Salt sensitivity of blood pressure: developmental and sex-related effects¹–⁴

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ABSTRACT

Epidemiologic studies have shown convincingly that drastically reducing salt intake in the community is accompanied by blood pressure reductions that are comparable to those achieved by antihypertensive medication. Moreover, many subjects with hypertension are salt sensitive. This implies that, in these subjects, blood pressure is more responsive to changes in salt intake than is that in subjects with normal blood pressure. The presence of conventional risk factors associated with the metabolic syndrome correlates with salt sensitivity. However, women appear to be more salt sensitive than men. Sparse data indicate that the salt sensitivity of blood pressure is greater in subjects with low birth weight. Experimental studies in rats have also shown that hypertensive offspring of dams maintained on low-protein diets throughout or in late pregnancy are more salt sensitive. This is accompanied by increased expression of the thick ascending limb Na-K-2Cl symporter (NKCC2). Perinatal interventions aimed at perinatal origins of hypertension are expected to be very effective and are often accompanied by a wave of natriuresis exclusively at 4 wk of age. In sum, in addition to conventional metabolic risk factors for cardiovascular disease, low birth weight and possibly its sequelae such as catch-up growth should be viewed as modifiable risk factors for salt sensitivity of blood pressure. Female sex may also be a nonmodifiable risk factor for salt sensitivity. Experimental data indicate that NKCC2 may well be an important determinant of salt sensitivity in acquired (developmental) hypertension. Am J Clin Nutr doi: 10.3945/ajcn.110.000901.

INTRODUCTION

In any population blood pressure has a Gaussian (“normal”) distribution (1). In the presence of another classic risk factor for cardiovascular disease (CVD), such as obesity, this distribution will shift to the right. Thus, if hypertension is defined as blood pressure above a certain threshold, then within an “obese” population the incidence of hypertension will be higher than in a “lean” population. Naturally, hypertension occurs at the upper end of the distribution in the “lean” population. Conversely, some obese individuals are not hypertensive. Moreover, body mass index is also a continuous trait. Therefore, predicting the ideal blood pressure for an individual is practical rather than scientific. However, population studies have shown convincingly that the relation between CVD and blood pressure is continuous and independent of age (2). Therefore, measures that reduce blood pressure in the community should be advocated.

HUMAN STUDIES

The relation between salt intake, high blood pressure, and CVD is well established (3, 4). Evidence is accumulating that reduction of salt intake in conjunction with other approaches to reducing blood pressure, such as a diet rich in fruit, vegetables, and low-fat dairy products [Dietary Approaches to Stop Hypertension (DASH)–Sodium Study] (5) or weight loss (6), has additive effects on blood pressure reduction. The underlying mechanism is a shift in the renal function curve, implying that when other risk factors for high blood pressure are alleviated, the kidneys can more effectively maintain sodium balance at a low blood pressure. A classic example of this is the near normalization of the renal function curve in obese subjects after weight loss (7).

Recently, a well-controlled prospective trial with a high-low-high-salt design was held in rural northern China (8, 9). Interventions in 1906 “normotensive” subjects lasted 1 week, and blood pressure was measured on days 5–7 when the subjects were expected to be in sodium balance (ie, excretion similar to intake). Baseline measurements, done directly before the low-salt week, showed that in this community, mean salt intake was very high (243 mmol/d = 14.2 g sodium chloride per day). The pressure responses to this regimen are shown in Table 1. During the low-salt week, when mean salt intake was <3 g/d, systolic pressure decreased by ≈8 mm Hg in women and 7 mm Hg in men. Similarly, when mean salt intake increased again to 14.4 g/d, systolic pressure rose by >6 mm Hg in women and >5 mm Hg in men. Diastolic pressure also decreased more in women than in men in the low-salt week and increased more in women than in men in the high-salt week. All of these sex differences were very significant. Importantly, the systolic and diastolic blood pressure responses to changes in salt intake were normally distributed

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Thus, within this population, a minority of subjects (25%) showed zero change, or even a “paradoxical” change, to a salt intervention simply because they fall within the tail-end of a normal distribution. These data clearly show that salt sensitivity is bidirectional, as one would expect from the renal function curve. They also show that the common practice of defining subjects in a bimodal fashion as salt sensitive or salt resistant is not evidence based. Finally, within this population, women appear to be more salt sensitive than do men, but the difference is probably not large enough to warrant sex-specific dietary advice. The authors also analyzed whether the number of metabolic risk factors correlated with the incidence of “high salt sensitivity,” arbitrarily defined as a change, either down or up, of >5 mm Hg. Not surprisingly, there was a linear correlation between the incidence of “high salt sensitivity” and the number of accepted metabolic risk factors identified (8). These data also strongly suggest that metabolic risk factors have additive effects on the setting (slope and intercept) of the renal function curve. Furthermore, the data are reassuring in that they suggest that, with respect to the incidence of hypertension within the population, it is good to prevent and diminish metabolic risk through lower salt intake.

Intrauterine growth retardation, whether it be due to environmental stimuli or genetic predisposition, is a well-recognized risk factor for a large number of acquired disease states such as diabetes, CVD, renal disease, hypertension, and stroke. In fact, there appears to be a continuous inverse relation between birth weight, an imperfect surrogate marker for early development, and the incidence of these disease states. This is supported by a large body of experimental and epidemiologic studies (10–12). Considering the effect of salt intake on blood pressure, surprisingly little attention has been paid to the interaction between salt intake and intrauterine growth.

In a single-center study in The Netherlands, 27 “healthy,” subjects were switched from their baseline salt intake of 8 g/d to a high intake of 14 g/d and then to a low intake of 3 g/d (13), thus a design essentially similar to that of the Chinese study with the exception of the sequence of the interventions and the difference in baseline intake. Salt sensitivity of blood pressure was defined as the mean of arterial pressure between the high- and low-salt periods. The data, which were analyzed in a continuous fashion, showed a continuous inverse relation between birth weight and salt sensitivity (R = 0.60, P = 0.002; Figure 2). Note that even within this small sample, blood pressure responses to changes in salt intake were normally distributed, indicating that the relation between salt sensitivity and birth weight is continuous.

To summarize these human studies, it is apparent that both low birth weight and high salt intake should be viewed as risk factors for CVD. Moreover, as for all other modifiable risk factors, their effects on blood pressure are normally distributed, and defined threshold values are not evidence based.
ANIMAL STUDIES

Maternal protein restriction

Many studies have shown that maternal protein restriction leads to hypertension in adult offspring (10). However, only a few have considered the role of salt intake on the manifestation of hypertension in this model. The most well known is the study by Woods et al (14), in which 22-wk-old male and female offspring of rat dams on a 19% (normal) protein diet throughout pregnancy were compared with age-matched offspring of dams on a 5% (low) protein diet throughout pregnancy. Arterial pressure was measured on normal sodium (0.2%) and after 2 wk on high sodium (3.15%). The increase in arterial pressure with the high-sodium diet (slope) was significantly greater in low-protein rats than in normal-protein rats (P = 0.03). Changes were similar in males and females (Figure 3).

FIGURE 2. Relation between birth weight and salt sensitivity of blood pressure in 27 normotensive adults (16 women and 11 men). Salt sensitivity of blood pressure is defined as difference in mean arterial pressure between high and low salt (slope of renal function curve). Reproduced with permission from reference 13.

FIGURE 3. Renal function curves showing sensitivity of arterial pressure to (change in) sodium intake in adult male and female offspring of dams that were maintained on normal-protein (NP; 19% protein) or low-protein (LLP; 5% protein) diets throughout pregnancy. Lower points represent arterial pressure with normal sodium (0.2%), and upper points represent arterial pressure in the same rats after 2 wk with high sodium (3.15%). The increase in arterial pressure with the high-sodium diet (slope) was significantly greater in LLP rats than in NP rats (P = 0.03). Changes were similar in males and females. Reproduced with permission from reference 14.

FIGURE 4. A: Western blot analysis of apical sodium transporters in kidneys of offspring from 6%-protein pregnancies at 4 wk of age [% of control (20% protein)]. Reproduced with permission from reference 15. B: Na-K-2Cl (NKCC2) gene expression in kidneys of offspring from 6%-protein pregnancies from embryonic day 19 (E19) to 8 wk of age. Reproduced with permission from reference 15. C: Western blot analysis of renal NKCC2 expression in male and female 4-wk-old rats exposed to either control or low-protein maternal diet during pregnancy. Changes were similar in males and females. Reproduced with permission from reference 16. NHE3, proximal tubule type III Na/H exchanger; BSC1, thick ascending limb Na-K-2Cl symporter (NKCC2); TSC, distal convoluted tubule sodium chloride symporter; ENaC, cortical collecting duct amiloride-sensitive Na channel; mRNA, messenger RNA; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; CM, control males; LPM, low-protein males; CF, control females; LPF, low-protein females.
The underlying mechanism is unknown but an obvious candidate is upregulation of an important sodium transporter in the kidney. Studies from 2 different groups provide evidence that this could well be the bumetanide-sensitive Na-K-2Cl symporter (BSC1 alias NKCC2 alias Slc12a1) located in the ascending limb of Henle’s loop. Manning et al (15) document an increase in the protein expression of this transporter in 4-wk-old rat offspring of dams on a 6% (low) protein (LP) diet throughout pregnancy, thus preceding overt hypertension in this model (Figure 4A). Gene expression studies show that in LP pups, renal NKCC2 expression is already increased at birth and this difference increases in comparison with age-matched controls (Figure 4B). This is not the case for any other transporter. Similarly, Alwasel and Ashton show that only NKCC2 is upregulated at 4 wk of age in offspring of rat dams exposed to 9% compared with 18% protein during pregnancy (Figure 4C) (16). Together, these studies strongly suggest that a maternal low-protein diet increases salt sensitivity in male and female adult rats, and that this may well be mediated by increased expression of NKCC2. Whether LP offspring on high salt intake are more sensitive to loop diuretics than are control offspring with matched salt intake remains to be shown.

Perinatal treatment in genetic hypertension

Perinatal interventions can have long-lasting beneficial effects on blood pressure regulation in male and female adult rats with genetic hypertension. This has been shown in spontaneously hypertensive rats perinatally treated with citrulline, an arginine precursor (17), or with a mixture of arginine, taurine, and vitamins C and E (18). Similar results were also shown in fawn-hooded hypertensive rats treated with the same mixture (19) or with molsidomine, a tolerance-free nitric oxide donor (20). In both the latter studies, we observed that exclusively at 4 wk of age a wave of natriuresis occurred (19, 20). Interestingly, this wave of natriuresis at 4 wk, which was always observed in both males and females, also always preceded persistent decreases in blood pressure. Increased natriuresis appeared to occur at normal food intake and body weight. Invariably, the phenomenon was no longer present at ≥5 wk of age. Considering the magnitude of the phenomenon (≈2 μmol·g body weight−1·d−1 more than in controls; Figure 5), maintaining this level of natriuresis at normal sodium chloride intake for more than a few days at most would be impossible, because of inevitable circulatory collapse.

CONCLUSIONS

Besides conventional metabolic risk factors for CVD, low birth weight and possibly its sequels such as catch-up growth, should be viewed as modifiable risk factors for salt sensitivity of blood pressure. Female sex may also be a nonmodifiable risk factor for salt sensitivity. Experimental data indicate that NKCC2 may well be an important determinant of salt sensitivity in acquired (developmental) hypertension.

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REFERENCES