The Role of Aldosterone in Obesity-Related Hypertension

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Obese subjects often have hypertension and related cardiovascular and renal diseases, and this has become a serious worldwide health problem. In obese subjects, impaired renal-pressure natriuresis causes sodium retention, leading to the development of salt-sensitive hypertension. Physical compression of the kidneys by visceral fat and activation of the sympathetic nervous system, renin–angiotensin systems (RAS), and aldosterone/mineralocorticoid receptor (MR) system are involved in this mechanism. Obese subjects often exhibit hyperaldosteronism, with increased salt sensitivity of blood pressure (BP). Adipose tissue excretes aldosterone-releasing factors, thereby stimulating aldosterone secretion independently of the systemic RAS, and aldosterone/MR activation plays a key role in the development of hypertension and organ damage in obesity. In obese subjects, both salt sensitivity of BP, enhanced by obesity-related metabolic disorders including aldosterone excess, and increased dietary sodium intake are closely related to the incidence of hypertension. Some salt sensitivity-related gene variants affect the risk of obesity, and together with salt intake, its combination is possibly associated with the development of hypertension in obese subjects. With high salt levels common in modern diets, salt restriction and weight control are undoubtedly important. However, not only MR blockade but also new diagnostic modalities and therapies targeting and modifying genes that are related to salt sensitivity, obesity, or RAS regulation are expected to prevent obesity and obesity-related hypertension.

Keywords: aldosterone; blood pressure; hypertension; obesity; salt; salt sensitivity of blood pressure.

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The prevalence of obesity and its associated cardiovascular, metabolic, and renal diseases has increased markedly and this has become a serious worldwide health problem over the past decade. The Obesity and Overweight Fact Sheet published by the World Health Organization revealed that more than 1.9 billion adults were overweight in 2014, of whom more than 600 million were obese, accounting for 39% and 13% of adults, respectively. Moreover, the medical costs of obese individuals were approximately 30% higher than those of normal weight peers.[1] Obesity appears to be responsible for a substantial economic burden in many countries.[2]

The risk of hypertension significantly increases in proportion with the amount of excess weight.[3] Moreover, obesity is associated with the incidence of cardiovascular disease (CVD),[4] type 2 diabetes mellitus, stroke, and dyslipidemia.[5] Obesity is related to a combination of metabolic and cardiovascular disorders and is strongly linked to the mortality risk.[6]

On the other hand, growing evidence recently suggested that both plasma and urinary aldosterone concentrations are increased in obese individuals,[7,8] and aldosterone is involved in cardiorenal and metabolic disease.[9] Classically, aldosterone has long been considered to play a central role in the regulation of electrolyte and fluid volume and the maintenance of blood pressure (BP) homeostasis.[10] However, the aldosterone/mineralocorticoid receptor (MR) system plays a key role in cardiovascular and renal damage.[11,12] These nonclassical actions of aldosterone and the involvement of MR activation in CVD were proven by 3 large-scale randomized clinical trials, the Randomized Aldactone Evaluation Study (RALES),[13] the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS),[14] and the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF).[15] Moreover, the recent clinical trials of the Eplerenone Combination versus Conventional Agents to Lower Blood Pressure on Urinary Antialbuminuric Treatment Effect (EVALUATE) study[16] and the Mineralocorticoid Receptor Antagonist Tolerability Study-Diabetic Nephropathy (ARTS-DN)[17] demonstrated the pathogenetic role of aldosterone/MR activation in chronic kidney disease (CKD). In this review, we focus on the role of the aldosterone/MR system in obesity-related hypertension.

OBESITY AND HYPERTENSION

Obesity, especially visceral obesity, is closely related to hypertension.[18,19] The relationship between human obesity and hypertension was first described by Vague in 1956.[20] He divided obese patients into "android" type (upper body obesity) and "gynoid" type (lower body obesity) and reported that cardiovascular and metabolic complications of obesity were more prevalent in the former. However, such complications do not develop in all obese individuals, and some normal weight adults exhibit metabolic syndrome and its comorbidities.[21,22] This is because abnormal body fat distribution, such as excess visceral adipose tissue, is a more important factor than body mass index for morbidity.[23,24] Visceral adiposity reportedly plays a major role in the occurrence of hypertension, diabetes mellitus, hyperlipidemia,

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and atherosclerosis in obese humans and in animal models.[24] Visceral and subcutaneous adipocytes may play a role in different ways. Visceral adipose tissue is a source of numerous adipokines, such as tumor necrosis factor-α, interleukin-6, plasminogen activator inhibitor-1, angiotensinogen (Agt), C-reactive protein, and leptin, most of which are deemed to be proinflammatory.[25] Unlike these adipokines, serum levels of adiponectin, an anti-inflammatory and vasculoprotective adipokine, are decreased in obesity. Furthermore, the plasma aldosterone concentration (PAC) is positively correlated with the amount of visceral adipose tissue, independent of plasma renin activity (PRA).[8] Several studies suggest that adipose tissue secretes adipokines that stimulate aldosterone release from adrenal cells,[26–29] so-called aldosterone-releasing factors (ARFs).

Aside from this, genetic studies of humans suggest the association of obesity-related hypertension with the variants of several genes, such as tumor necrosis factor-α,[30] glucocorticoid receptor,[31] CYP11B2,[32] and serum and glucocorticoid-regulated kinase 1 (SGK1).[33] Most of these are closely related to aldosterone secretion and signaling. For example, SGK1, a downstream effector of aldosterone, has gene variants, which confer predisposition to hypertension, stroke, obesity, and type 2 diabetes mellitus.[33] A high-fructose or high-fat diet, leading to hyperinsulinism and obesity, sensitizes BP to high salt intake in wild-type mice, but not in SGK1-knockout mice.[33,34] In this mechanism, activation of SGK1 by insulin presumably stimulates renal tubular salt reabsorption and contributes to the development of hypertension. In obese subjects, increased visceral adiposity enhances an imbalance of pro- and anti-inflammatory adipokines, hyperaldosteronemia, and metabolic disorders including hyperinsulinemia, and aldosterone and its related factors are deeply involved in the development of hypertension.

MECHANISM UNDERLYING OBESITY-RELATED HYPERTENSION

Obese subjects exhibit extracellular fluid volume expansion and increased blood flow in many tissues and have increased venous return and cardiac output.[35] Cardiac output increases in parallel with weight gain because blood flow should supply the increased adipose tissue and other tissues to meet metabolic demands. In the early stage of obesity, the increased glomerular filtration rate and renal blood flow induce an increase in renal sodium absorption. With prolonged hypertension, renal vasodilation, glomerular hyperfiltration, and neurohumoral activation lead to severe hypertension, glomerular injury, and an impaired renal capacity for sodium excretion, resulting in the gradual loss of nephron and kidney function. In this way, obese subjects require a higher BP than lean subjects to maintain the sodium balance, indicating impaired renal-pressure natriuresis,[36] and thus obese subjects can exhibit salt-sensitive hypertension (Figure 1). Important factors that influence the renal capacity for sodium excretion in obese subjects include physical compression of the kidneys by increased visceral fat, and activation of the sympathetic nervous system (SNS), renin–angiotensin systems (RAS), and aldosterone/MR system.[37] Moreover, obese subjects are characterized
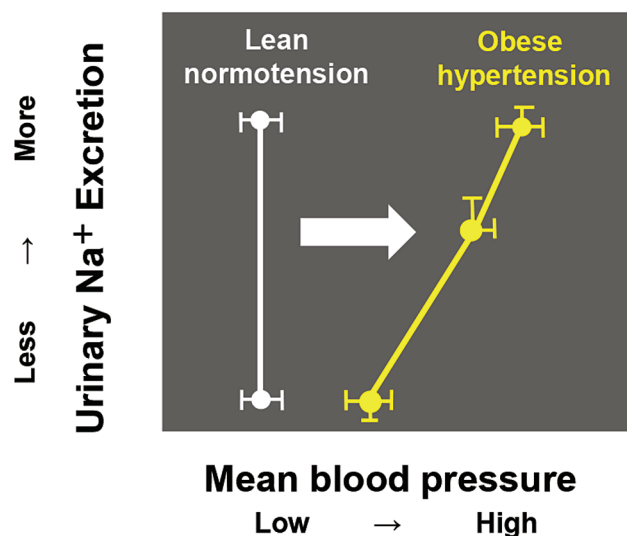

Figure 1. The blood pressure (BP)–natriuresis curve of obese subjects. In obese subjects, the increased glomerular filtration rate and renal blood flow induce increased renal sodium absorption, which in turn initiates impaired renal-pressure natriuresis, resulting in hypertension. Because obese hypertensive subjects require a higher BP than lean normotensive subjects to maintain the sodium balance, the BP–natriuresis curve is slanted and shifted to the right, indicating impaired renal-pressure natriuresis. As a result, obese patients exhibit salt-sensitive hypertension.

by metabolic disorders, such as hyperinsulinemia, glucose intolerance, dyslipidemia, and inflammation, and most of these accelerate renal sodium reabsorption and renal injury. These factors influence each other, and aldosterone plays a key role in the pathophysiology of obesity-related hypertension (Figure 2).

Sympathetic nervous system

Increased sympathetic nerve activity has been demonstrated in many animal models of obesity[38,39] and human obese subjects.[40,41] Multiple lines of evidence indicate that increased SNS activity contributes to obesity-related hypertension.[35] Moreover, administration of α/β-adrenergic blockers reduces SNS activity and prevents obesity-related hypertension.[42] In addition, obese hypertensive patients and animals often exhibit both salt sensitivity of BP and increased SNS activity, specifically in the kidney.[43,44] These reports also suggested that the renal SNS is an important factor influencing the salt sensitivity of BP. The anti-natriuretic effect of increased renal SNS activity is considered to be mainly mediated by increased renin secretion, reduced renal blood flow, and increased renal tubular reabsorption.[45] According to norepinephrine-induced tubular sodium reabsorption, stimulation of β2-adrenergic receptors leads to activation of the Na–Cl cotransporter through suppression of the serine-threonine protein kinase WNK4 in the distal tubule.[46] WNK kinases are modulated by changes in dietary sodium through effects on the circulating RAS and SNS and thus influence Na–Cl cotransporter activity.[46–48] On a low-salt diet, increased angiotensin II (AngII) is involved in Na–Cl cotransporter activation in an STE20/SPS-1-related proline/alanine-rich kinase-dependent manner.[49,50] Aldosterone
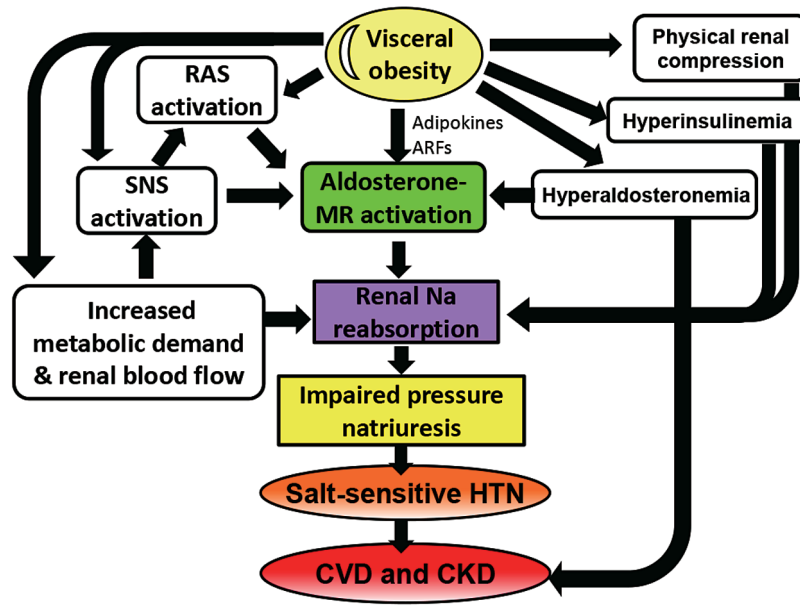
Figure 2. The mechanism underlying obesity-related hypertension and kidney impairment. Obesity induces functional vasodilation to fulfill the increased metabolic demand of the tissue. In the early stage of obesity, the increased renal blood flow induces an increase in renal sodium reabsorption, which in turn initiates impaired renal-pressure natriuresis. Physical compression of the kidneys by increased visceral fat, hyperinsulinemia, and hyper-aldosteronemia and activation of the SNS, RAS, and aldosterone/MR system also promote renal tubular sodium absorption. Prolonged hypertension, glomerular hyperfiltration, and neurohumoral activation cause further severe glomerular injury, increased impairment of renal-pressure natriuresis, and HTN and finally result in gradual nephron loss and kidney disease. Abbreviations: ARF, aldosterone-releasing factor; CKD, chronic kidney disease; CVD, cardiovascular disease; HTN, hypertension; MR, mineralocorticoid receptor; RAS, renin–angiotensin systems; SNS, sympathetic nervous system.

also promotes the dietary salt-mediated increase in Na–Cl cotransporter protein levels through the WNK4-extracellular signal-regulated kinase 1/2 signaling pathway.[48] In this way, SNS overactivity in obesity is indicated to be responsible for salt-sensitive hypertension in cooperation with AngII or aldosterone.

Several candidates may activate the SNS in obesity, including impaired baroreceptor reflexes, activation of chemo-receptor-mediated reflexes associated with sleep apnea, intermittent hypoxia, hyperinsulinemia, AngII, adipokines (such as leptin, tumor necrosis factor-α, and interleukin-6), and the pro-opiomelanocortin pathway of the central nervous system. In particular, leptin and the pro-opiomelanocortin pathway are important in obesity-induced SNS activation and hypertension.[51] The plasma leptin concentration is increased in obese hypertensive subjects.[52] Leptin influences leptin-sensitive neurons in the central nervous system and is involved in the regulation of appetite, energy expenditure, and the appropriate balance of automatic nerve activities.[37]

Renin–angiotensin systems

RAS activation is deeply related to the development of obesity-induced hypertension.[37,53] Obese subjects, especially those with visceral obesity, often have mild-to-moderate increases in PRA, Agt, angiotensin-converting enzyme (ACE) activity, AngII, and aldosterone.[54] Despite sodium retention, RAS activation occurs in obese subjects. RAS activation in obesity is induced by multiple factors, such as compression of the kidneys, increased SNS activation, and possibly the local RAS in adipose tissue.[55] Adipose tissue

contains all the components of the RAS, including Agt, renin, ACE, AngII, and AngII receptor type 1 (AT1R) and type 2, and can produce AngII.[56] In general, Agt is produced mainly in the liver; however, Agt secretion by adipose tissue is substantially augmented in obese subjects.[57] Yiannikouris *et al.* suggested the importance of adipocyte-derived AngII in the development of obesity-related hypertension by using adipocyte Agt-deficient mice (AgtaP2).[58] They found that a high-fat diet induced an increase in BP only in wild-type littermate, while there was no increase in AgtaP2, although both gained weight similarly and the amounts of fat mass were almost the same. Plasma Agt protein levels were similar in these 2 types of mice; however, the plasma AngII level was only increased in wild-type littermate on a high-fat diet, not in AgtaP2. This study suggested that adipose tissue serves as a major source of AngII in the development of obesity hypertension. However, it is yet to be determined whether adipocyte-derived Agt or AngII has a major influence on BP regulation in obesity. The adipose tissue RAS not only has the classic pathway of AngII generation catalyzed by ACE but also by cathepsins and chymase.[59] It has not been established whether this system is associated with hypertension and obesity and this needs to be studied.

ALDOSTERONE AND OBESITY-RELATED HYPERTENSION

Several studies show that aldosterone excess is often present in obesity and suggest its involvement in the pathogenesis of obesity-related hypertension.[60,61] Tuck *et al.* demonstrated that weight loss is accompanied by reductions in PRA and aldosterone, irrespective of sodium intake,

and this affects the decline in BP in obese patients.[60] On the other hand, Rocchini *et al.* showed that obese adolescents had a significantly higher PAC than nonobese adolescents, and weight loss elicited a significant reduction in both the PAC and BP without a decrease in PRA.[61] In addition, the decrease in the PAC significantly correlated with the decrease in BP. Similarly, weight loss linked to a reduction in the PAC and BP in menopausal obese woman was reported.[62] Interestingly, high levels of PRA, ACE, aldosterone, and insulin with sodium retention and potassium loss were found in patients with visceral obesity, but all of these tended to disappear upon weight reduction and were not found in patients with peripheral obesity.[63] On the other hand, Goodfriend *et al.* demonstrated that the PAC is positively correlated with the amount of visceral adipose tissue and is inversely correlated with insulin sensitivity, independent of the PRA level.[8] This suggested that a fat derived-substance contributes to aldosterone excess in patients with visceral obesity. Furthermore, they reported that a candidate ARF is 12,13-epoxy-9-keto-10(*trans*)-octadecenoic acid, an oxidized fatty acid derivative.[28] Ehrhart-Bornstein *et al.* validated that adipocyte secretory products directly stimulate aldosterone secretion in human adrenocortical cells (NCI-H295R) and suggested that unknown ARFs exist and might explain a direct link between obesity and hypertension.[27] Moreover, Nagase *et al.* investigated aldosterone secretagogue activity in conditioned medium of rat visceral adipocytes and found it was significantly higher in adipocytes from obese rats than in the adipocytes from nonobese rats.[26] The aldosterone-releasing activity of these cells was not inhibited by candesartan. These data suggest that ARFs are not regulated by the systemic RAS and contribute to the aldosterone excess in obese rats. Complement-C1q tumor necrosis factor-related protein 1 (CTRP1) is another candidate ARF.[29] CTRP1 is expressed at high levels in adipose tissues of obese Zucker diabetic fatty (fa/fa) rats, specifically in the zona glomerulosa of the adrenal cortex, where aldosterone is produced.[29,64] CTRP1 dose dependently promoted aldosterone production and expression of the aldosterone synthase CYP11B2 in the human adrenal cortical cell line H295R. AngII-induced aldosterone production is mediated, at least in part, by stimulation of CTRP1, and levels of CTRP1 were significantly upregulated in the serum of hypertensive patients.[29] Recently, Huby *et al.* newly reported that the adipokine leptin is a direct transcriptional upregulator of aldosterone synthase *CYP11B2* in adrenal glomerulosa cell and enhances aldosterone production via calcium-dependent mechanisms.[65] They also implied that leptin-mediated hyperaldosteronemia contributes to CVD in obese subjects by promoting endothelial dysfunction and increasing profibrotic markers in the heart. Aldosterone excess is closely associated with visceral adipose tissue and contributes to obesity-related hypertension and organ damages.

To maintain a normal BP in normotensive lean subjects, there is a negative correlation between dietary salt intake and the PAC. On a high-salt diet, the level of plasma aldosterone is appropriately decreased through suppression of the RAS, leading to natriuresis. By contrast, in obese hypertensive subjects, ARFs lack negative feedback regulation by salt, and consequently plasma aldosterone is inappropriately

secreted on a high-salt diet despite the decreased PRA, resulting in MR activation. Supporting this, salt loading did not only aggravate podocyte injury and albuminuria[66] but also induced diastolic dysfunction with severe perivascular fibrosis[67] in obese hypertensive rats. However, treatment with an MR antagonist apparently inhibited salt-induced abnormalities in the heart and kidneys of these rats. Of note, continuous infusion of aldosterone in Sprague Dawley rats fed a high-salt diet causes a marked elevation in BP and albuminuria, whereas aldosterone-induced elevation of BP and albuminuria disappear on a low-salt diet.[68] These findings clearly suggest that dietary salt is needed for the effects of aldosterone. Taken together, excessive salt intake and aldosterone excess due to ARFs synergistically activate the MR in the heart and kidneys of obese hypertensive humans and animals, leading to BP elevation, CKD, and CVD.

THE PATHOGENETIC ROLE OF ALDOSTERONE/MR ACTIVATION IN OBESITY-RELATED ORGAN DAMAGE

Classically, aldosterone has long been considered to play a central role in regulation of the electrolyte and fluid volume and maintenance of BP homeostasis.[10] Moreover, the aldosterone/MR system plays a key role in cardiovascular and renal damage.[11,12] In mineralocorticoid target epithelial tissues, such as the kidney and colon, the ligand selectivity of the MR is guaranteed by the presence of HSD11β2, which converts cortisol in humans and corticosterone in rodents to their inactive 11-keto analogues.[69] Although the concentration of glucocorticoids in the circulation is 100–1,000-fold greater than that of aldosterone, aldosterone acts as the ligand for the MR in the kidney.[69] HSD11β2 activity plays a role in hypertension.[70,71] Indeed, decreased activity of HSD11β2, inducing overstimulation of the MR by intrarenal cortisol excess, was detected in hypertensive obese children in comparison to normotensive obese and nonobese children.[72] In the heart, MRs are occupied by glucocorticoids because cardiomyocytes almost completely lack HSD11β2, but the glucocorticoid-MR complex does not activate the MR under physiological conditions. Some investigators postulated that this complex becomes active under conditions of increased oxidative stress in pathological states, such as myocardial infarction.[73] However, this remains to be explored. On the other hand, aldosterone acts directly on kidney, nonepithelial cells in the heart, vasculature, and brain to cause tissue remodeling, inflammation, fibrosis, and endothelial dysfunction through induction of oxidative stress.[74] Supporting this, endothelial-specific, but not cardiomyocyte-specific, MR-knockout prevents the heart from pressure overload. Clinically, the pathological influence of aldosterone in left ventricular hypertrophy[75] and myocardial perfusion[76] was established by studies of patients with primary hyperaldosteronism. As mentioned earlier, the involvement of the aldosterone/MR system in CVD was proven by 3 large-scale randomized clinical trials, RALES, EPHESUS, and EMPHASIS-HF.[13–15] Addition of MR antagonists to standard therapy with ACE inhibitors, AngII receptor blockers, diuretics, and beta-blockers significantly improved the outcomes of patients with severe congestive heart failure or left ventricular systolic dysfunction after myocardial infarction.

In the 1950s, Selye and others realized that aldosterone acts on nonepithelial tissues through the induction of inflammatory processes, collagen formation, fibrosis, and necrosis.[77] In the early 1990s, interest in the nonclassical aspect of aldosterone actions resurfaced. Weber and colleagues studied the effects of aldosterone in cardiac remodeling and reported that chronic aldosterone excess in the presence of salt loading caused cardiac fibrosis in experimental rodents,[78] which was ameliorated by a MR blocker.[79] This implied the involvement of MR activation in salt-induced cardiac fibrosis.[79] Rocha et al. also showed that a MR blocker significantly reduces vascular injury in saline-drinking stroke-prone spontaneously hypertensive rats (SHRs).[80] Clinically, the pathological influence of aldosterone in left ventricular hypertrophy[75] and myocardial perfusion[76] was established by studies of patients with primary hyperaldosteronism.

In the kidney, aldosterone/MR activation causes podocyte injury, which leads to proteinuria and glomerulosclerosis,[81] and proinflammatory responses, mediating perivascular and interstitial fibrosis.[82,83] Indeed, numerous clinical studies have shown that MR antagonists effectively ameliorate proteinuria in patients with hypertension,[84,85] diabetes mellitus,[86] and CKD.[87] Furthermore, MR antagonists had a renoprotective effect in patients who experienced aldosterone breakthrough after they received ACE inhibitors or AngII receptor blockers, associated with residual albuminuria.[88,89] Results of the 2 recent double-blind, randomized, placebo-controlled trials named EVALUATE[16] and ARTS-DN[17] showed that addition of a selective MR antagonist to RAS inhibitors markedly decreased residual albuminuria in both nondiabetic[16] and diabetic CKD[17] hypertensive patients without serious safety concerns. Nagase et al. examined the role of aldosterone/MR signaling in obesity-associated CKD using obese SHRs, which are models of metabolic syndrome.[26] As these rats got older, they developed marked proteinuria with podocyte injury accompanied by an elevated PAC and renal MR activation, while lean SHRs did not show these complications, despite having a similar BP. However, this was effectively suppressed by the selective MR antagonist eplerenone. These results suggested that aldosterone/MR signaling is deeply involved not only in hypertension but also in kidney injury in obese subjects.

Moreover, obese/insulin-resistant subjects are characterized by endothelial dysfunction and endothelial resistance to the effect of insulin on endothelium-dependent vasodilation enhancement, contributing to atherosclerosis.[90] Endothelial-specific MR deletion in mice prevented obesity-induced endothelial dysfunction.[91] MR antagonism improved insulin resistance in patients with primary aldosteronism.[92] Garg et al. demonstrated that spironolactone did not change insulin resistance, despite a reduced systolic BP, in normotensive obese individuals with insulin resistance.[93] However, a randomized, double-blind, placebo-controlled, cross-over study by Hwang et al. showed that eplerenone-dependent improvements in vascular endothelial function were positively associated with changes in total and abdominal adiposity and baseline fasting glucose in healthy older adults taking 100 mg eplerenone for 1 month.[94] A MR antagonist did not improve insulin resistance in obese patients, but the

MR influences vascular function in an adiposity-dependent manner; therefore, further studies are needed to elucidate the association of MR signaling with obesity-related vascular dysfunction.

Several studies have implicated MR signaling in adipocyte biology.[95] Importantly, given the lack of significant 11HSD2 expression and activity in adipocytes, physiological glucocorticoid is the main endogenous ligand of the MR. Selective MR stimulation of white adipocytes with aldosterone, within the physiologic range, promoted the expression of proinflammatory genes.[96] By contrast, adipose tissue-specific amplification of active cortisol in transgenic mice resulted in the typical phenotype of full metabolic syndrome, including central obesity.[97] In white adipose tissue, although both aldosterone and corticoids are ligands of the MR, the MR plays a key role in the differentiation and proliferation of adipocytes by upregulating peroxisome proliferator-activated receptor γ and CCAAT-enhancer-binding protein α and in inflammation by recruiting macrophages with proinflammatory cytokines.[98] MR antagonism in animals with metabolic syndrome improved insulin sensitivity, suppressed inflammation, and reduced hypertrophic adipocytes.[98]

In this way, aldosterone/MR activation is involved in various obesity-related organ injuries. However, there is no large clinical study of MR blockade in obese patients; therefore, further studies are expected.

SALT INTAKE, OBESITY, AND ALDOSTERONE

Epidemiological studies demonstrate that the amount of daily salt intake, as estimated by urinary sodium excretion over 24 hours, is proportionally increased with the incidence of high BP and obesity.[99] Ma et al. showed that salt intake was higher in overweight and obese individuals and that a 1 g/d increase in salt intake was associated with an increase in the risk of obesity by 28% in children and 26% in adults.[100] In their study, higher salt intake was also significantly related to higher body fat mass in both children and adults after adjusting for age, sex, ethnic group, and energy intake.[100] This direct association of salt intake and body fat mass was also observed in another epidemiological study.[101] Previously, salt intake was considered to be associated with obesity through energy intake such as the consumption of sugar-sweetened beverages or salty energy-dense food; however, Ma et al. showed that salt intake is a potential risk factor for obesity independent of energy intake.

In addition to the deep association with salt intake, obese people show higher salt sensitivity of BP than nonobese people.[102] Rocchini et al. reported that obese adolescents showed a significantly larger BP change than nonobese adolescents when they were changed from 2-week periods of a high-salt diet to a low-salt diet. After a 20-week weight loss program, weight loss of more than 1 kg was accompanied by a reduced salt sensitivity of BP. Chen et al. showed increased salt sensitivity of BP in patients with metabolic syndrome and a positive relationship between the salt sensitivity of BP and risk factors of metabolic syndrome, including waist circumference, hypertriglyceridemia, low high-density lipoprotein concentration, hypertension, and hyperglycemia. These studies suggested that the salt sensitivity of BP

in obese subjects is affected by obesity-related metabolic disorders, including hyperinsulinemia, aldosterone excess, proinflammatory adipokines from the large amount of adipose tissue, and increased activity of the SNS, which are all characteristics of obesity. As previously mentioned, salt-sensitive hypertension in obese subjects is solely due to impaired renal-pressure natriuresis (Figure 1). The progression of obesity is associated with increased visceral fat mass, hyperaldosteronemia, and metabolic disorders and results in the increased salt sensitivity of BP and cardiovascular injury in obese subjects who consume a large amount of salt (Figure 3).

Moreover, Lee *et al.* examined single nucleotide polymorphisms related to salt-sensitive genes and sodium intake in children.[103] BP, insulin resistance, and serum cholesterol and triglyceride levels are positively correlated with an increased body mass index. Regardless of sex, as dietary sodium intake increased, the risk of obesity significantly increased, especially in those with *G-protein–coupled receptor kinase type 4 (GRK4) A486V*, and *CYP11β-2* variants among girls and with *GRK4 A486V, ACE*, and *SLC12A3* variants among boys. This showed there is a gender-based difference in the interaction between sodium intake and obesity. Dopamine produced by the kidney is natriuretic and antihypertensive and disruption of any of the dopamine receptor genes in mice increases BP.[104] GRK4 suppresses the renal dopaminergic signal through desensitizing D1 and D3 dopamine receptors. *GRK4* gene variants are associated with salt-sensitive or low-renin hypertension, decreased sodium excretion in hypertensive subjects,[104,105] and insulin resistance in obesity.[106] Moreover, GRK4 plays a key role in counter-regulation between the renal dopamine system and RAS in the renal tubular sodium reabsorption. Yatabe *et al.* indicated the interaction between GRK4 and AT1R may be important in the overall regulation of sodium balance and BP.[107] When

the renal expressions of AT1R were inhibited in SHR, BP increased because the interruption of the renin–angiotensin negative feedback loop resulted in increased circulating renin and AngII. But the inhibition of both GRK4 and AT1R in the kidney decreased BP in SHR to a greater extent than when only GRK4 was inhibited. These studies imply that combinations of salt sensitivity-related gene variants, which are also involved in the pathogenesis of obesity or regulation of the RAS, affect the interaction of obesity and sodium intake, causing hypertension. Further investigations of this may be useful to realize personalized diagnosis and therapy in obesity-related hypertension and salt sensitivity.

SUMMARY AND PERSPECTIVES

Obesity, especially visceral obesity, is closely related to salt-sensitive hypertension. A hyperfiltration-induced increase in renal sodium reabsorption is a trait of obese subjects, and obese hypertensive subjects have impaired renal-pressure natriuresis and require a higher BP than lean normotensive subjects to maintain the sodium balance. Physical compression of the kidneys and activation of the SNS, RAS, and aldosterone/MR system are involved in the development of obesity-related hypertension. As described previously, aldosterone excess, presumably prolonged by adipose-derived ARFs independently of the systemic RAS, is often present in obese subjects, and aldosterone/MR activation in the kidney and cardiovascular system induces organ injuries. Given the inappropriate secretion of aldosterone from adrenal glands by ARFs during the salt load, both the increased salt sensitivity of BP and salt-induced cardiorenal injury appear in obese hypertensive animals through MR activation. Moreover, increased dietary sodium intake is closely associated with the incidence of hypertension and obesity. Some salt sensitivity-related gene variants affect the risk of obesity, and together with salt intake, its combination is possibly associated with the development of hypertension in obese subjects. People often consume a large amount of salt, mainly as a food preservative and taste enhancer, with a high-calorie diet. Both high-salt and high-calorie diets are closely linked and synergistically promote obesity and hypertension. Salt restriction and weight control is important; however, not only MR blockade but also new diagnostic modalities and therapies targeting and modifying genes that are related to salt sensitivity, obesity, or RAS regulation are expected to prevent obesity and obesity-related hypertension.
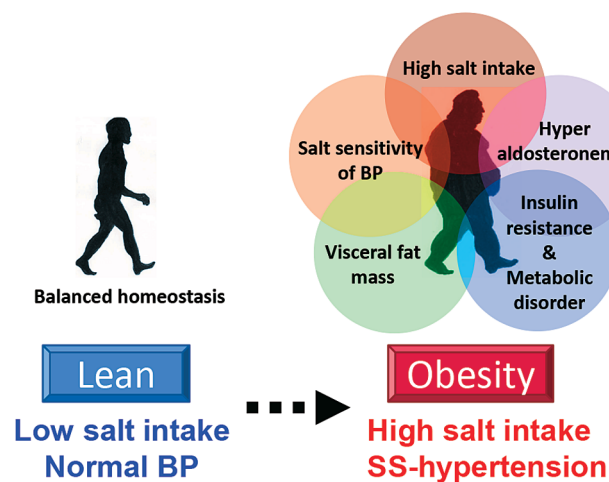

Figure 3. High salt intake increases the risk of obesity. The level of salt intake proportionally increases with the incidence of hypertension and obesity. Obese subjects consume more salt and exhibit a higher salt sensitivity of BP than lean subjects, and this is synergistically enhanced by obesity-induced homeostatic environmental changes, including a large amount of visceral fat, hyperaldosteronemia, and metabolic disorders. Abbreviations: BP, blood pressure; SS, salt-sensitive.

DISCLOSURE

The authors declared no conflict of interest.

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