The metabolic syndrome, hypertension, and the frontier between

Editorial Focus on:
Sodium-sensitive elevation in blood pressure is ENaC independent in diet-induced obesity and insulin resistance

Carolyn M. Ecelbarger

February 12, 2016
Revised February 19, 2016

1Department of Medicine, Georgetown University, Washington DC, 20057

Running Title: Metabolic syndrome and blood pressure

Address Correspondence to: Carolyn M. Ecelbarger, Ph.D., Associate Professor, Department of Medicine, Georgetown University, 4000 Reservoir Rd, NW, Washington, DC, 20007; Phone: (202) 687-0653, Fax: (202) 687-2040, e-mail: ecelbarc@georgetown.edu.
Key words: ENaC, obesity, insulin, sodium balance, hypertension

Abstract

The metabolic syndrome (MetS) is associated with a rise in blood pressure (BP) however the mechanisms underlying this association are not known. Nivar and colleagues utilize a number of innovative approaches to evaluate the role of the epithelial sodium channel (ENaC) of the renal collecting duct in the sodium retention and hypertension associated with MetS. C57Bl/6 male, mice fed a high-fat diet for 12 weeks developed several features of MetS including: hyperinsulinemia, hypercholesterolemia, obesity, and elevated BP. They also showed salt-sensitive hypertension and sodium retention in the early time course of switch from normal to a high-NaCl diet. Nonetheless, they found no evidence of over-activity of ENaC, using both perfused tubules and in vivo (sensitivity to benzamil) approaches. The authors concluded alternative, perhaps upstream sites of sodium retention. The studies are important in that they highlight the complexity of metabolic syndrome, and shed some new light in a controversial area. They do support renal sodium retention may be at the core, and elucidation of these upstream pathways is in need of additional study.
Metabolic syndrome (MetS) is associated with elevations in blood pressure (BP); however, the relationships between key variables remain murky. First of all defining and modeling MetS is difficult at best. In its simplest terms, MetS may be described as a “disease state” or set of conditions resulting from an excess of stored and/or circulating energy. Associated conditions include: visceral adiposity, hyperinsulinemia (due to insulin resistance of major metabolic tissues), dyslipidemia, and hypertension. A current estimate by the American Heart Association is that 1 in 3 U.S. adults has MetS (1). How (or whether) the various metabolic features of MetS lead to hypertension is an area of intense scrutiny, not only due to the large numbers of persons afflicted, but also due to the high life-time cardiovascular risk of chronically elevated BP.

Utilizing a number of elegant approaches, Nizar et al. (8) recently examined the role of the epithelial sodium channel (ENaC) in the sodium retention and hypertension associated with MetS. The investigators initially screened two different mouse models of MetS, i.e., chronically high-fat-fed and high-fructose-fed male C57Bl/6 mice. After several weeks of treatment, only the mice on the high-fat regimen (60% high-fat diet for 12 weeks) developed symptoms of MetS including weight gain, hyperinsulinemia, hypercholesterolemia, glucose intolerance, and modestly elevated BP (~3 mm Hg, by radiotelemetry). Therefore, they used this model to perform additional studies. One stumbling block in modeling hypertension associated with MetS is that many rodent models do not develop significant hypertension when obese. The obese Zucker rat, e.g., is markedly obese, insulin resistance, and hypertriglyceridemic; however, they show only a modest elevations in BP except when infused with aldosterone (9). Fructose-fed rats develop insulin resistance, hypertriglyceridemia, and hypertension, but are not necessarily obese. Moreover, the strain of mice selected in the Nizar study (8), i.e., C57Bl/6, have inconsistent changes in BP with high-fat diets (5). Nonetheless, in agreement, not all human subjects with MetS have hypertension.
Nizar et al. (8) demonstrated that high-fat-fed mice had relatively impaired natriuresis when switched from a normal to a high-NaCl diet, and this impairment coincided with a significantly greater salt-sensitive rise in BP. It is assumed they chose to focus on ENaC because it is a prime candidate with regard to linking the metabolic factors associated with MetS to hypertension (Figure 1). ENaC is expressed in the collecting duct, the final regulatory step in sodium handling, where fine-tuning of sodium reabsorption occurs. Mutations in the β- or γ-subunit of ENaC (Liddle’s syndrome) are associated with constitutively active ENaC, and a 15-30 mm Hg rise in systolic BP (7). Moreover, there are numerous circulating, paracrine, and basic physiological conditions, i.e., acid-base homeostasis, which may be altered in MetS, and have been found to increase ENaC activity (4). These include, but are not limited to, angiotensin II, aldosterone, superoxide, and insulin. ENaC has been demonstrated to be activated by insulin; however, ex vivo doses needed to show activation (1-100 nM) are often much higher than the physiological range for insulin (~0.02-2 nM or 14-290 μIU/ml). Frindt and Palmer et al. (3) did not find activation of ENaC by insulin in split-open rat cortical collecting duct using 2 nM insulin. In contrast, we found that administration of insulin to achieve a circulating level of no greater than 0.3 nM, resulted in anti-natriuresis. This anti-natriuresis was partially attenuated by benzamil (10) or in collecting duct principal cell insulin receptor knockout mice (6). Acute insulin administration was also associated with greater ENaC localization of the apical membrane of the collecting duct (10). Additional studies will be needed to clarify insulin’s actions on ENaC.

Nevertheless, in the Nizar et al. (8) study, ENaC activity was found not to be different between high-fat fed mice and controls, as measured in vivo by benzamil (ENaC antagonist) sensitivity and using isolated perfused cortical collecting ducts. Antagonizing ENaC with benzamil in a more chronic fashion also did not affect the elevation in BP. Moreover, the investigators also found no differences in aldosterone excretion between the groups. Therefore, they concluded that MetS, at least in this particular mouse model, was associated with sodium
retention and an elevation in BP independent from elevated ENaC, and likely due to activation of more upstream sodium-retentive mechanisms.

This group of investigators did not set out to test the role of elevated insulin or any other specific metabolic factor in their analyses. More than likely, they were aiming to develop a meaningful model of human MetS, with all its complexity. The mice were hyperinsulinemic and insulin has been demonstrated to be anti-natriuretic at a number of sites along the renal tubule in addition to the collecting duct, including, the proximal tubule, the thick ascending limb, and the distal convoluted tubule. Therefore there are a number of potential alternative sodium-retentive pathways that could be activated by insulin or another factor.

Insulin may explain sodium retention, but its direct effects on BP are less certain. There are other systems that manage BP as their principal action, e.g., the renin-angiotensin-aldosterone, the autonomic nervous, and the sympathetic nervous systems, as well as local mediators, e.g., NO and endothelin (2). Moreover, insulin has been demonstrated to have two distinct opposing actions on BP, i.e., sodium retention and NO release. The balance of these countering actions may underlie some of the inconsistencies observed. Finally, the high-fat fed mice in the current study were found not only to be hyperinsulinemic, but also insulin resistant (using the HOMA-IR assay). Insulin receptor resistance can diminish but also alter intracellular signaling, so that the end-point ramifications are markedly different. Whether or not the kidney insulin receptor becomes resistant in MetS is uncertain.

Thus, it is likely that a combination of factors or a distinct “metabolic milieu” is required in order for MetS to result in hypertension. In addition to insulin, important factors likely include, the RAAS, inflammatory mediators, free radicals, and adipokines. The authors provide keen evidence of a renal role in this hypertension with sodium-retention distinct from ENaC as a characteristic feature in C57Bl/6 mice fed a high-fat diet.
References


Figure 1- Putative mechanisms linking the metabolic syndrome with hypertension. A. Approximate relative amount of the filtered load of sodium reabsorbed along the renal tubule and major contributory transporters, exchangers, and channels involved. Various factors associated with MetS have been shown to act at a number of these sites. B. Collecting duct principal cell and candidate underlying signaling whereby insulin may influence ENaC (as well as other electrolyte routes) in this cell type.