Insulin resistance and salt-sensitive hypertension in metabolic syndrome

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Introduction

Metabolic syndrome, which is caused by obesity, is now a global pandemic. Metabolic syndrome is an aggregation of dyslipidaemia, hypertension and diabetes. Moreover, metabolic syndrome is a highly predisposing condition for cardiovascular disease. Recent clinical studies have shown that metabolic syndrome also increases the risk for proteinuria and chronic kidney disease (CKD) [1]. For a definition of metabolic syndrome, indeed, visceral obesity is essential and more than two of the following components: blood pressure, glucose and lipid abnormalities. However, insulin resistance is a key factor to developing these components of metabolic syndrome. Based on recent progress of research on adipocytes, visceral obesity plays a critical role in the development of insulin resistance. Indeed, angiotensionogen, one of adipokines such as TNF-α and NEFA, which are produced by visceral fat, might contribute to the development of insulin resistance in the muscle and adipose tissues [2]. In contrast, lack of insulin resistance in the kidney increases tubular sodium reabsorption by hyperinsulinaemia, leading to sodium retention in the body, and resultant salt-sensitive hypertension [3]. Therefore, there is an intimate relationship between insulin resistance and salt-sensitive hypertension in obese hypertensive patients with metabolic syndrome [4–7].

Insulin resistance in metabolic syndrome

Insulin resistance is a key factor to developing these components of metabolic syndrome. Indeed, insulin resistance is a good predictor of metabolic syndrome. Hypertensive patients often exhibit insulin resistance; in the glucose tolerance test, hypertensives have been reported to show a greater degree of hyperinsulinaemia as compared with normotensives [8]. According to assessment by computed tomography, hypertensives show a higher visceral fat area than normotensives, although the subcutaneous fat area is comparable between the two groups. Moreover, while the visceral fat area was negatively correlated with the insulin sensitivity as measured by insulin-induced glucose uptake, the subcutaneous fat area was not [9]. This led us to hypothesize that visceral adiposity may play a key role in the development of insulin resistance. In support of this contention, weight reduction by bariatric surgery has been shown to improve insulin resistance in severely obese patients, apparently associated with the reduction of the visceral fat area [10]. In contrast, moderate reduction of subcutaneous fat by liposuction neither decreased the visceral fat area nor improved the insulin resistance in obese patients [11]. Therefore, it suggests that visceral fat, rather than subcutaneous fat, is involved in insulin resistance.

There is a growing body of evidence indicating that adipocytes produce several cytokines, the so-called adipokines, such as leptin, TNF-α, NEFAs, adiponectin, resistin and angiotensinogen, which can influence insulin sensitivity. According to the contribution of visceral fat to insulin resistance, a recent study revealed that mice fed with a high-fat diet showed up-regulation of the angiotensinogen gene expression in the visceral fat but not subcutaneous fat [2]. In obese humans, the levels of the circulating components of the RA system are elevated, however, weight loss is associated with a decrease in the levels of these components of the RA system [12]. Therefore, the adipocyte-related RA system may play an important role in the pathogenesis of metabolic syndrome.
Angiotensin and insulin resistance

Angiotensin II (Ang II), which is generated from angiotensinogen, is well known to be a key substance influencing endothelial function and involved in the development of cardiovascular disease, through the activation of NADPH oxidase. Moreover, Ang II is also involved in the development of insulin resistance, possibly by oxidative stress production. To evaluate the mechanism of Ang II-induced insulin resistance, we studied the effect of a 2-week infusion of Ang II on the insulin sensitivity in rats using the hyperinsulinaemic-euglycaemic glucose clamp method. Both the glucose infusion rate and the insulin-induced glucose uptake into the muscle were found to be markedly decreased [13]. Thus, chronic administration of Ang II caused insulin resistance in the muscle and adipose tissues. In the Ang II-infused rats, the plasma level of lipid peroxide, a marker of oxidative stress, was also increased. Moreover, treatment with tempol, a membrane-permeable superoxide dismutase mimetic, reversed the Ang II-induced decrement in the glucose infusion rate in the evaluation using the hyperinsulinaemic-euglycaemic glucose clamp, and increased the glucose uptake in isolated skeletal muscle [13]. Thus, oxidative stress may play an important role in Ang II-induced insulin resistance. Indeed, it has been reported that Ang II-induced ROS up-regulation affects several levels of the intracellular insulin signalling pathways. In vitro, ROS has been shown to impair IRS-1 phosphorylation and IRS-1-induced PI3-kinase activation in cultured adipocytes, leading to impaired translocation of GLUT-4 to the membrane and consequently, insulin resistance [14]. Accordingly, treatment with blockers of RA system may improve insulin resistance, possibly through the inhibition of oxidative stress.

In addition to producing several other adipokines besides angiotensinogen that also have the potential to decrease insulin sensitivity, such as TNF-α, resistin, leptin and NEFAs [15], adipocytes also secrete adiponectin and adrenomedullin (AM) which increase insulin sensitivity (Figure 1). In contrast to Ang II, AM inhibits the generation of ROS [16]. Infusion of Ang II has been shown to induce more severe insulin resistance in AM-deficient mice than in wild-type mice [17], suggesting antagonistic effects between endogenous AM and Ang II. Moreover, old, but not young, AM-deficient mice show insulin resistance in the muscle, possibly through overproduction of ROS [18], since oxidative stress might accumulate with advancing age. Lending support to this idea, treatment with tempol, an antioxidant, normalized the impaired glucose uptake by the muscle in both Ang II-infused rats [16] and old AM-deficient mice [18]. In AM-deficient mice, moreover, the administration of Ang II [16], hypoxia [19] and arterial cuff injury [20], all of which produce oxidative stress, was found to induce severe coronary arterial sclerosis, pulmonary arterial hyperplasia and arterial intimal hyperplasia, respectively. Taken together, in obese subjects with metabolic syndrome, imbalance in the production of several adipokines influencing insulin sensitivity may be involved in the development of insulin resistance, possibly through the overproduction of oxidative stress (Figure 1).

The mechanism for salt-sensitive hypertension in metabolic syndrome

There is a plausible hypothesis that insulin resistance plays a crucial role in the development of hypertension, diabetes and dyslipidaemia. Although the precise mechanism for insulin resistance-induced hypertension is still unknown, it has been hypothesized that while insulin resistance is observed in the muscle and adipose tissues, it is not seen in the kidney or the sympathetic nervous system. Under this circumstance, since insulin can increase sodium reabsorption in the proximal tubules and stimulate sympathetic tone, hyperinsulinaemia increases the blood pressure by inducing salt retention and central sympathetic overactivity. This hypothesis is strengthened by our recent ex vivo study [3] using the proximal tubules of IRS-1- and IRS-2-deficient mice, in which while both mice showed insulin resistance and the resultant hyperinsulinaemia, only the former showed hypertension. Administration of insulin probably increased the sodium reabsorption in the proximal tubules of the IRS-1-deficient mice, similar to that in the wild-type mice, by the activation of Na-HCO₃ co-transport, but not in the proximal tubules of the IRS-2 deficient mice [3], suggesting that the renal action of insulin is mediated by IRS-2. Consequently, IRS-1-deficient mice showed higher blood pressure than IRS-2 deficient mice, possibly mediated by the greater sodium retention in the body. Thus, insulin resistance in the muscle, which is attributable to derangements of IRS-1, induces glucose intolerance and dyslipidaemia; in turn, hyperinsulinaemia induces sodium retention via IRS-2 phosphorylation in the kidney, resulting in volume-dependent, salt-sensitive hypertension (Figure 2).
Lending support to this concept, the Olivetti Heart Study showed, using the lithium clearance method, that obese insulin-resistant subjects with metabolic syndrome showed a higher fractional sodium reabsorption in the proximal tubules [21].

In addition to hyperinsulinaemia, Ang II [22], which is generated from angiotensinogen produced by adipocytes, aldosterone, of which secretion is also stimulated by adipocytes [23], and the increased renal SNS activity [24], which is mediated by hyperinsulinaemia and hyperleptinaemia, can directly stimulate sodium reabsorption in the proximal and distal tubules (Figure 3). Furthermore, compression of the kidney by the huge abdominal fat mass might also influence tubular sodium reabsorption; the elevated interstitial hydrostatic pressure caused by compression could reduce medullary blood flow (vasa recta) and consequently increase sodium reabsorption in the ascending limb of the loop of Henle [25]. Taken together, all of these abnormalities might be involved in promoting sodium retention in the body (Figure 3). In fact, obese hypertensives show a more pronounced hypertensive response to salt restriction than non-obese hypertensives, but after they reduce their body weight, they also show a less pronounced salt-sensitivity of the blood pressure. Thus, obese patients with metabolic syndrome often have salt-sensitive hypertension [26]. Conversely, salt-sensitive hypertension is characterized by the same features as those characterizing patients with metabolic syndrome, namely, obesity, insulin resistance, low serum HDL cholesterol, microalbuminuria, intraglomerular hypertension and high incidence of cardiovascular diseases [27,28].

**CKD in metabolic syndrome**

Obese subjects with metabolic syndrome often exhibit microalbuminuria, CKD and non-dipping hypertension [1,29,30], which are all independent risk factors for cardiovascular disease. The appearance of microalbuminuria might be attributable to glomerular hyperfiltration [31]. According to the reported mechanism of occurrence of intraglomerular hypertension, increased tubular sodium reabsorption in the proximal tubules and loop of Henle reduces the macula densa NaCl delivery [32], which leads to a feedback-mediated vasodilatation of the afferent arterioles, elevation of the glomerular filtration rate and stimulation of the
RA system, despite the volume expansion (Figure 3). These compensatory responses are aimed at overcoming the increased tubular reabsorption and maintaining the sodium balance [25]. However, persistent glomerular hyperfiltration also causes proteinuria and CKD.

In addition to the renal haemodynamics, adipocyte-related humoral factors may also be involved in the occurrence of albuminuria and CKD. Some investigators have demonstrated that aldosterone-releasing factors are produced by adipocytes [23]. Consistent with this, plasma aldosterone concentrations are increased in obese subjects with metabolic syndrome [33]. Hyperaldosternism induces sodium retention in the body by the increased sodium reabsorption in the distal and collecting tubules, resulting in salt-sensitive hypertension. Moreover, we have recently showed that mineralocorticoid receptor (MR) is present not only in the tubular cells but also glomerular podocytes; the hyperaldosteronism-induced MR activation might induce glomerular podocyte injury to cause proteinuria in obese hypertensive rats with metabolic syndrome, possibly through the overproduction of ROS [34]. Moreover, salt loading aggravates podocyte injury and proteinuria markedly in these obese hypertensive rats, associated with increased MR-dependent gene expressions. It is well known that salt and aldosterone have an unfavourable synergistic action on the cardiovascular system since the administration of aldosterone induces severe cardiac damages in rats on a high-salt diet, but does not affect it in those on a low-salt diet [35]. However, the treatment of eplerenone, a selective aldosterone receptor blocker, was shown to dramatically reduce the podocyte injury and proteinuria in obese hypertensive rats, even those on a high-salt diet [34,36,37]. Accordingly, PREVEND study shows that salt intake affects urinary albumin excretion especially in overweight subjects [38], although plasma aldosterone was not measured. Thus, changes in renal haemodynamics and humoral factors can induce progressive renal failure in metabolic syndrome. In turn, impaired renal function in relation to sodium excretion increases the salt-sensitivity of blood pressure (Figure 3).

**Role of salt and potassium in metabolic syndrome**

There is an intimate relationship between salt-sensitivity and insulin sensitivity in hypertensive patients [4–7]. Accordingly, a high-salt diet not only increases the blood pressure, but also decreases the insulin sensitivity in Dahl salt-sensitive rats [39]. However, treatment with tempol, an antioxidant, normalized the salt-induced insulin resistance, suggesting that salt-induced insulin resistance might be attributable to the overproduction of ROS. Accordingly, the Finnish epidemiological study showed that the prevalence of diabetes was higher among obese, but not lean, people on a high-salt diet [40]. In contrast to sodium, potassium possesses anti hypertensive [41,42] and anti-oxidant effects [39]. Potassium supplementation not only attenuated salt-induced elevation of blood pressure [41,42], but also improved salt-induced insulin resistance [39] in salt-sensitive hypertensive patients and animals, associated with the normalization of ROS overproduction, suggesting that it inhibits salt-induced ROS overproduction. Consistent with this, the DASH diet, consisting of vegetables and fruits rich in potassium, which could lower lipid-induced oxidative stress in obesity [43], decreased not only blood pressure, but also the fasting blood sugar in hypertensive patients [44]. Thus, dietary potassium can counteract the effects of dietary sodium to increase the insulin sensitivity in patients with salt-sensitive hypertension, possibly through decreasing the production of reactive oxygen species (Figure 1). Moreover, in Dahl salt-sensitive rats, a high salt intake induced cardiac diastolic dysfunction, because of increased ROS production in the heart, but potassium supplementation could reverse this abnormality through the inhibition of ROS production [45]. Thus, dietary salt and potassium stimulate and inhibit ROS production, respectively (Figure 1); in turn, overproduction of ROS might induce not only insulin resistance, but also cardiac dysfunction and atherosclerosis in salt-sensitive hypertensive humans and animals. In support of this suggestion, potassium supplementation could reduce the incidence of stroke in salt-loaded Dahl salt-sensitive rats, independent of the blood pressure [46]. Treatment with antioxidants is also effective in inhibiting salt-induced cardiac and renal damage in Dahl salt-sensitive hypertensive rats [45,47]. Taken together, ROS might play a critical role not only in the development of insulin resistance and salt-sensitive hypertension, but also in that of salt-induced cardiovascular damage in patients of salt-sensitive hypertension with metabolic syndrome [48]. Therefore, salt restriction and dietary intake of fruits and vegetables rich in potassium should be prescribed as a first-line lifestyle therapy for patients with metabolic syndrome, together with physical exercise, with the goal of improving the obesity-associated risk profile, such as insulin resistance and salt-sensitive hypertension (Figure 1).

**Conclusion**

Finally, it is evident that there are several endogenous and exogenous factors that can influence insulin sensitivity. Not only adipokines released from visceral fat but also salt from processed foods can induce insulin resistance in the muscle and adipose tissues, through the overproduction of oxidative stress. Based upon the lack of insulin resistance in the kidney, however, hyperinsulinaemia causes sodium retention by stimulating sodium reabsorption in the proximal tubules. In addition, increased Ang II, increased aldosterone and reduced medullary flow by visceral fat-induced compression of the kidney might also be involved in the increased sodium reabsorption in the
proximal and distal tubules, promoting sodium retention, and consequently, inducing salt-sensitive hypertension (Figure 3). Not only chronic glomerular hypertension but also hyperaldosteronism might induce proteinuria and CKD. Taken together, patients with metabolic syndrome are often associated with salt-sensitive hypertension and CKD. Therefore, salt restriction is important for obese patients with metabolic syndrome to prevent CKD, since salt restriction is effective in improving not only salt-sensitive hypertension but also insulin resistance.

**Conflict of interest statement.** None declared.

**References**

Inflammation in the genesis of hypertension and its complications—the role of angiotensin II

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Hypertension remains a major clinical syndrome characterized by small artery disease and subsequent accentuated development of atherosclerosis [1]. The affected arteries usually have diminished wall compliance and elevated stiffness resulting from arterial remodelling and atherosclerosis. With the progression of hypertension, the risk of cardiovascular complications such as myocardial infarction and stroke increases [2]. Recently, an emerging concept contends that inflammation plays a predominant role in the progression of hypertension and is also involved in the triggering of hypertension-associated cardiovascular complications.

Recent studies have indicated a close relationship between hypertension and inflammation, showing that tissue expression and plasma concentration of inflammatory mediators are increased in patients with essential hypertension and in experimental models of hypertension. These inflammatory mediators include C reactive protein (CRP) [3,4], interleukin (IL)-6, IL-1 [5], tumour necrosis factor-α (TNF-α), monocyte chemoattractant protein-1 (MCP-1), intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) [6], and have been linked to the activation of the nuclear factor kappa B (NF-κB) system [7,8]. For example, in peripheral monocytes from hypertensive patients, the production of IL-1β and TNF-α was significantly increased upon lipopolysaccharide stimulation [9]. With this evidence for inflammation in hypertension, new questions arise. Does inflammation contribute to hypertensive vascular disease? Who are the players involved? Could vascular inflammation be a link between hypertension, atherosclerosis and aneurysm?

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