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HYPERTENSION AND METABOLIC SYNDROME (J SPERATI, SECTION EDITOR)

Molecular Mechanisms of Sodium-Sensitive Hypertension in the Metabolic Syndrome

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Abstract
Purpose of Review We review the known mechanisms of sodium-sensitive hypertension in the metabolic syndrome with a focus on preclinical models, differences between these models, and methodological limitations. We also identify future directions for a better understanding and treatment of this common condition.
Recent Findings Rigorous methodologies to measure blood pressure in preclinical models may clarify some of the inconsistencies in the literature. Renal, neural, hormonal, and cardiovascular systems are dysregulated and contribute to elevated blood pressure. Local renin-angiotensin systems enhance systemic hormone signaling to increase blood pressure.
Summary Since the original description of metabolic syndrome, investigators from many fields have contributed to an increasingly complex and mechanistic understanding of this common condition. These systems integrate to regulate sodium transport in the kidney leading to hypertension and enhanced sodium sensitivity. An array of non-uniform preclinical models are used and support clinical studies to inform which models are pathophysiologically relevant for further mechanistic studies to guide targeted therapy.

Keywords High fat diet · Obesity · Insulin resistance · Sodium sensitivity · Mineralocorticoid receptor

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Introduction

What is the Metabolic Syndrome?

The metabolic syndrome, as defined by the International Diabetes Federation, is a group of factors that includes visceral adiposity, dyslipidemia, and hypertension [1]. The term, metabolic syndrome, was first coined by Haller [2] in 1977, though a clustering of conditions predisposing to atherosclerosis had been noted in the 1920s [3]. In 1988, Reaven [4] posited insulin resistance as the central etiology of the metabolic syndrome, or syndrome X. Today, the metabolic syndrome affects up to one-third of Americans [5].

What is Sodium Sensitivity?

The magnitude of rise or fall in blood pressure with increases or decreases of sodium intake is termed sodium sensitivity and is caused by a primary increase in renal sodium reabsorption. In both humans and animal models, sodium sensitivity is widely variable across individuals. Kawasaki and Bartter demonstrated this wide variation in the first description of sodium sensitivity in humans [6]. Despite this variability, individuals with the metabolic syndrome are more sodium-sensitive than healthy controls.

Epidemiology of Sodium Sensitivity Hypertension in the Metabolic Syndrome

Among factors in the metabolic syndrome, obesity and insulin resistance are independently associated with hypertension. In the GenSalt study, the metabolic syndrome was associated with a ~40% increase in sodium sensitivity compared with controls after multivariate adjustment [7]. In the INTERSALT study [8], which observed epidemiologic trends

in blood pressure and sodium intake across communities throughout the world, each 10 kg increase in body weight associated with an average of 3.0 and 2.2 mmHg increase in systolic and diastolic blood pressure, respectively. The Framingham study [9] estimated obesity, or adiposity, as a major predictive factor for almost 75% of individuals with hypertension, and the Trials of Hypertension Prevention study [10] demonstrated dramatic reductions in blood pressure with weight loss. Approximately one-half of patients with essential hypertension have insulin resistance [11]. In turn, obesity and insulin resistance-associated hypertension is more sodium-sensitive than in hypertensive controls without obesity [12].

Sodium-Sensitive Hypertension in the Metabolic Syndrome via Renal Sodium Transport

Based on Guyton's theory, the final common pathway for all forms of hypertension is decreased renal sodium excretion [13], which expands the blood volume, and increases systemic blood pressure to excrete excess sodium to achieve steady-state. While increased vascular smooth muscle tone may acutely increase blood pressure under many physiologic scenarios, including the metabolic syndrome, compensatory sodium excretion must be impaired to permit this increased blood pressure to persist (i.e. hypertension). Evidence of many endocrine and metabolic pathophysiologic processes have been described in the metabolic syndrome including enhanced general and renal sympathetic nervous system activity [14, 15]; oxidative stress [16, 17] and inflammation [18] in the kidney; insulin activation of renal tubular epithelial cells [19–22]; and/or activation of the systemic, or local renin-angiotensin systems including enhanced mineralocorticoid action [23–25]. The final common pathway for these mechanisms is impaired glomerular filtration rate, or increased tubular sodium reabsorption via expression or post-translational modification of sodium transporters and/or their regulatory components [26].

Despite what we have learned regarding the mechanisms of sodium-sensitive hypertension, major guidelines for blood pressure management do not define specific classes of antihypertensive medications for individuals with the metabolic syndrome [27]. In this review, we will outline the advantages and disadvantages of commonly used preclinical models, highlight the known mechanisms of the sodium-sensitive hypertension associated with parameters of the metabolic syndrome, and discuss current gaps in the literature and future directions in this important field of research.

Preclinical Models of Obesity, Insulin Resistance, and the Metabolic Syndrome

It is important to distinguish obesity and insulin resistance from the metabolic syndrome, although all three are strongly associated with hypertension [8, 28, 29]. The metabolic syndrome represents a specific subset of individuals with insulin resistance, a high, but not universal, prevalence of obesity [30], and dyslipidemia. In the existing literature of preclinical models, these distinct disease states are often used interchangeably. For example, a high fat diet in mice is referred to as a mouse model of the metabolic syndrome and leads to obesity, insulin resistance, sodium-sensitive hypertension, but not the dyslipidemia (elevated triglycerides) seen in humans with the metabolic syndrome per se [31]. While this may be inaccurate, the mechanisms of sodium-sensitive hypertension in obesity, insulin resistance, and the metabolic syndrome are likely shared based on common pathophysiologic features. However, several of the pathways we will discuss may be particularly relevant for a subset of these conditions.

Preclinical Models of Sodium-Sensitive Hypertension in the Metabolic Syndrome

There is little uniformity across species and models (e.g. a high fat-fed dogs vs. high fat-fed C57Bl/6 mice vs. *db/db* mice) of identified mechanisms of hypertension in the metabolic syndrome. We characterized changes in body weight, plasma insulin, plasma lipid profile, urinary sodium excretion, and blood pressure in C57BL/6 mice fed high fat and/or high fructose diets previously associated with obesity and insulin resistance [32, 33]. While high fat-feeding faithfully recapitulated many features of the metabolic syndrome, high fructose feeding in mice, unlike rats, does not always induce obesity and insulin resistance. Among mouse models of the metabolic syndrome, NZBWF1, and $KKA^{y/a}$ strains develop obesity, insulin resistance, and elevated blood pressure, but the mechanisms are unknown. Leptin receptor-deficient *db/db* mice develop obesity and insulin resistance, but hypertension is variable [34]. Of note, these mice also develop diabetes with glycosuria and osmotic diuresis [35] that can stimulate compensatory sodium reabsorption, thereby confounding the assessment of sodium excretion and the renin-angiotensin-aldosterone system, a commonly ascribed pathway in hypertension.

Although the majority of transgenic mice are produced on a C57BL/6 background, these mice are well known to be resistant to elevations in blood pressure compared with other mouse strains or with rats [36]. Therefore, small changes in blood pressure may translate to a clinically significant difference in humans. For example, patients with hypertension due to Liddle's syndrome, i.e., gain of function mutations in subunits of the *epithelial sodium channel* (ENaC), have an average mean arterial pressure 43 mmHg higher than controls [37]. Transgenic mice on a C57Bl/6 background carrying similar mutations do not have an elevated blood pressure on a normal sodium diet and only a ~10 mmHg increase in mean arterial pressure on a high sodium diet [38]. Similarly, some patients with Gordon's syndrome, another form of sodium-

sensitive hypertension, have systolic blood pressures >200 mmHg [39], but transgenic mice with mutant, inactive *with no lysine kinase 4* (WNK4), recapitulating this condition, have a systolic blood pressure <10 mmHg higher than controls, and only 13 mmHg higher than mice overexpressing wild-type WNK4 [40].

We have observed a consistent, reproducible, small increase in blood pressure in high fat-fed mice [31], as well as increased sodium sensitivity [31, 41]. However, as reviewed by Kennedy et al. [42], there are multiple, inconsistent studies of hypertension in mouse models of the metabolic syndrome. Table 1 summarizes experiments comparing high fat or fructose-fed C57BL/6 mice to controls. In chronically high fat-fed mice, blood pressure varied widely from −13 to +37 mmHg [33, 43–60] compared to controls. Blood pressure measurement in mouse models of the metabolic syndrome are confounded by technical considerations such as dietary sodium, phytoestrogen content, and feeding patterns [61].

Feeding patterns will be different between high fat-fed and control groups due to the dramatic difference in the caloric content and, presumably, taste of diets. Differences in food, and therefore sodium, intake can significantly confound the interpretation of blood pressure data. Similarly, blood pressure is acutely regulated by fasting, another potential confounder if diets are particularly unpalatable [62]. Mouse models based on fructose-spiked drinking water also dramatically decrease sodium intake, as the mice will also eat less food.

Multiple groups have validated [63, 64] or invalidated [65, 66] tail-cuff plethysmography. Its low cost and relative simplicity may perpetuate its use, though radiotelemetry systems are generally accepted as the gold standard. A thorough discussion of protocols for blood pressure measurement is beyond the scope of this review, but Van Vliet [61] provides an elegant summary on the justification and protocols for radiotelemetric blood pressure measurement. One limitation of plethysmography in studying blood pressure in models of the metabolic syndrome is the inability to measure pressure in active, unrestrained mice. Obese mice are often less active, and we observed that changes in blood pressure with locomotion are a significant contributor to differences in blood pressure between control and high fat-fed mice. Thus, mouse models, and certainly other species, require standardization to study the mechanisms of hypertension in the metabolic syndrome. Published results should detail dietary constituents, locomotion, and methods of blood pressure measurement.

Mechanisms of Sodium-Sensitive Hypertension in the Metabolic Syndrome

Renal Sodium Reabsorption in the Metabolic Syndrome

Within the kidney, several tubular sodium transporters are potential mediators of the observed impaired sodium excretion. Huang et al. [41] demonstrated that deletion of *serum and glucocorticoid kinase 1*, a kinase that activates the ENaC, prevented high fat diet-induced hypertension, but this kinase can also modulate sodium transporters proximal to the aldosterone-sensitive distal nephron [67–69]. Using microperfusion, we examined sodium transport in isolated cortical collecting ducts, and found no difference in sodium flux between low fat and high fat-fed mice, excluding the ENaC, *thiazide-sensitive sodium-driven chloride bicarbonate exchanger*, and *pendrin* as potential mediators. We also excluded ENaC activity as a mechanism for impaired natriuresis and increased blood pressure of high fat feeding as benzamil, a pharmacologic inhibitor of ENaC, had no differential effect on sodium excretion or blood pressure in low fat- vs. high fat-fed mice [31]. Based on these data, high fat feeding likely increases sodium transport in upstream segments of the nephron. In mice, insulin-mediated activation of *insulin receptor substrate 2* in proximal tubule cells stimulates sodium reabsorption [70], although these experiments have not been performed in a model of insulin resistance. Davies et al. [71] showed that high fat feeding of mice increases *sodium-potassium-2 chloride cotransporter* (NKCC2) phosphorylation and decreases *AMP kinase* activity. *Sodium-chloride cotransporter* (NCC) expression is increased in obese Zucker rats [48], and its activity is stimulated by insulin infusion in Sprague Dawley rats [72]. These findings provide a basis for future experiments using genetic knockouts or pharmacotherapies to measure the contribution of upstream transporters in mediating the effect of high fat diet on the kidney tubule.

Role of the Sympathetic Nervous System in Sodium-Sensitive Hypertension of the Metabolic Syndrome

Several investigators have demonstrated a role for the systemic and renal sympathetic nervous system in hypertension of the metabolic syndrome. Data from obese individuals [73, 74] and animal models, including carbohydrate- and high fat-fed mice [75], rats [76], and dogs [77, 78] demonstrate increased production of catecholamines and blood pressure sensitivity to vasopressors and alpha adrenergic blockade. Hyperleptinemia, associated with obesity and the metabolic syndrome, permissively stimulates the sympathetic nervous system and increases blood pressure [79, 80], despite selective resistance to its anorexigenic effects. *Melanocortin 4 receptors* (MC4R) likely mediate leptin-dependent effects on blood pressure. Using a combination of leptin receptor deficient mice and MC4R knockout mice, Rahamouni et al. [81] elegantly demonstrated that both leptin and insulin centrally activate renal sympathetic nerve activity via MC4R. Concordant observations were made using MC4R agonists in mice and humans [81–83] and antagonists in mice [84, 85] and spontaneously hypertensive rats [86]. In contrast, melanocortin 4 receptor knockout mice and

Table 1 Summary of experiments comparing the blood pressure of high fat or fructose-fed mice to controls

Reference	Year	Strain	Sex	Age (weeks)	Type of diet	Fat/sugar content (%)	Sodium content (%)	Control diet	Equivalent phytoestrogens?	Duration (weeks)	Method	Delta (mmHg)
Mills, et al.	1993	C57BL/6J	Male	4	HFSC	35/35	0.4	Std chow	No	12	Carotid/tail-cuff	+23
Williams, et al.	2003	C57BL/6J	Male	5	Fat	58	NA	Std chow	No	12–15	Telemetry	+5/+9
Rahmouni, et al.	2005	C57BL/6J	Male	6	Fat	45	0.1	Std chow	No	10	Telemetry	+10
Farah, et al.	2006	C57BL/6 Harlan	Male	24–29 g	Fructose	60	NA	Std chow	No	8	Telemetry	+12
Rodriguez, et al.	2006	C57BL/6J	Male	4	Fat	45	NA	10% fat	Yes	6	Carotid	+17
Huang, et al.	2006	C57BL/6 × SV129J	Male/female	5	Fat	45	1% in water	4% fat	Yes	17	Tail-cuff	+17
Huang, et al.	2006	C57BL/6 × SV129J	Male / Female	5	Fat	45	0.25	4% fat	Yes	17	Tail-cuff	+11
Huang, et al.	2006	C57BL/6 × SV129J	Male / Female	NA	Fructose	10	0.2	NA	No	3	Tail-cuff	n.s.
Huang, et al.	2006	C57BL/6 × SV129J	Male / Female	NA	Fructose	10	0.4	NA	No	3	Tail-cuff	+11
Roncon-Albuquerque, et al.	2008	C57BL/6J	Male	5	HFSC	35/35	3.9	5% fat	No	12	Tail-cuff	+15
Deji, et al.	2009	C57BL/6	Male	6	Fat	60	NA	10% fat	Yes	12	Tail-cuff	−8
Deji, et al.	2012	C57BL/6	Male	NA	Fat	60	0.1	10% fat	Yes	12	Tail-cuff	+25
Gupte, et al.	2008	C57BL/6J	Male	8	Fat	60	NA	10% fat	Yes	16	Telemetry	+9
Gupte, et al.	2008	C57BL/6J	Male	8	Fat	60	NA	10% fat	Yes	1	Tail-cuff	n.s.
Gupte, et al.	2012	C57BL/6J	Male	8	Fat	60	NA	10% fat	Yes	16	Telemetry	+9–11
Gupte, et al.	2012	C57BL/6J	Female	8	Fat	60	NA	10% fat	Yes	16	Telemetry	n.s.
Police, et al.	2009	C57BL/6J	Male	8	Fat	60	NA	10% fat	Yes	1–4	Tail-cuff	−13
Symons, et al.	2009	C57BL/6J	Male	10	Fat	56	NA	10% fat	Yes	10–12	Telemetry	+15
Rong, et al.	2010	C57BL/6J	Male	8	Fat	60	NA	Std chow	No	12	Tail-cuff	n.s.
Belin de Chantemele, et al.	2011	C57BL/6J	Male	8	Fat	60	NA	4% fat	No	32	Telemetry	−3
Purkayastha, et al.	2011	C57BL/6J	Male	NA	Fat	NA	0.25	Std chow	No	24	Telemetry	+21/+27
Costa, et al.	2011	C57BL/6	Male	8	Fat	60	7.25	10% fat	Yes	9	Tail-cuff	n.s.
Costa, et al.	2011	C57BL/6	Male	8	Fat	60	0.1	10% fat	Yes	9	Tail-cuff	n.s.
Liu, et al.	2012	C57BL/6 J	Male	5	Fat	45	NA	10% Fat	Yes	12	Tail-cuff	+9–11
Mingorance, et al.	2012	C57BL/6	Male	6	Fat	42	0.15	Std chow	No	9	Tail-cuff	n.s.
Marshall, et al.	2013	C57BL/6 × SV129J	Male	15	Fat	58.4	NA	4% fat	No	12	Telemetry	+5–10
Inoue, et al.	2013	C57BL/6	NA	16	Fat	20	NA	Std chow	No	12	Tail-cuff	+17
Gamliel-Lazarovich, et al.	2013	C57BL/6	Male	9	Fat	60	NA	Std chow	No	20	Tail-cuff	+21
Davies, et al.	2014	C57BL/6J	Male	8	Fat	43	0.1	5% fat	No	3	Tail-cuff	+1
Nizar, et al.	2016	C57BL/6J	Male	6	Fat	60	0.1	10% fat	Yes	12	Telemetry	+3
Nizar, et al.	2016	C57BL/6J	Male	6	Fat	60	1.6	10% fat	Yes	12	Telemetry	+5.4

NA not available, *n.s.* non-significant

humans with inactivating mutations develop obesity, hyperinsulinemia, and hyperleptinemia, but not hypertension [87–89].

Granger et al. were the first to demonstrate a role for renal nerves in this form of hypertension. For this study, authors demonstrated that high fat feeding in mongrel dogs decreased sodium excretion and increased blood pressure, but that bilateral renal denervation abrogated these effects [90]. The development of clinical renal denervation technology has made possible the targeting of renal nerves. for the treatment of hypertension. In the first reported phase 3 clinical trial, SYMPLICITY III, there was a trend toward improvement in blood pressure in obese vs. non-obese individuals, but further studies are needed to determine if this therapy vs. sham control is more efficacious in individuals with metabolic syndrome-related hypertension [91].

The mechanisms by which obesity and/or insulin resistance-mediated renal sympathetic nerve activity increases renal sodium transport will be an interesting area for future research. Classic studies have demonstrated that renal nerves regulate *sodium-hydrogen exchanger 3* [92, 93] and NKCC2 [93, 94] via norepinephrine, renin, angiotensin II, and nitric oxide [95–97]. More recently, Ellison and colleagues have shown that norepinephrine activates the NCC [98]. The contribution of sympathetic nerves to activity of specific renal transporters within the metabolic syndrome will be the next frontier in this field.

Role of Oxidative Stress and Inflammation in Sodium-Sensitive Hypertension of the Metabolic Syndrome

Obesity stimulates systemic and renal oxidative stress in mice [17] and rats [16]. By inhibiting nitric oxide signaling, oxidative stress results in endothelial dysfunction, resistance vessel constriction, and increased sodium reabsorption. The *sodium-potassium-2 chloride cotransporter* [99] is disinhibited by declining nitric oxide, as is *oxidative stress-response kinase-1*, indirectly activating *sodium-potassium-2 chloride cotransporter* [100]. Both hypertension and inflammation are reduced with infusion of tempol, a free radical scavenger, in high fat-fed rats [18].

Recent studies by Harrison et al. [101, 102] have implicated T_H1 and T_H17 cell infiltration in the renal parenchyma as a direct mechanism to enhance both proximal and distal sodium transport. Moreover, Obesity is known to modulate these same lymphocyte subtypes [103]. It remains to be explored to what degree these inflammatory mechanisms contribute to hypertension in the metabolic syndrome.

Role of Insulin in Sodium-Sensitive Hypertension of the Metabolic Syndrome

A compelling case has been made that insulin resistance promotes hypertension in the metabolic syndrome through compensatory hyperinsulinemia. Physiologic concentrations of insulin increase renal sodium reabsorption in rats [104], dogs [105], and humans [106]. Yet, insulin infusion does not increase blood pressure in mice or humans [107, 108]. In addition, genetic causes of obesity, e.g., deletions or mutations in MC4R or leptin, are not associated with hypertension despite insulin resistance and concomitant hyperinsulinemia [34].

Given the robust and long-standing association of insulin and blood pressure, absence of evidence is not evidence of absence. There are several potential reasons for an association between insulin levels and blood pressure without tangible proof of causality. Several investigators have hypothesized that insulin increases renal sodium reabsorption either directly or indirectly due to vasodilation [109]. A natural experiment that could answer this question is the measurement of renal sodium reabsorption with the use of diet-induced insulin resistance (e.g., high fat diet) in vascular endothelial specific insulin receptor knockout mice. However, to our knowledge, this experiment has not been reported.

Another important area of knowledge is the impact of insulin resistance (and the resultant metabolic milieu) on insulin-mediated blood pressure regulation. Deletion of renal tubular insulin receptors have demonstrated a paradoxical increase in blood pressure and decreased nitric oxide production in otherwise insulin-sensitive mice [110, 111], though constitutive deletion that may have alter tubule development in utero [112]. We are currently studying renal tubular insulin receptor knockout mice to address the contribution of insulin signaling in the kidney to hypertension of the metabolic syndrome. Brands and colleagues published compelling data on the role of insulin to stimulate renal sodium transport under conditions of type 1 diabetes mellitus, i.e., hypoinsulinemic hyperglycemia [105]. Whether a putative role for insulin in hypertension requires overt diabetes rather than the metabolic syndrome is currently unknown.

Role of Systemic and Local Renin-Angiotensin Systems in Sodium-Sensitive Hypertension of the Metabolic Syndrome

The renin-angiotensin-aldosterone system plays a pathophysiologic role in hypertension of the metabolic syndrome both directly, by increasing of renal sodium reabsorption, and indirectly, via many of the pathways previously described. In obese mice [113, 114] and humans [115], adipocytes increase their production of angiotensinogen. Genetic deletion of angiotensinogen in adipocytes lowers plasma angiotensin II and systolic blood pressure in mice, and weight loss lowers angiotensin II in humans [116].

Aldosterone, via the mineralocorticoid receptor, may play a critical role in the magnitude of hypertension in the metabolic syndrome. Aldosterone levels correlate with obesity in dogs [117] and humans [118], possibly via adipocyte-derived

angiotensinogen or adipocyte-derived mineralocorticoid releasing factors [119]. Drugs inhibiting the mineralocorticoid receptor are effective antihypertensive agents in individuals with the metabolic syndrome [56] independent of the reduction of insulin resistance associated with mineralocorticoid receptor blockade [120]. Moreover, high fat-fed mice do not exhibit elevated aldosterone, and have only mildly elevated blood pressure despite obesity and insulin resistance [31]. Whether mineralocorticoids are needed to more accurately model hypertension of the metabolic syndrome in mice is unknown.

Angiotensin II and aldosterone also influence the vasculature to induce or maintain hypertension, possibly by reducing nitric oxide bioavailability [121]. Activation of the mineralocorticoid receptor in vascular endothelial cells can raise blood pressure prior to a detectable increase in sodium reabsorption [122], and vascular smooth muscle cell-specific mineralocorticoid receptor deletion lowers blood pressure [123].

Local renin-angiotensin systems may play a distinct role in hypertension of the metabolic syndrome. The intrarenal renin-angiotensin system appears to amplify the effect of systemic angiotensin II [124] on sodium transport and blood pressure. Whether ablation of this intrarenal axis is sufficient to ameliorate the hypertension seen in diet-induced or genetic models of the metabolic syndrome is unknown. The local renin-angiotensin system in adipocytes can stimulate the sympathetic nervous system via leptin, or production of aldosterone-releasing factors [119]. Adipocyte-specific knockout of angiotensinogen protects mice from elevated systemic angiotensin II and high blood pressure in a diet-induced model of the metabolic syndrome [113]. Massiera et al. [114] demonstrated that adipocyte-derived angiotensinogen contributes to growth of adipose tissue, and increase of circulating angiotensinogen and systemic blood pressure. Moreover, renin-angiotensin system inhibitors decrease obesity and hyperinsulinemia in male NZO/BL6 F1 rats, a genetic model of insulin resistance [125].

While this evidence provides a rationale for renin-angiotensin system blockade in patients with the metabolic syndrome, few studies have specifically addressed the use of these agents in obese individuals. One notable study is the TReatment in Obese Patients with HYpertension (TROPHY) trial [126], which compared the efficacy of an ACE inhibitor, lisinopril, or a diuretic, hydrochlorothiazide, given at various doses to obese and hypertensive individuals. The number of individuals who responded to this antihypertensive regimen was greater with lisinopril (40% versus 33%, $P < 0.05$), although plasma glucose improved in the lisinopril group and worsened in the hydrochlorothiazide group [126].

Conclusion

Obesity, insulin resistance, and the metabolic syndrome engender hypertension through multiple pathways in preclinical animal models, and very likely in humans as well. Renal, neural, hormonal, and cardiovascular systems integrate information to maintain blood pressure despite the substantial stressors that occur in daily life (e.g., eating, fasting, breathing, and locomotion). This integration and interdependence greatly complicate the study of hypertension associated with the metabolic syndrome. Yet, important work from an equally diverse group of investigators has progressively mapped out the mechanisms of this condition. Increased standardization within species would improve the reproducibility of data. In addition, differences in the dominant pathophysiologic pathway within and across species limit the translational power of any one pathway in elucidating hypertension in humans with the metabolic syndrome. Thus, knowledge gleaned from human studies or human samples will be critical in directing future investigation of mechanisms within preclinical models. Despite these challenges, hypertension in the metabolic syndrome has a profound impact on global human health, highlighting the need for further study.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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