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COMMENTARY

Metabolic syndrome and blood pressure: the salty connection

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Hypertension is considered 'salt-sensitive' when blood pressure responses due to changes in dietary salt vary beyond arbitrary preset levels. Indeed, widely varying methodologies have been used to assess human salt sensitivity of blood pressure, with different criteria for its characterization. However, some individuals are consistently more sensitive to the blood pressure effects of salt depletion or loading than others. Blood pressure variability in response to dietary salt intake is heterogeneous, continuously distributed but fairly reproducible within individuals. Salt sensitivity of blood pressure is also more frequent among black hypertensives and elderly subjects. Interestingly, salt sensitive subjects share several characteristics including increased forearm vascular resistance, decreased venous compliance, suppressed plasma renin activity and lower circulating aldosterone concentration.[1]

Many pathophysiological factors – including genetic polymorphisms[2] – have been implicated in salt sensitivity of blood pressure. Among those mechanisms, we could highlight insulin resistance and hyperinsulinemia. Physiologically, insulin promotes sodium reabsorption by the kidneys, presumably through direct modulation of tubular mechanisms or sympathetic activation of renal nerves. Paradoxically, it has been shown that the anti-natriuretic effect of insulin is preserved in obese and diabetic subjects with and without hypertension despite insulin resistance, suggesting that hyperinsulinemia exacerbates sodium reabsorption and increase blood pressure in these conditions.[3]

Of note, several reports have supported a role of insulin resistance in salt-sensitive hypertension,[4,5] which is not necessarily associated with overt hyperinsulinemia.[4] Indeed, the insulin resistance index positively correlates with the sodium sensitivity index and is negatively correlated with fractional excretion of sodium measured during high dietary salt.[6] Giner *et al.*[7] have reproduced most of these results under strictly controlled experimental conditions. Insulin sensitivity index was determined by the euglycemic hyperinsulinemic clamp and salt sensitivity was assessed by ambulatory blood pressure responses to low (50 mmol of Na^+/day) and high (240 mmol of Na^+/day) salt intake for 7 days in lean hypertensive subjects, and salt sensitiveness was strongly associated with increased insulin resistance.

Other studies have nonetheless challenged this classical concept. For instance, it has been observed that fasting insulin or insulin responses to glucose tolerance test does not predict blood pressure responses to changes in salt intake in lean and obese normotensive and hypertensive subjects.[8] Furthermore, exogenous administration of insulin did not alter renal sodium handling differentially in salt-sensitive and salt-resistant hypertensives with similar levels of insulin sensitivity measured by euglycemic hyperinsulinemic clamp.[9]

The renin–angiotensin–aldosterone system might play an important role in the blood pressure responses to salt. Angiotensin II hyper-responsiveness in hypertensive subjects is associated with sodium retention, independently of glomerular filtration rate and aldosterone concentration.[10] Furthermore, normotensive subjects with parental history of hypertension exhibit impaired suppression of aldosterone in response to salt loading and an exaggerated and prolonged secretion of aldosterone in response to angiotensin II.[11] Conversely, larger reductions in blood pressure in hypertensive as compared with normotensive subjects due to acute reductions in salt intake may reflect a less-responsive renin–angiotensin–aldosterone system in hypertension.[12]

Perhaps atrial natriuretic peptide (ANP) could be another important mediator of salt sensitiveness of blood pressure. Under conditions of high salt intake, salt-sensitive hypertensive black subjects exhibit paradoxical reductions in ANP secretion that may account for a reduced ability of these subjects to excrete excess sodium despite increased blood pressure.[13] Interestingly, salt-sensitive hypertensive

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subjects manifest sustained increases in plasma glucose and insulin after exogenous infusion of ANP, suggesting that ANP–insulin interactions might contribute to sodium retention in salt-sensitive hypertension.[14]

Renal mechanisms involving 20-hydroxyeicosatetraenoic acid (20-HETE), a cytochrome *P*450-dependent metabolite of arachidonic acid, could also play a role in renal sodium handling in hypertensive subjects.[15] 20-HETE causes vasoconstriction and promotes natriuresis. In salt-sensitive and salt-resistant hypertensives, urinary 20-HETE substantially increases in response to salt loading, indicating that sodium balance regulates the renal excretion of 20-HETE independently of salt sensitiveness. Noteworthy, whereas urinary 20-HETE positively correlates with natriuresis in salt-resistant hypertensives, there is no correlation between these two variables in salt-sensitive hypertensive subjects. Thus, the reduced ability of 20-HETE to promote natriuresis in salt-sensitive hypertensives may lead to change in the pressure–natriuresis relationship and, consequently, increases in blood pressure. Salt sensitivity of blood pressure may also be partly determined by impaired nitric oxide production in response to high salt intake that could alter pressure–natriuresis curve and thus increase blood pressure.[16]

The metabolic syndrome is characterized by the aggregation of several risk factors for cardiovascular diseases and type II diabetes. Along with glucose intolerance and dyslipidemias, hypertension and central obesity are important components of the metabolic syndrome. Both hypertension and obesity are associated with salt sensitivity of blood pressure. However, the number of human studies reporting the correlation between the metabolic syndrome and the salt sensitivity of blood pressure is still small.

In this issue of the *Journal of Human Hypertension*, Hoffman and Cubeddu[17] report a strong correlation between salt sensitivity of blood pressure and metabolic syndrome, in participants from Caracas, Venezuela. Importantly, it is shown that salt sensitivity of blood pressure increases as the number traits of metabolic syndrome accumulate in a given individual with at least three diagnostic criteria for metabolic syndrome. Notably, severe dietary salt restriction substantially reduced the systolic blood pressure in subjects with 4–5 metabolic syndrome traits by approximately 9 mm Hg, independently of subjects' gender. Also, salt restriction reduced the percentage of metabolic syndrome subjects with blood pressure levels meeting the criteria for hypertension from 23.8 to 8.2%. Overall, these results suggest that augmented blood pressure associated with metabolic syndrome is particularly sensitive to the depressor effects of salt restriction, notably in hypertensive subjects.

What are the potential implications of these findings? Metabolic syndrome has been more frequently associated with nocturnal non-dipping of blood pressure than in subjects without the syndrome.[18,19] Importantly, during sodium restriction and diuretic therapy, the normal circadian pattern of blood pressure was re-established, suggesting that the non-dipping phenomenon observed in metabolic syndrome patients is partly caused by increased salt sensitivity of blood pressure. In addition, multiple logistic analysis indicates that central obesity was an independent predictor of salt-sensitive hypertension. As 'non-dipping' is associated with end-organ damage, salt-sensitive hypertension could substantially increase the cardiovascular risk in metabolic syndrome patients.

The potential mechanisms of salt sensitivity of blood pressure in metabolic syndrome merit comment. Barbato *et al.*[20] found that metabolic syndrome was associated with reduced fractional excretion of lithium, reflecting increased reabsorption of sodium in the proximal tubule in Caucasians but not in the other ethnic groups with more profound insulin resistance. Recently, Strazzullo *et al.*[21] reported abnormal renal sodium handling in participants of the Olivetti Heart Study with metabolic syndrome. Importantly, only the proximal fractional sodium reabsorption was significantly increased after adjustment for age and use of antihypertensives. In fact, abdominal adiposity in men is associated with increased proximal tubular sodium reabsorption, even after adjustments for blood pressure and insulin resistance.[22] Thus, increased abdominal adiposity might be an important predictor of increased proximal tubular reabsorption of sodium in metabolic syndrome. Other factors related to increased adiposity, such as increased leptinemia and reduced adiponectinemia, might have a substantial effect on renal sodium handling in the metabolic syndrome.

Altogether, these studies highlight the relevance of salt sensitivity of blood pressure in metabolic syndrome that might be closely related to prevalent hypertension in subjects with central obesity. They also show that salt sensitivity in metabolic syndrome is not invariably associated with insulin resistance and hyperinsulinemia. However, despite conflicting evidence, the role of insulin resistance and hyperinsulinemia in the pathophysiology of salt sensitiveness associated with metabolic syndrome remains attractive, at least in some populations.

The ethnic variation in the relationship among increased sodium reabsorption, metabolic syndrome and insulin resistance might be associated with genetic propensity for the development of salt-sensitive hypertension. For example, the Gly460Trp polymorphism in the alpha-adducin gene was found to be in linkage disequilibrium with hypertension in two Caucasian populations and the 460Trp genotype was significantly associated to salt sensitivity.[23] In contrast with this observation, Melander *et al.*[24] reported that the Gly460Trp polymorphism is more prevalent among normotensive Scandinavians as compared with hypertensive

counterparts. Furthermore, the association between salt sensitivity and the Gly460Trp polymorphism in Venezuelan normotensives has not been confirmed,[25] suggesting that the Gly460Trp polymorphism of the alpha-adducin gene could contribute to salt sensitivity of blood pressure only in certain populations. Other polymorphisms were associated with salt-sensitive hypertension as, for example, the 'insertion' genotype of the ACE I/D polymorphism.[26]

In conclusion, salt sensitivity of blood pressure, like hypertension, is more prevalent among metabolic syndrome patients but may correlate variably in populations with distinct environmental and genetic backgrounds. Furthermore, salt sensitivity in metabolic syndrome is not invariably associated with insulin resistance. Thus, distinct pathophysiological mechanisms may contribute to the salt sensitivity in different populations. Alternatively, the net contribution of insulin resistance and hyperinsulinemia within a multiple-component pathophysiological model may vary substantially across different populations. Although salt sensitivity of blood pressure has been associated with several genetic polymorphisms in healthy and hypertensive subjects, these polymorphisms have not been specifically studied in metabolic syndrome patients. Indeed, pharmacogenomic research may eventually disclose useful strategies to treat the metabolic syndrome and its many complications.

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