Dr. Cechova and a multinational investigative team describe a novel model of hypertension in a susceptible murine model. Their initial studies of collectrin knockout in a mixed genetic mouse strain did not reveal a significant effect on blood pressure (BP). However, previous research demonstrated that the collectrin gene is located on a region of the X chromosome with loci linked to hypertension in humans and rats. Moreover, renal expression of collectrin is upregulated after subtotal nephrectomy and in salt-sensitive hypertension.

With this background, the authors studied the effects of collectrin null mutations on BP in a 129S6 mouse strain that is susceptible to hypertension and salt sensitivity. Under standard feeding conditions, the gene–gene interaction in the collectrin knockout/129S6 strain male mice led to a modest 9-mm Hg elevation in BP compared with wild-type control 129S6 mice. The rise in BP was accompanied by increased left ventricular mass. The investigative team then studied the effects of a high-salt diet on BP in these 2 mice strains. With this gene–environment interaction, BP rose a net 7 mm Hg over a 2-week period. The collectrin knockout/129S6 mouse model.

Based on previous studies documenting an important role for collectrin in amino acid transport, the authors conducted mechanistic studies to elucidate the root cause(s) for the gene–gene and gene–environment interactions that led to basal and salt-induced differences in BP between the collectrin knockout/129S6 and 129S6 rat strains. The collectrin knockout strain had decreased levels of amino acid transporters in endothelial cells, reduced arginine uptake, and decreased homodimeric nitric oxide synthase, which generates nitric oxide, to monomeric nitric oxide synthase, which generates superoxide. The investigators further documented impaired endothelium-dependent vasodilation and pressure natriuresis, which can be attributed to the documented changes in nitric oxide and superoxide. Tempol, a superoxide scavenger, lowered BP minimally and insignificantly in both mice strains on usual diets and in control 129S6 mice on high-salt diets, which did not suggest a major role for superoxide in BP regulation in these conditions. However, Tempol lowered BP significantly in the collectrin knockout/129S6 mice on a high-salt diet and eliminated the difference in salt-sensitive BP responses between the two strains. These findings suggest a major role for superoxide in the excessive rise of BP during a salt stress in the collectrin knockout/129S6 mice.

These original observations are potentially relevant to human hypertension. First, an array of gene–gene and gene–environment interactions, rather than single-gene defects, likely account for the majority of human hypertension. The majority of humans with hypertension have comparatively modest elevations of BP in the prehypertensive (120–139/80–89) and Stage 1 hypertensive (140–159/90–99) range, similar to collectrin knockout/129S6 mice. Third, individuals with hypertension are more likely than their normotensive counterparts to manifest evidence for salt sensitivity, reduced antioxidant capacity, or increased oxidative stress, which is seen in the collectrin knockout mouse model.

Fourth, diets, such as DASH (for Dietary Approaches to Stop Hypertension), that are high in antioxidants and minerals attenuates salt sensitivity and oxidative stress responses and vascular dysfunction in obese and salt-sensitive humans similar to Tempol in collectrin knockout mice on high salt. Fifth, collectrin affects insulin secretion. Hypertensive humans are more likely to have and develop diabetes mellitus and related abnormalities of carbohydrate and lipoprotein metabolism than normotensive individuals. Whether collectrin has a role in the dysmetabolic syndrome affecting most hypertensive patients is unknown, although it does participate in insulin secretion.

These novel studies in collectrin null mice are likely to raise interest in studies of collectrin in human BP regulation, especially among individuals with genetic risk for hypertension (gene–gene) and salt sensitivity (gene–environment) and those with chronic kidney disease. Additional studies on changes in BP and salt sensitivity with aging in normal mice and those at risk for hypertension and salt sensitivity may inform additional human studies on pathogenesis, prevention, and treatment.

In summary, Dr. Cechova and colleagues have identified a novel role for collectrin in BP regulation in a mouse strain susceptible to hypertension and salt sensitivity. This model of gene–gene and gene–environment interactions has the potential to inform additional human studies on pathogenesis, prevention, and treatment.
potential to inform studies on the pathogenesis, prevention, and treatment of human hypertension.

Disclosures
None.

References

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Collectrin, an X-Linked, Angiotensin Converting Enzyme 2 Homolog, Causes Hypertension in a Rat Strain Through Gene–Gene and Gene–Environment Interactions: Relevance to Human Hypertension

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