Hypertension is present in about 40% of the world’s population, and it is responsible for 12.8% of total deaths. However, these statistics do not include normotensive individuals who are salt (NaCl)-sensitive. Salt sensitivity, independent of BP, is a risk factor for not only cardiovascular morbidity and mortality but also other diseases, including metabolic syndrome. Several organs, including the kidney, participate in whole-body sodium homeostasis and BP regulation. The importance of the kidney in BP regulation is supported by renal transplantation studies in humans and rodents. The inability of the kidney to excrete a sodium load would result in a positive sodium balance, an increase in BP, and eventually, hypertension.

Renal autoregulation maintains renal blood flow and GFR, independent of perfusion pressure between 80 and 180 mmHg, and protects the kidney from hypertensive injury. This is afforded by myogenic and macula densa (MD) tubuloglomerular feedback responses. Several vasoactive agents have been proposed to mediate or modulate tubuloglomerular feedback, including nitric oxide and angiotensin II. Neuronal nitric oxide synthase (nNOS) is expressed in the MD, and direct blockade by specific inhibitors increases tubuloglomerular feedback. However, the inhibition of nitric oxide synthesis modulates but does not impair the myogenic vasoconstriction of the afferent arteriole in spontaneously hypertensive rats. Lu et al. have previously reported that splice variants of nNOS in MD cells may be important in the regulation of tubuloglomerular feedback during salt loading.

In this report, Lu et al. extend the aforementioned study by testing the hypothesis that nitric oxide synthase 1β (NOS1β) may be the salt-sensitive isoform of NOS1 in the MD that modulates tubuloglomerular feedback response, promotes sodium excretion, and protects against the development of salt-sensitive hypertension. To test this hypothesis, Lu et al. deleted all of the NOS1 splice variants specifically from the MD of C57Bl/6 mice. Compared with control wild-type mice, mice with MD-specific knockout of all nitric oxide synthase 1 isoforms (MD-NOS1KO) had enhanced tubuloglomerular feedback response after acute volume expansion, and their BPs were increased by a high-salt diet. Relative to wild-type mice, MD-NOS1KO mice on a high-salt diet also had greater BP responses to chronic infusion of angiotensin II. Because MD nitric oxide production was similar in the isolated perfused juxtaglomerular apparatus of wild-type and NOS1α-knockout mice, these studies suggest that the phenotype that results from MD-NOS1KO is caused by NOS1β. Although a more direct evaluation of the specific NOS1 isoform in the regulation of tubuloglomerular feedback would have been MD-specific deletion of NOS1β, these elegant experiments support the conclusion that NOS1β is the salt-sensitive isoform of NOS1 expressed in the MD that regulates the tubuloglomerular feedback response and protects against the development of salt-sensitive hypertension.

These studies highlight another important finding. The consequences of global germline deletion may not give the appropriate information. Previous studies using the global NOS1KO mouse indicated that NOS1 is not important in the regulation of salt-water balance or BP. However, as stated by Lu et al., this finding is not consistent with the studies showing that blockade of NOS1 by 7-nitroindazole results in hypertension in Sprague-Dawley rats and salt-sensitive hypertension in Dahl salt-resistant rats. As it turns out, global germline deletion of NOS1 by disruption of exon 1 deletes only the NOS1α isoform. Lu et al. show that nitric oxide generation by the MD is not affected in NOS1KO mice generated by deletion of NOS1 exon and that the BP of these mice is not affected by a high-salt diet.

Genome-wide association studies have identified genes that influence only 2% of BP variability and have not identified genes that influence the salt sensitivity of BP. Only a few genes have been found to be associated with salt-sensitive hypertension using candidate gene association studies. nNOS1 may be causal of salt-sensitive hypertension in humans. Glazier et al. have suggested several criteria for the determination of the genetic cause or causes of heritable complex disease (i.e., linkage or association study, circumstantial evidence, and functional test [definitive test]). In humans, the locus of nNOSβ, 12q24, is linked to several diseases, including essential hypertension, dyslipidemia and diabetes, and obesity, and it is protective in others (e.g., preeclampsia).
NOS1 polymorphisms (rs3741473, rs1875140, and rs1123425) are also associated with essential hypertension in several ethnic groups. However, it is not known if these polymorphisms affect nitric oxide production. Of particular interest is that the NOS1 polymorphisms are associated with hypertension in Japanese women and probably, Italian women. Women may be more salt-sensitive than men.

Glazier et al. have stated that the value of genetic markers for disease increases if there is a correlation between the presence of single-nucleotide polymorphisms and physiologic response. Lu et al. show that deletion of NOS1 in the MD causes salt-sensitive hypertension. This is an important step. It will be important to determine if expression of an inactivating polymorphism of NOS1 causes salt-sensitive hypertension in mice.

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DISCLOSURES

None.

REFERENCES


