The discovery of hypertension: evolving views on the role of the kidneys, and current hot topics

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Submitted 8 September 2014; accepted in final form 31 October 2014

THE DISCOVERY OF PRIMARY (“essential”) hypertension can be ascribed to Frederick Mahomed, who in the early 1870s, as a medical resident at Guy’s Hospital in London, measured blood pressure (BP) in the general population. Working with a watchmaker, he made a spring-based device that could measure the tension of the radial pulse, a portable version of the sphygmograph invented by Étienne-Jules Marey a decade earlier in France. While it was known that patients with kidney disease and albuminuria could have high BP, he discovered a subset of the population that had high pressures in the absence of proteinuria (98).

Despite Mahomed’s discovery, the measurement of blood pressure (BP) was not commonly performed until the 1890s, when Scipione Riva-Rocci (1863–1937) invented the BP cuff and mercury manometer (121) and Nikolai Sergeivich Korotkoff (1874–1920) used auscultation of the artery below the cuff to be sure that a complete occlusion of blood flow was achieved and permitted determination of diastolic BP (90, 132) (Fig. 1). Both Theodore Janeway and Harvey Cushing helped introduce the sphygmomanometer in the United States. Early studies by Janeway and others found systolic BP was rare >140 mmHg in adults <65 yr old (0.5–1%), whereas in those >65 the cutoff was closer to 160 mmHg (21). By 1906, insurance companies recognized that subjects with hypertension had increased mortality (21), which was confirmed by a report by the Metropolitan Life Insurance Company in 1912 (1). Soon, measurement of BP was a standard procedure by clinicians, and a cutoff of 140/90 mmHg was defined as hypertension (38). Hypertension was found not only to increase the risk for mortality, but also for stroke, congestive heart failure, and chronic kidney disease. Furthermore, a complication of congestive heart failure is that it can result in impaired perfusion to the kidney, causing kidney function to worsen, a syndrome known as cardiorenal syndrome (11).

The Epidemiology of Hypertension

In the past, there were differing opinions over whether hypertension, especially mild hypertension, should be treated,
Metabolic: High uric acid, insulin resistance, high hematocrit

Diet/toxin: High salt intake, low potassium intake, high intake of added sugars containing fructose (high-fructose corn syrup and sucrose), low calcium intake, low

Congenital: Low birth weight and maternal malnutrition (low nephron number), maternal hypertension, preeclampsia

Genetic: Family history, genetic polymorphisms (adducin, angiotensinogen, endothelial nitric oxide synthase, β2-adrenoceptor, others)

Physical: Borderline and “white coat” hypertension, obesity, aging, African American, increased heart rate (>82 beats/min), increased psychosocial stress

Risk factors for hypertension

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Renal Abnormalities in Primary Hypertension

BP is determined by the product of cardiac output and systemic vascular resistance (SVR). Most subjects with primary hypertension have a high SVR with relatively normal cardiac output. Hypertension is usually associated with disease of the small blood vessels (arterioles) with thickening and scarring (arteriolosclerosis), and is frequently accompanied by the presence of proteinaceous debris in the subendothelial space (hyalinosis) (104, 136). The kidney is especially involved in primary hypertension, with elevated renal vascular resistance, low renal blood flow, and for a relatively long time, preserved glomerular filtration rates (GFR). Renal arteriolar involvement with thickening and narrowing is present in the vast majority (98%) of subjects with primary hypertension, and the degree of narrowing of the arterioles correlates with the severity of the hypertension (136, 142). However, as many as one-third of subjects have relatively mild renal arteriolar disease (135). Nevertheless, classic functional studies done more than six decades ago have shown a reduced ratio of effective renal blood flow to functional tubular mass (53), indicating relative renal ischemia. The ischemia is due to the presence of renal arteriolar vasoconstriction and is present regardless of whether arteriolosclerosis is present (54, 146). Indeed, ischemic changes are common, including wrinkling of the basement membranes in the glomeruli and mild tubular injury and...
often associated with an interstitial inflammatory response, eventually resulting in the kidney appearing “contracted and granular” (136). In some subjects, glomerular and tubulointerstitial scarring develops, leading to progressive kidney failure.

Hypertension and Salt Sensitivity: A Disease of the Kidney

While a role for the kidney in driving hypertension was long suspected (75), the first supporting evidence was indirect and resulted from studies showing that salt restriction could lower BP in many hypertensive subjects (3, 4, 87). Chlorothiazide, the first modern diuretic, also lowered blood pressure, providing further evidence that salt retention played a role (147). Dahl (28) and MacGregor (96) further showed a relationship between salt intake and the prevalence of hypertension in various populations. Indeed, Dahl also developed rat models of hypertension in which BP increased markedly on exposure to high-salt diets (28).

In 1963, Borst and Borst-De Geus (10) proposed that hypertension resulted from a relative inability of the kidney to excrete salt; they hypothesized that “hypertension is part of a homeostatic reaction to deficient renal sodium output”. Guyton further developed this hypothesis, postulating that the long-term control of BP rested on the ability of the kidney to respond with an appropriate natriuresis at normal BP (57). An impairment in the pressure-natriuresis relationship required an increment in BP to maintain extracellular fluid volume within normal limits (58).

In human evolution, we have become adapted to a dramatic increment in sodium intake and a reduction in potassium intake. At the present time, salt intake ranges from 50 mg/day in the Yanomamo Indians living on their native diets (113) to 16 g in some areas of rural China (152), with an average global consumption of 9.8 g of salt daily (106). The relative inability of the kidney to meet this challenge, is more evident in the aging population; At the age of 80, as many as 30% of the total population of glomeruli may be sclerotic (82) and the kidney to the Framingham Heart Study (74). However, some studies suggest that genetic polymorphisms in these rare disorders may account for only a small percentage of primary hypertension (22, 83).

Direct evidence that the kidney was critical to the development of hypertension was then demonstrated by the transfer of hypertension by kidney transplantation of hypertensive rats to normotensive rats (29). Other groups have also shown a key role for the kidney in models of hypertension (8, 25, 120). Similarly, Curtis et al. (27) showed that African Americans suffering from kidney failure from primary hypertension could be cured of their hypertension by receiving kidney transplants from normotensive donors. However, transplantation today is often associated with the development of hypertension in the transplant recipient, likely because of the use of calcineurin inhibitors that were not used in the original study by Curtis et al. (27). Nevertheless, these studies provide evidence that abnormalities in the kidney were sufficient to cause hypertension and that a normally functioning kidney prevents the increment in BP even when there is systemic microvascular disease present.

What are Potential Mechanisms for Renal Abnormalities in Primary Hypertension?

**Genetic mechanisms.** Given that the primary defect in the kidney might involve defective excretion of sodium, genetic polymorphisms that modulate salt excretion would be excellent candidates for playing a role in hypertension (reviewed in Ref. 43). This hypothesis was supported by the discovery by Rick Lifton’s group (94) that several types of hereditary hypertension are due to specific genetic defects in renal sodium handling, especially involving the epithelial sodium channel (ENaC) of the collecting duct, such as Liddle syndrome, the syndrome of apparent mineralocorticoid excess, and glucocorticoid-remediable aldosteronism. Other monogenic disorders, such as Bartter’s syndrome and Gitelman’s syndrome, may be associated with low BP and result in sodium wasting due to mutations in the Na-K-2Cl transporter (SLC12A1) and the Na-Cl cotransporter (SLC12A3), respectively. The strength of these observations led Lifton to postulate that hypertension is likely driven by multiple genetic polymorphisms that in aggregate result in defective sodium excretion (94). Consistent with this hypothesis, genetic polymorphisms in renal sodium handling were found to influence the frequency of hypertension in the Framingham Heart Study (74). However, some studies suggest that genetic polymorphisms in these rare disorders may account for only a small percentage of primary hypertension (22, 83).

Candidate gene approaches (2) and genome-wide association studies (GWAS) (72, 93) have also identified genetic polymorphisms associated with hypertension (reviewed in Ref. 43). Some of the candidate genes are involved in vasoconstriction or vasodilation, such as angiotensinogen (73) and endothelial nitric oxide synthase (111). However, while genetic polymorphisms involved in renal salt handling or in systemic vascular reactivity are risk factors for hypertension, nongenetic mechanisms may be more important. Indeed, a study of 635 identical twins reported that 60% of twins that were hypertensive had a twin that was normotensive (16). Thus, despite identical genetics, hypertension can be discordant. In summary, genetics play an important role in hypertension, but other mechanisms (epigenetic and acquired) may have a more critical role in the majority of patients presently grouped under the term “primary” hypertension.
Congenital reduction in the number of nephrons. Epidemiological studies have documented an increased frequency of hypertension in adults born with low birth weight (5). The kidneys develop during the third trimester, and hence low-birth weight babies commonly have incomplete development of the kidney with a reduced number of nephrons. This led Brenner et al. (12) to suggest that a low nephron number may represent the renal abnormality that predisposes an individual to develop hypertension. Indeed, experimental studies in laboratory rats showed that maternal malnutrition can lead to small pups with reduced nephrons, and these rats show an increased propensity to develop salt-sensitive hypertension later in life (149). Furthermore, a study of subjects with hypertension who died in traffic accidents found that these subjects had a reduced number of nephrons compared with age-matched controls (86).

However, most studies suggest that the effect of birth weight on BP is modest (31) and can only explain 20% of those with hypertension (37). Other studies could not show a relationship between nephron number and BP in African Americans (71). Thus, while it is likely that stress during fetal development may lead to epigenetic changes or alterations in nephron development that increase the risk for hypertension later in life, these changes are not required for the development of primary hypertension. Thus fetal programming is more likely a risk factor than the cause of primary hypertension.

Acquired renal injury. The observation that the kidney appears ischemic led Goldblatt (52) to propose that disease of the renal microvasculature might be responsible and that a decrease in blood flow to the kidney might result in the release of substances that raise BP. Kidney extracts were known to contain a substance (renin) that could raise BP when injected into animals (140), and hypertension due to a release of renin could be induced by mechanically constricting the renal artery of dogs (52). However, plasma renin activity tends to be normal or suppressed in most patients with hypertension, consistent with normal or increased body sodium content (91). Furthermore, while renal microvascular disease was present in most subjects, in up to one-third the severity was not enough to account for the ischemic changes (17), and since microvascular disease tends to be more severe with longer duration of hypertension (116), the vascular disease was more likely an aggravating or secondary factor rather than the primary cause.

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ACQUIRED HEMODYNAMIC CHANGES IN THE KIDNEY: INTRARENAL ACTIVATION OF VASOCONSTRICTOR SYSTEMS WITH SODIUM REABSORPTION. Despite the fact that earlier studies suggested that the histological changes in the kidney were secondary to hypertension, it has long been recognized that the sine qua non of hypertension is renal vasoconstriction, primarily of the preglomerular vasculature (55). Numerous studies over the last few decades have shown that this renal vasoconstriction is mediated by an imbalance in intrarenal vasoconstrictors and vasodilators, favoring intrarenal vasoconstriction, and that it has an important role in causing hypertension (reviewed in Refs. 126 and 146). Key participants include increased intrarenal oxidative stress, a decrease in local endothelial nitric oxide, and activation of the renal sympathetic nervous system (SNS) (33, 146). The presence of the vasoconstrictor systems is also tightly linked with sodium reabsorption via both hemodynamic and nonhemodynamic effects.

Salt-sensitive hypertension is generally associated with suppression of the systemic renin-angiotensin system (RAS) due to the tendency for sodium and volume retention, but plasma renin activity is often not fully suppressed, suggesting some continued activation of the systemic RAS (91). However, recent studies have emphasized activation of the intrarenal RAS as a primary mechanism driving renal vasoconstriction and salt-sensitive hypertension (109). Intrarenal angiotensin II levels are elevated in salt-sensitive hypertension, even in the setting of plasma volume expansion (45, 103, 110, 112). The heightened renal angiotensin activity contrasts with suppressed plasma angiotensin II levels (Fig. 2) (45). Renal angiotensin II is produced in part by angiotensinogen and ACE activity in renal tubular cells (108, 109), which then acts on AT1 receptors in the proximal tubule, collecting duct, and intercalated cells to stimulate sodium reabsorption and raise BP (reviewed in Ref. 24). Intrarenal angiotensin II levels may also be regulated by ACE2. Specifically, a decrease in ACE2 activity will lead to an increase in angiotensin II and decrease in Ang 1–7 levels, resulting in elevated renal vascular resistance and BP.

The intrarenal mineralocorticoid axis may also be involved in salt-sensitive hypertension. Despite suppressed plasma aldosterone levels, there is activation of the mineralocorticoid receptor, which also contributes to inappropriate sodium retenion. For instance, activation of the mineralocorticoid receptor

Fig. 2. Plasma and renal angiotensin II concentrations in salt-sensitive hypertension induced with transient L-NAME administration. Studies were done after 5 wk of a high-salt diet (4% sodium diet) in rats previously treated with L-NAME orally for 3 wk. Renal angiotensin II levels were determined in renal interstitial fluid. SSHTN, salt-sensitive hypertension; MMF, rats treated similarly but receiving mycophenolate mofetil as immunosuppressive anti-inflammatory treatment. Control rats received a high (C-HSD) or a normal (0.4%)-sodium diet (C-NSD). X-axis is shown as log 2. Values are means ± SD; n = 8–10 rats (all groups). Figure is drawn from data previously reported (44).
may be secondary to Rac1 (133). Rac1 is a member of the Rho-guanine triphosphate hydroxylase family and has been shown to activate the mineralocorticoid receptor via an aldosterone-independent mechanism in the Dahl salt-sensitive, but not in the salt-resistant rat. Downstream of the mineralocorticoid receptor, serum- and glucocorticoid-inducible kinase 1 (Sgk1) is upregulated by salt loading with stimulation of the thiazide-sensitive sodium chloride cotransporter (NCC) and epithelial sodium channel (ENaC)-mediated reabsorption of sodium in the connecting and collecting duct areas of the nephron. Nevertheless, adrenalectomy suppresses Rac1 activation in salt-sensitive rats, and therefore a certain level of aldosterone is necessary for salt-induced Rac1 activation and development of salt-driven hypertension (48).

The SNS also regulates BP via both renal and extrarenal mechanisms (34). A high-salt diet results in higher plasma norepinephrine levels in patients with salt-sensitive hypertension (15, 51). In addition to causing systemic and preglomerular arteriolar vasoconstriction, activation of the SNS increases sodium reabsorption due to a reduction in the activity of the With-no-lysine kinase 4 (WNK4) (107), which is a negative (down) regulator of the NCC (150). The reduction in WNK4 activity and the resulting upregulation of the NCC is prevented by renal denervation and stimulated by a norepinephrine infusion in salt-sensitive rats. The effects of norepinephrine are reversed by propanolol and are absent in the β-adrenergic knockout mice. Therefore, the β2-adrenergic receptor plays a key function in salt-sensitive hypertension by augmenting sodium reabsorption in the distal convoluted tubule of the nephron.

Finally a role for intrarenal nitric oxide has been demonstrated in a variety of studies (6, 146). A loss of nitric oxide can lead to endothelial dysfunction, intrarenal vasoconstriction, and reduced sodium excretion (146). Reducing nitric oxide in the renal medulla of rats can result in sodium retention and an impairment in pressure-natriuresis (44, 45, 123). Subsequently, we and others could induce salt-sensitive hypertension by transiently administering other vasoconstrictive agents that could induce renal microvascular and interstitial inflammatory changes (77).

The role of low-grade renal inflammation in the renal parenchyma was investigated using mycophenolate mofetil (MMF), an immunosuppressive agent. MMF was administered to the rats after the angiotensin II infusion (123). Surprisingly, this treatment blocked the subsequent renal vasoconstriction and salt-sensitive hypertension (123). Further studies showed that the infiltrating inflammatory cells consisted of both T cells and macrophages and were expressing oxidants and angiotensin II (123). The sodium retention that results from local angiotensin activity appeared to be dependent on the presence of the inflammatory cells since suppressing renal inflammation with MMF blocks the local increase in angiotensin II and subsequent salt-sensitive hypertension (45, 122). Additional experiments with a variety of immune-suppressive agents and anti-inflammatory strategies showed that blocking the interstitial inflammatory response prevented, corrected, or ameliorated hypertension in a wide variety of genetic models and acquired models of hypertension (124, 125).

More recently, evidence that the T cells were responsible for the induction of hypertension has been obtained (50, 59). While early experimental studies suggested that a normally functioning thymus was necessary for the chronic elevation of BP (138), the role of T cells in the pathogenesis of hypertension was conclusively demonstrated in the studies of Harrison and colleagues (59), who showed that adoptive transfer of T cells restored the hypertensive response to angiotensin II that was absent in mice strains devoid of lymphocytes. Subsequent studies by these and other investigators established the contribution of inflammation in the vessel walls in the development of hypertension and the protection offered by T-regulatory cells (59, 62, 129). The T cells not only produce angiotensin II, but also the inflammatory cells may respond to local angiotensin II via the angiotensin AT1 receptor to limit their inflammatory response (26). Evidence accumulated in recent years has now firmly established the role played by inflammation in the kidney, central nervous system (CNS) arteries in hypertension and the involvement of immune reactivity in the development of these inflammatory phenomena.

In retrospect, it is evident that structural renal microvascular disease (arteriolosclerosis) is not necessary for the hypertensive response. However, it may still have an important role in altering the pressure-natriuresis response. For example, in the setting where the renal vasoconstriction is uniform, the ischemia would be expected to be evenly distributed throughout the kidney, and the rise in BP would increase renal perfusion pressure to relieve the ischemia. In these circumstances, while BP is increased, the slope of the pressure-natriuresis relationship is normal, a characteristic of salt-resistant hypertension. In contrast, if there are heterogeneous vascular lesions present, then a rise in BP and renal perfusion pressure might result in overperfusion of some regions of the kidney and underperfusion of others. The presence of persistent ischemia in some regions of the kidney might favor greater BP variability in
response to high and low salt intakes than that observed in normal subjects (77, 131). Furthermore, as arterioles become fibrotic, the ability to autoregulate may also be impaired, leading to greater transmission of pressure to the glomerulus, favoring progression of kidney disease (127).

Current Hot Topics

Could primary hypertension be an autoimmune disease? Our studies showed that the transient administration of agents that caused renal vasoconstriction (such as angiotensin II or blockade of the nitric oxide system) resulted in an infiltration of T cells and macrophages that cause persistent vasoconstriction, an impairment in pressure-natriuresis, and the development of salt-sensitive hypertension. Initially, our thought was that ischemia was stimulating the nonspecific release of chemokines that was eliciting the immune response and renal vasoconstriction. However, what was the stimulus for maintaining the renal vasoconstriction?

One possibility was that the T cells were reacting to neoantigens expressed in the ischemic tissue, resulting in an autoimmune response (117). Experimental studies have suggested that the accumulation of \( \gamma \)-ketotaldehydes (isoketals) induced by lipid peroxidation resulting from oxidative stress cause aggregation of proteins in the dendritic cells that are then capable of activating T cells and stimulating the production of cytokines (IL-6, IL-1\( \beta \), and IL-23) and an increase in co-stimulatory proteins (CD80 and CD86) that predispose to autoimmunity (88). One of the autoantigens that has been identified in animal models of salt-sensitive hypertension is heat shock protein-70 (117). Tolerizing rats with a HSP-70 peptide can protect rats from salt-sensitive hypertension that occurs following inhibition of nitric oxide synthesis (117).

Studies of the role of the immune system in human hypertension are limited, but there is some evidence that patients with primary hypertension have both T cell reactivity and antibodies to HSP-70 (117) as well as isoketal-modified proteins in circulating monocytes and dendritic cells (88). There is also one study that suggests that MMF can reduce BP in hypertensive subjects suffering from psoriasis and rheumatoid arthritis (68). Furthermore, subjects with autoimmune deficiency syndrome who have a low CD4 count have a lower prevalence of hypertension compared with those on retroviral therapy with improved CD4 counts (130).

Continued controversies related to salt. The average salt intake in most countries in the world is in the range of 9–12 g/day (14). A reduction of 2–5 g of salt/day has been estimated to reduce cardiovascular events and stroke by \( \sim 20\% \) in meta-analyses (64–66). The benefit of a reduction in salt intake has led to recommendations by the World Health Organization to restrict sodium intake to 1,500–2,000 mg daily, equivalent to 4–6 g of salt each day. Recent studies estimate that 1 of every 10 deaths from cardiovascular causes may be attributed to salt ingestion \( > 2 \) g daily, and 5 of these deaths occurred in individuals younger than 70 yr of age (106). In contrast, a large population study concluded that a higher daily intake of salt (between 3 and 6 g of sodium and \( > 1.5 \) g of potassium) was associated with a lower risk of death and cardiovascular events (112).

While controversy continues to exist related to the degree of salt restriction, there is also evidence that it may not be the amount of salt that is ingested, but rather the balance of salt and water intake. The original concept was that salt might act to increase BP by increasing blood volume, but more recent studies suggest that salt may also raise BP through its effects on osmolarity (32, 78). For example, a study reported that the administration of 6 g of salt in soup to normotensive volunteers resulted in an acute increase in serum sodium levels of 3 mmol/l associated with a 5.7 mmHg rise in systolic BP (137). It has been proposed that the rise in serum and cerebrospinal sodium activates the SNS in the CNS, resulting in the release of cardiotoxic steroids (ouabain and marinobufagenin) from the adrenal gland. In turn, these substances block Na\(^{+}\)-K\(^{+}\)-ATPases in vascular smooth muscle cells, leading to intracellular sodium that activates the Na/Ca exchanger, resulting in intracellular calcium accumulation and contraction of the vascular smooth muscle (9). The rise in serum sodium also activates macrophages, resulting in a stimulation of vascular endothelial growth factor that increases tissue permeability that results in the sequestration of sodium in the interstitial space (141).

Thus, if correct, these studies suggest that the hyperosmolar mechanism by which salt intake raises BP might be mitigated provided sufficient water was ingested to prevent the development of hypertonicity. Studies investigating this potential mechanism are encouraged as it would help separate the effects of volume expansion from hyperosmolarity in driving the hypertensive response. In addition to the direct effects of salt on BP, recent evidence also links salt with the development of autoimmunity since a high-salt diet results in the induction of pathogenic IL-17-producing CD4 (helper) T cells (89).

Role of obesity and metabolic syndrome in hypertension. The marked rise in obesity over the last century parallels the rise in hypertension, and indeed \( \sim 65–75\% \) of primary hypertension today may be accounted for by obesity (148). Obesity is associated with impaired natriuresis and salt retention (60), but the specific reason this occurs remains unclear. Several factors might be involved (Table 2) (30).

First, there is evidence for increased SNS activity both in the brain and in the kidney. Activation of the SNS might be due to a variety of factors, including coexistent obstructive sleep apnea, impaired baroreflex sensitivity, hyperinsulinemia, or alterations in adiponectin or leptin. Recent studies suggest leptin signaling may play an important role (30). Leptin is an adipokine (a hormone released from adipose tissue) that has a

Table 2. Potential pathogenic factors associated with hypertension in obesity

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
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<tbody>
<tr>
<td>Endothelial dysfunction</td>
<td>(impaired endothelial nitric oxide bioavailability)</td>
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<tr>
<td>Hyperinsulinemia</td>
<td></td>
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<tr>
<td>Hyperleptinemia</td>
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<td>Hyperuricemia</td>
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<tr>
<td>Hypoadiponectinemia</td>
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<tr>
<td>Impaired baroreflex sensitivity</td>
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<tr>
<td>Increased CNS SNS activation</td>
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<tr>
<td>Intrarenal SNS activation</td>
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<tr>
<td>Physical compression of the kidney by fat</td>
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<tr>
<td>Renin-angiotensin system activation (intrarenal)</td>
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<tr>
<td>Sleep apnea (obstructive)</td>
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<tr>
<td>Sugar intake (fructose)</td>
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CNS, central nervous system; SNS, sympathetic nervous system.
primary function to stimulate satiety following ingestion of a meal. Leptin is released after food ingestion and then binds to leptin receptors in the hypothalamus that lead to a reduction in food intake and increase energy expenditure, but in many individuals with obesity a state of leptin resistance occurs. As a consequence, serum leptin levels rise. However, while the satiety centers are resistant to leptin, other parts of the brain remain sensitive to the increasing leptin levels (119). Specifically, leptin binds to leptin receptors in pro-opiomelanocortin-expressing cells in the arcuate nucleus of the hypothalamus, stimulating the release of $\alpha$-melanocyte-stimulating hormone ($\alpha$-MSH) that binds melanocortin-4 receptors in the paraventricular nucleus and lateral hypothalamic area to stimulate SNS activity, that stimulates renal SNS activity, resulting in sodium reabsorption and an impairment in pressure-natriuresis. Indeed, hypertension in obese animals can be prevented if various specific measures were performed to address whether the renal SNS activity was blocked (7). Nevertheless, it raises the question of whether other mechanisms may contribute to the hypertensive response in subjects with difficult-to-control hypertension (7).

One emerging candidate is hyperuricemia, which is common in subjects with obesity, particularly those with the metabolic syndrome, and has been found to consistently predict the development of hypertension (40). Relatively higher uric acid levels are also seen in low-birth-weight children and have been correlated with endothelial dysfunction and higher BP (47, 114). Raising uric acid in rats causes renal vasoconstriction and hypertension in association with the development of microvas-

Fig. 3. Proposed mechanism for the development of hypertension. Certain risk factors, such as low birth weight, diets high in fructose or salt, and obesity may increase the risk for hypertension. Low birth weight and dietary intake of added sugars, for example, can both result in mild hyperuricemia that may result in generation of reactive oxygen species (ROS), activation of the renin-angiotensin system (RAS), and endothelial dysfunction with low nitric oxide (NO) levels (41). Elevated leptin levels present in subjects with obesity or metabolic syndrome can also stimulate sympathetic outflow from the central nervous system (CNS). The generation of these vasoconstrictors results in renal vasoconstriction that causes mild ischemia, leading to nonspecific chemokine release as well as the induction of neoantigens [heat shock protein (HSP) 70, isoketal-induced protein aggregates] that activates dendritic cells and an autoimmune response. The local inflammation results in intrarenal generation of vasoconstrictors that perpetuate the ischemia and block pressure-natriuresis. Sodium is retained, resulting in an increase in serum osmolarity that leads to CNS sympathetic nervous system (SNS) activation and the release of cardiotonic steroids such as ouabain and marinobufagenin that cause vascular smooth muscle cell (VSMC) constriction and a rise in systemic vascular resistance (SVR). As blood pressure increases, the increase in renal perfusion pressure relieves tubular ischemia, allowing sodium handling to reset but with a parallel shift in the pressure-natriuresis curve (salt-resistant state). However, with the development of microvascular disease the relief of the ischemia is not uniform, leading to persistent ischemic areas that result in a rightward shift and change in slope of the pressure-natriuresis curve, resulting in salt-sensitive hypertension. ECV, extracellular volume.
cular disease and interstitial inflammation (102, 128). Initially, the hypertension responds to the lowering of uric acid, but once the microvascular disease and interstitial inflammation develop the animals will develop salt-sensitive hypertension even if the serum uric acid returns to the normal range (143). These studies suggest that an elevation in uric acid might be more important in the initiation of hypertension, but that once the microvascular and interstitial inflammation take hold, the kidney will drive the hypertensive response. Indeed, elevated uric acid is present in almost 90% of adolescents with primary hypertension (39), and pilot clinical studies also suggest lowering uric acid might be of benefit in improving BP in hypertensive and hypertensive adolescents (42, 134). While uric acid is a good candidate for driving hypertension, some studies suggest that the hypertension may be mediated more by xanthine oxidase, which produces both oxidants and uric acid (49). Furthermore, while some genetic studies have linked genetic polymorphisms that increase uric acid levels with hypertension (99, 115), others have not (18, 151). Hence, more clinical evidence is needed.

There have also been a number of studies linking intake of added sugars, particularly soft drinks, with the development of hypertension (70, 85, 110). One potential mechanism may relate to the fructose component in high-fructose corn syrup (HFCS) and sucrose, as fructose is known to raise uric acid in humans (23, 92) and also to increase BP (13). While studies linking fructose intake with hypertension have been mixed (97), there is evidence that reducing sugar intake can result in lowering of BP (19). Further studies are necessary to better evaluate this relationship.

Summary

We have made great progress since Mahomed discovered primary hypertension over 140 years ago. A figure summarizing the current proposed mechanism for hypertension is shown (Fig. 3). We propose that hypertension is initiated by a variety of mechanisms that result in renal vasoconstriction. The vasoconstriction induces renal ischemia that brings in inflammatory (T cells and macrophages) cells that drive continuing intrarenal vasoconstriction and oxidative stress that lead to impaired pressure-natriuresis. The ischemia results in the expression of neoantigens such as HSP-70 that result in an autoimmune reaction that maintains the local inflammatory reaction, leading to persistent renal vasoconstriction and salt sensitivity.

The factors initiating the hypertensive response likely involve a variety of genetic, epigenetic, and acquired mechanisms. The potential role of fructose and uric acid also deserves further study. Once the cause is delineated, we should expect major advances in both prevention and treatment of this very important disease.

DISCLOSURES

R. J. Johnson and M. A. Lanasa are inventors with several patent applications related to blocking fructose metabolism in metabolic and renal diseases (University of Colorado). R. J. Johnson, M. A. Lanasa, and L. G. Sánchez-Lozada are also founders of Colorado Research Partners. R. J. Johnson is also on the Scientific Board of Amway and XORT Therapeutics.

AUTHOR CONTRIBUTIONS


REFERENCES


