New Approaches to Pathogenesis and Management of Hypertension

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Upon the initiative of Smithwick and Thompson (1) of the Massachusetts General Hospital, resection of the splanchnic nerves through a posterior infradiaphragmatic approach plus removal of the sympathetic chain from the level of the eighth dorsal ganglion to the second lumbar ganglion had been used with relative frequency in cases of desperate hypertension at the time when anti-hypertensive medication was not yet available. In the hands of other investigators, the results were spectacular in a minority of patients but not quite satisfactory in many patients (2,3). Despite improvement of headache, reversal of papilledema in malignant hypertension, etc., the long-term reduction of BP was quite variable and the 5-yr mortality remained approximately 40% (2). A 10-yr follow-up compared 100 patients who were subjected to thoracolumbar sympathectomy with 1500 patients who received symptomatic therapy. Lasting BP reduction was seen only in one third of the patients (4). Whereas the average BP levels were reduced, occasional BP spikes were not. The average difference of preoperative to postoperative systolic BP values was 21 mmHg. The authors saw reduction of cerebrovascular accidents and less symptomatic therapy. Lasting BP reduction was seen only in one third of the patients (4). Whereas the average BP levels were reduced, occasional BP spikes were not. The average difference of preoperative to postoperative systolic BP values was 21 mmHg. The authors saw reduction of cerebrovascular accidents and less symptomatic therapy. Lasting BP reduction was seen only in one third of the patients (4). Whereas the average BP levels were reduced, occasional BP spikes were not. The average difference of preoperative to postoperative systolic BP values was 21 mmHg.

With today’s better insight into the role of sympathetic activity in the genesis of hypertension and particularly the role of the kidney in sympathetic activation, there has been a renaissance in the interest of the renal sympathetic nervous system, including its role in primary hypertension—apart from its undoubted role in the hypertension of chronic kidney disease (5–10). Renal disease and, in animal experiments, even minor renal tissue damage such as injection of minute volumes of phenol, trigger afferent signals that ascend via the spinal cord to the posterior hypothalamus, resulting in increased efferent sympathetic activity (8,9).

In the distant past, it had been assumed that sympathetic activation is restricted to advanced kidney disease and the presence of uremic toxins. Increased sympathetic activity had been documented by the methodologic gold standard of microneurography in end-stage kidney disease but later on also in earlier stages of chronic kidney disease (11,12). It is interesting that after renal transplantation BP decreases and microneurographic overactivity is normalized when the recipient’s own anuric kidneys are removed by bilateral nephrectomy, clearly illustrating the important role of the kidney independent of its excretory function (13). A new twist has been introduced by the recognition that the kidney secretes a proform of an enzyme called reninalse, which retards catecholamine breakdown (14). The complexity of sympathetic activation in chronic renal failure was recently reviewed by Schlach et al. (10).

There is little argument about Guyton and Coleman’s postulate that “all forms of hypertension are ultimately a consequence of resetting of the pressure-natriuresis relationship” (15). This concept is supported by observations such as that transplantation of a kidney from a donor with normotension causes persistent normotension in the recipient, that high urinary albumin excretion precedes the onset of overt hypertension, that patients with essential hypertension have fewer nephrons, and that asymptomatic heterozygotic carriers of the Gitelman mutation have lower BP than the background population (Mendelian randomization) (16–19). Apart from these observations, however, there is good evidence that renal sympathetic activity is also crucial for the initiation and maintenance of systemic hypertension even in the absence of kidney disease (5,20,21). Young humans with borderline hypertension exhibit already increased norepinephrine spillover, an index of sympathetic nerve activity, in the kidney (22). Barajas and Muller (23) found in experimental studies that bilateral renal denervation prevented the development or attenuated the magnitude of hypertension. Sympathetic activity affects a great spectrum of renal functions, for example, increasing renal tubular sodium reabsorption independent of changes in GFR by releasing norepinephrine and stimulating postsynaptic α-1 adrenal receptors on the basolateral membrane of renal tubular epithelial cells (24). Hypertension control remains poor worldwide, and one partic-
ular problem is the management of “resistant hypertension” defined as hypertensive BP values despite use of three antihypertensive agents, including a diuretic (25). Past efforts to correct this condition included administration of the mineralocorticoid receptor antagonist spironolactone, which lowered BP on average by 21.9/9.5 mmHg in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) study (26). As a procedure competing with the approach described next, carotid baroreceptor stimulation is under investigation as well (27,28).

In view of the aforementioned important role of the renal sympathetic overactivity in the genesis of hypertension, this has recently again become a target for intervention. In a proof-of-principle study, Krum et al. (29) took up again the idea to eliminate the function renal sympathetic nerves. In contrast to the past nonselective surgical denervation riddled by numerous adverse effects, the authors adopted percutaneous selective renal denervation to eliminate the afferent and efferent sympathetic nerves that conveniently lie within and immediately adjacent to the wall of the renal artery. To this end, a catheter connected to a radiofrequency generator was introduced into the lumen of the main renal artery. The study comprised 50 patients at five Australian and European centers with expertise in catheter-based interventions. For assessment of the efficacy of elimination of sympathetic denervation, renal noradrenaline spillover was measured in a subgroup of patients, an elegant indirect method to assess the activity of the sympathetic nervous system (5). The spillover data documented substantial afferent renal denervation in almost all patients. Renal angiography as well as magnetic resonance angiography was performed early and late to exclude potential renovascular damage; renal artery aneurism or renal artery stenosis were not observed. In such expert hands, only one major complication—a renal artery dissection—occurred without long-term complications, but the safety in less expert hands awaits further evaluation.

The effect on BP control was remarkable: Average office BP decreased progressively by 14 mmHg systolic and 10 mmHg diastolic at month 1 and by 27 mmHg systolic and 17 mmHg diastolic at month 12, but not all patients showed a response. One can even speculate that in the long run, interruption of sympathetic nerve traffic to and from the kidney may be beneficial by BP-independent effects (e.g., reduction of left ventricular hypertrophy) of insulin resistance and of vascular catastrophes. The progressive decrease of BP is remarkable because of the theoretical possibility of regrowth of sympathetic nerves as documented after renal transplantation.

It is still early to assess the potential clinical role of this innovative therapeutic approach and, as the authors indicated, controlled prospective trials will be necessary. Several aspects in the study are not ideal. Office BP is far from ideal for assessing BP, and 24-h BP measurements would have been preferable. This proof-of-principle study did not have a control group. Furthermore, given the efficacy of spironolactone and reduction of dietary salt intake in several studies of resistant hypertension, it would have been desirable to assess the efficacy of the novel procedure in patients who did not respond to such proven interventional procedures (26,30). It is also of note that not all patients responded, suggesting heterogeneity of the role of sympathetic overactivity in the genesis of resistant hypertension. The challenge in the future will be to provide long-term controlled data on safety (particularly in less experienced hands) and quantification of the efficacy compared with proven treatments in resistant hypertension and to work out criteria to identify nonresponders (26,30).

References

16. Curtis JJ, Luke RG, Dustan HP, Kashgarian M, Whelchel...
Klotho gene delivery prevents the progression of spontaneous hypertension and renal damage. *Hypertension* 54: 810–817, 2009
Wang Y, Tsun Z

In 1997, the klotho gene was identified and named after the Greek goddess who spins the thread of life (1). Defective klotho gene expression in mice causes shortened lifespan, growth retardation, hypogonadism, skin and muscle atrophy, vascular calcification, loss of bone mass, pulmonary emphysema, and neural dysfunction, thus presenting an “aging phenotype” (2). The condition is associated with elevated concentrations of 1,25-dihydroxyvitamin D₃, of phosphate, and of calcium. The function of Klotho has been identified as a co-factor that increases the affinity of the phosphaturic hormone fibroblast growth factor 23 (FGF-23) to some FGF receptors (3). One puzzling fact concerning the phosphaturic effect of FGF-23 is that control of phosphate excretion occurs in the proximal tubule, whereas the glycosidase klotho is expressed in the distal tubule (4). Thus, the interaction is potentially indirect. Klotho can exert its effects in tissues or cells that do not express Klotho, suggesting that it may function as an endocrine hormone (5).

The serum phosphate concentration is of major importance for the cardiovascular risk not only in end-stage kidney disease but also in chronic kidney disease before the end stage, and even phosphate concentrations within the normal range are predictive of cardiovascular events in patients without kidney disease (6–8). These observations point to phosphate toxicity in states of disruption of the bone–kidney–endocrine axis.

It has been known for some time that the production of klotho is drastically reduced in human chronic renal failure, but decreased plasma levels of klotho have also been found in patients who were older than 40 yr (9,10). In this context, the article by Wang and Sun (11) provides provocative information concerning the effect of the antiaging hormone klotho on hypertension and renal damage.

It is known that overexpression of the klotho gene extends the lifespan (12). Some of the downstream mechanisms potentially relevant for life expectancy and cardiovascular risk had been identified, for instance effects on insulin/IGF-1 signaling, increased nitric oxide availability, regulation of oxidative stress, and regulation of calcium channel activity (13). Of particular interest for the cardiovascular and renal effects described next is that klotho also protects against endothelial dysfunction (14).

The authors of this study administered adeno-associated virus carrying mouse klotho full-length cDNA to spontaneously hypertensive rats (SHR) and matched Wistar Kyoto rats. The readout of this study was changes in BP and production of superoxide and NADPH oxidase activity (as indicators of oxidative stress) and NOX1, NOX2, and NOX4 in aorta and kidney. Furthermore, the morphology of the kidney was assessed and plasma levels of the membrane and secreted forms of klotho were measured.

The results were remarkable. Whereas in untreated SHR BP increased progressively, the BP increase was abrogated in SHR
that were treated with adenovirus and carried full-length klotho cDNA. The BP level did not decrease, however, to the level measured in WKY controls.

Plasma levels of the klotho isoforms (membrane and secreted form) were significantly decreased in untreated SHR but increased to the levels seen in WKY controls in the SHR that were treated with adenovirus and carried full-length klotho cDNA. In the kidney, klotho expression was decreased in untreated SHR and was increased in the treated SHR. This was paralleled by similar changes in urinary klotho.

In the SHR that were treated with adenovirus and carried full-length klotho cDNA, the anti-inflammatory cytokine IL-10 was upregulated. IL-10 is known to ameliorate hypertensive organ damage (15).

Evidence of oxidative stress was seen in the aorta and kidney of untreated SHR (vascular superoxide production and NADPH oxidase activity), but this was reduced in treated rats. In the kidney, NOX2 expression was selectively upregulated in untreated SHR, and this was reverted by klotho gene delivery. There was no change in the expression of endothelial NO synthase. These findings were paralleled by changes in renal histology: Untreated SHR had atrophic cortical tubules with dilation and proteinaceous material in the tubular lumen as well as glomerular collapse. These lesions were no longer seen in SHR with klotho gene delivery. In parallel, the elevated protein excretion in untreated rats was significantly decreased in the rats that treated with adenovirus and carried full-length klotho cDNA.

These findings raise several points. The prevention of the progression of hypertension in this animal model of spontaneous hypertension is remarkable, but the generalizability of this observation to other forms of hypertension awaits further studies. The authors point to the remarkable parallelism that circulatory Klotho decreases with age while conversely the prevalence of hypertension increases with age in humans (10,16). Further studies must show whether this is just association or is causal.

The effect of klotho gene delivery was limited: It did prevent the BP increase but failed to decrease the BP of SHR to the level seen in WKY controls. Thus, the BP increase was aborted, but the treatment had no antihypertensive effect.

It is known that vascular and renal superoxide production is increased in SHR and plays a role in the pathogenesis of hypertension (17). In view of the crucial role of the kidney for the genesis of any form of hypertension, it is therefore of interest that klotho reduced oxidative stress in the kidney with its presumed causal role in the genesis of hypertension (18). Furthermore, the impressive effects on kidney morphology raise the issue to what extent klotho is involved in progression of renal damage in general or whether the observed effect is unique to BP-induced kidney damage. It is of note, however, that impressive amelioration of kidney damage was seen, although the BP failed to be lowered to the level seen in the WKY controls. The kidney apparently is not only a major site of klotho production (apart from the central nervous system) but also a target organ for klotho action.

One remarkable point is the observation that the vasculature did not express klotho, yet the vessels were affected by klotho gene delivery. Because gene delivery had increased plasma klotho concentrations, klotho apparently acted as a hormone (5).

This experimental study points to a novel aspect of the endocrine bone–kidney–phosphate axis, namely BP and kidney damage. The findings have no immediate consequences for patient treatment, but watch out for further surprises from the phosphate–FGF-23–klotho connection.

References


14. Shimada T, Takeshita Y, Murohara T, Sasaki K, Egami K,


A classical concept about the relationship between salt (NaCl) and extracellular volume was that salt was retained as an osmotic fluid and that equilibration between sodium intake and extracellular volume was that salt was retained as an isosmotic expansion of the extracellular fluid. This unexpected violation of past paradigms found partially positive sodium balance without gaining weight, apparently storing salt without expanding the extracellular fluid space (2,3). This unexpected violation of past paradigms found an explanation in the observation of Titze et al. (4) that sodium, i.e., in addition to or instead of expanding the extracellular fluid space, may undergo ionic interaction with negatively charged glycosaminoglycans (GAG) of the skin by binding directly as a cation to the polysulfated negatively charged GAG GAG. This has important implications for salt-induced changes in body weight, tissue hydration, and BP regulation (5). These novel findings concerning the mechanism of sodium retention without commensurate weight gain are irreconcilable with the classical concept that sodium is retained primarily or exclusively by isosmotic expansion of the extracellular fluid.

Salt does not only cause edema and hypertension but also BP-independent target organ damage (e.g., of heart and kidney) (6–8).

The article discussed here now goes one step further and documents that salt not only can be stored nonosmotically (i.e., without expanding the extracellular fluid) but also can trigger lymphangiogenesis in the skin. A number of past experimental studies had documented that salt loading caused BP-independent organ damage and inflammation (6,9,10).

This issue of BP-independent effects of salt has been given a new twist by this study by Machnik et al.: The authors amplified past observations of nonosmotic storage sodium in the skin and documented added complexity. They now show that storage of salt in the skin triggers lymphangiogenesis by a complicated sequence of events and thus further impacts on BP. The pointer in this direction was recent observations that macrophages (i.e., the mononuclear phagocyte system) influence lymphangiogenesis and that, in a malignancy model, hypertonicity macrophage–produced factors triggered peritumoral lymph vessels (11,12). Furthermore, osmotic stress had been defined as a critical feature of the lymphoid microenvironment (13).

The authors tied all of these suggestions together and documented that hypertonicity of the interstitium as produced by feeding a high-salt diet provoked macrophage signaling, resulting in the secretion of an isoform of vascular endothelial growth factor (VEGF), VEGF-C, a known factor that promotes lymphangiogenesis.

The authors found stimulation of lymphangiogenesis in mice fed a high-salt compared with a low-salt diet as documented by three-dimensional reconstruction of the lymph system. The causal role of macrophages for lymphangiogenesis was proved by the experiment that selective deletion of macrophages by clodronate-containing liposomes prevented lymphangiogenesis: Clodronate-containing liposomes are taken up by macrophages but are toxic for them. Elimination of macrophages by clodronate-containing liposomes caused greater expansion of the extracellular space and higher BP values.

These observations raised the issue of which signal is responsible for lymphangiogenesis. Promotion of lymphangiogenesis by macrophages was dependent on a molecule that has been known to immunologists for quite some time as toxicity-responsive enhancer–binding protein (TonEBP) (13). Incubation of macrophages at high as compared with low NaCl concentrations increased the expression of TonEBP on the mRNA and protein level. TonEBP binds the promoter of the gene encoding VEGF-C, causing VEGF-C secretion by macrophages. The causal role of VEGF-C secretion by macrophages was proved by depletion or trapping VEGF by soluble VEGF-C receptor 3: Blocking VEGF-C signaling augmented interstitial hypertonic volume retention and decreased endothelial nitric oxide synthase (eNOS) expression, causing major BP elevation in response to high-salt diet. So VEGF-C has been identified as the osmosensitive hypertonicity-driven gene involved in the genesis of salt-induced hypertension.

The issue that arises is whether this Na⁺ overload–triggered macrophage response via TonEBP and VEGF-C is injurious or is beneficial by counteracting the effect of high salt. The authors showed that VEGF-C binds not only to the VEGF receptor (VEGFR3) of lymphatic vessels but also to the endothelial VEGFR2 receptor, activation of which upregulates the production of vasodilatory NO. In other words, sodium overload, which tends to raise BP, also causes compensatory production...
of vasodilatory NO, which counteracts the pressure-inducing effect of salt. The efficacy of this compensatory mechanism is illustrated by the observation that eNOS knockout animals develop more severe hypertension upon salt loading (14).

The sequence of events can be summarized as shown here:
Na load → interstitial Na⁺ ↑ → TonEBP activated → VEGF-C ↑ → lymphangiogenesis → drainage → endothelial cell eNOS ↑ → vasodilation

The human relevance of this pathway is illustrated by the finding that in 25 patients with refractory hypertension—as compared with 15 control individuals—the plasma VEGF-C concentrations were significantly higher.

This study adds one further potential mechanism to the genesis of high BP. The ramifications for hypertension in chronic kidney disease are difficult to predict. It is an expression of the intelligence of nature that salt loading automatically increases NO synthesis by endothelial cells to limit salt-induced increase in BP, but the question that has to be addressed is whether this compensatory mechanism is disturbed in renal failure and whether this is relevant for the particular salt sensitivity of patients with chronic kidney disease.

The storage of sodium without a commensurate increase in water must certainly caution against equating sodium retention with weight gain in dialysis patients; the aforementioned mechanism would allow for sodium retention in the absence of weight gain—similar to what has been observed in astronauts (2). This has implications for the dry weight, which had originally been defined as the “body weight in the normotensive, nonedematous patient on dialysis”—the rationale to rely on weight alone deserves to be rethought. The storage of sodium may also be relevant to understanding the lag phenomenon (i.e., the delayed decrease of BP in response to reduction of extracellular volume) (15,16). Potentially prolonged elevation of BP may reflect the delayed release of sodium certainly not strictly related to the size of the extracellular space.

In retrospect, one can only admire the clinical acumen of Scribner et al. (17), who wrote in 1960, “As in the case of nephrectomized dogs, hypertension appears to be influenced by the size of the extracellular space. The combination of dietary sodium restriction and ultrafiltration during dialysis permits regulation of extracellular volume—although the explanation may no longer be perfectly correct, the practical consequences certainly are.”

References