function and ultimately the renal responses to arterial pressure can be markedly influenced by the extrinsic and intrinsic factors. Activation of the renin-angiotensin-aldosterone axis and alteration of renal sympathetic outflow may directly affect intrarenal handling of sodium and water, which may interrupt the normal maintenance of extracellular fluid volume homeostasis. These factors also do not function in a fashion that is mutually exclusive. In this regard, elevation of circulating Ang II or activation of renal sympathetic outflow may also cause major changes in intrarenal physical factors, Ang II, prostaglandins, kinins, glomerular filtration rate, or intrarenal hemodynamics. Any one or a combination of these factors may sufficiently alter renal function in such a way that the renal ability to rapidly elevate urinary sodium excretion in response to a challenge of increased sodium intake is reduced. Under these circumstances, the resultant expansion of extracellular fluid volume elevates arterial pressure to overcome this excretory deficit and thereby return body fluid volumes to a normal state. Thus, the kidney functions in a vital capacity in the long-term control of arterial pressure by regulation of extracellular fluid volume. Subtle alterations in renal excretory function during periods of elevated sodium intake result in the maintenance of normal body fluid volumes at the expense of chronically elevating arterial pressure and thus producing the onset of arterial hypertension.

References

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