Salt-sensitive hypertension (SSH) is characterized by impaired sodium excretion and subnormal vasodilatory response to salt loading. High dietary sodium intake and genetic predisposition to salt sensitivity of blood pressure (BP) are of particular clinical relevance in Asian populations. Sacubitril/valsartan (LCZ696), a first-in-class angiotensin receptor neprilysin inhibitor, was hypothesized to increase natriuresis and diuresis and result in superior BP control compared with valsartan in Asian patients with SSH. In this randomized, double-blind, crossover study, 72 patients with SSH received sacubitril/valsartan 400 mg and valsartan 320 mg once daily for 4 weeks each. SSH was diagnosed by Angiotensin II (p 79)

Caveolin-1 Mediates Organ Damage by Angiotensin II (p 79)

Hypertension is a disease marked by chronic vascular dysfunction and inflammation leading to vascular remodeling and end-organ damage. Angiotensin II, a principal player in essential hypertension, mediates both blood pressure elevation and cardiovascular remodeling. Investigation has shown that caveolin-1 (Cav1), a structural component of membrane caveolae, facilitates signal transduction events that are activated by the angiotensin type-1 receptor. In humans, at least 3 Cav1 single nucleotide polymorphisms have been identified and are associated with metabolic syndrome, arterial stiffness, and coronary artery disease, whereas a heterozygous Cav1 null mutation elicits premature aging and lipodystrophy. Given these clinically relevant studies, we aimed to identify the contribution of Cav1 in angiotensin II-induced hypertensive vascular remodeling and inflammation because Cav1 is expressed in the vascular smooth muscle layer and endothelium. Using Cav1 knockout mice, we show that vascular hypertrophy (Figure), perivascular fibrosis, and endothelial induction of an adhesion molecule are attenuated in Cav1 knockout mice, and these changes are independent of alterations in blood pressure and cardiac hypertrophy. In addition, we note that vascular Cav1 expression is correlated with epidermal growth factor receptor activation, which we have previously shown to be a key player in hypertensive end-organ damage. Cumulatively, we helped to show the contribution of Cav1 in hypertensive pathophysiology and have identified a molecular mechanism to seek for a new therapy to reduce cardiovascular mortality.

CADASIL (Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy) is a paradigmatic cerebral small vessel disease—a group of pathological processes that collectively are a leading cause of age- and hypertension-related stroke and cognitive decline worldwide—caused by stereotyped mutations in the Notch3 receptor. Although a reduction in lumen diameter in maximally dilated cerebral arteries is an important feature in the well-established TgNotch3R169C mouse model of CADASIL, the underlying cause is unknown. A similar vascular change is commonly seen in chronic hypertension, and although it can protect the downstream circulation against elevated pressure, it can also be deleterious, adversely affecting local blood flow by decreasing microvascular pressure and maximal vasodilator capacity. Considering its physiological importance and because reduction in maximal vasodilation occurs in CADASIL in the absence of increased blood pressure, we thought it important to understand the mechanistic basis. In the present study, we found that the R169C archetypal CADASIL mutation is associated with altered mechanical and structural properties of cerebral arteries consistent with an increased stiffness, and increased Notch3 activity in 2 distinct mouse models. Conditional reduction of Notch activity in smooth muscle prevented these changes in mice expressing the R169C mutation, whereas conditional activation of Notch3 in smooth muscle recapitulated the changes (Figure). Together these results indicate that increased Notch3 activity mediates pathological structural changes of brain arteries in CADASIL, uncovering an unsuspected role of Notch3 signaling in vascular mechanics and structure that occur independently of increases in blood pressure.
Clinical Implications

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