Adding Accessories for Hypertension

α₂δ-1 Subunits Upregulate Caᵥ1.2 Channels in Arterial Myocytes in a Model of Genetic Hypertension

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Hypertension is a major risk factor for the development of stroke, coronary artery disease, heart failure, and renal disease. Although the principal cause of hypertension is likely renal, vascular dysfunction is critical, and the increased arterial tone associated with hypertension contributes to the development of the pathology. This is highlighted by recent studies indicating that the endogenous vasoconstrictor angiotensin II is a likely contributor to vascular dysfunction in human and hypertension models.

In the current issue of Hypertension, a study from Bannister et al addressed an important and yet unresolved question in vascular physiology: what are the molecular mechanisms underlying changes in the function of dihydropyridine-sensitive, voltage-gated L-type Ca²⁺ channels in arterial myocytes during hypertension? Through a series of elegant experiments they provide an interesting and unexpected answer to this difficult conundrum. Below, we describe the context and implications of their findings.

In arterial smooth muscle, L-type Ca²⁺ currents are produced by channels composed of pore-forming Caᵥ1.2 α₁ subunits and accessory β and α₁δ-1 subunits. These accessory subunits regulate the expression and voltage-dependencies of the pore-forming Caᵥ1.2 subunit. The opening of a single or a small cluster of Caᵥ1.2 channels produce local elevations in intracellular Ca²⁺ ([Ca²⁺]ᵢ) called “Ca²⁺ sparklets.” The activation of multiple Ca²⁺ sparklets increases global [Ca²⁺]ᵢ, which induces contraction and activates multiple signaling cascades involved in the expression of proteins important in the regulation of artery contraction. Increased Caᵥ1.2 channel (ie, Ca²⁺ sparklets) activity in arterial myocytes is critical for the development of vascular dysfunction during hypertension.

As noted above, Bannister et al addressed the missed molecular link of upregulation of Caᵥ1.2 channel function in arterial myocytes during hypertension. Previous studies led Bannister et al to determine the potential answer to this important question. First, increased Caᵥ1.2 channel function is associated with an increase in the expression of this channel during the development of hypertension. Second, the accessory α₁δ-1 subunit increase trafficking of Caᵥ1.2 channels to the sarcolemma of smooth muscle cells. On the basis of these findings, Bannister et al hypothesized that an increase in α₁δ-1 subunits was directly responsible for the increase in sarcolemmal expression of Caᵥ1.2 channels in arterial myocytes in spontaneously hypertensive rats, widely used during genetic hypertension.

To test their hypothesis, Bannister et al implemented an integrative approach. They used biochemical and molecular biological approaches to determine transcript and protein expression in arterial smooth muscle. Patch-clamp electrophysiology was used to determine the function of Caᵥ1.2 channels, and arterial myography was used to evaluate arterial function. Pharmacological tools were used to determine the role of α₁δ-1 subunits in Caᵥ1.2 upregulation during hypertension.

Using these approaches, Bannister et al elegantly demonstrated that upregulation of α₁δ-1 subunits increases surface expression of Caᵥ1.2 channels during genetic hypertension in spontaneously hypertensive rats. This translates into an increase in Ca²⁺ influx into arterial smooth muscle that result in exacerbated vasoconstriction during this pathological condition. The data supporting this model are compelling. First, genetic hypertension in spontaneously hypertensive rats is associated with an increase in α₁δ-1 and Caᵥ1.2 transcript and surface protein expression, which relates to an increase in arterial myocyte. Second, pregabalin, which binds to the α₁δ-1 subunit of Caᵥ1.2 channels, decreased surface expression of these channels, decreased Ca²⁺ influx, and lowered myogenic tone in hypertensive arteries.

The findings of Bannister et al are important because they establish α₁δ-1 subunit as a molecular culprit for hypertension-induced increases in Caᵥ1.2 channel function in arterial myocytes. Previous studies suggested increased Caᵥ1.2 expression as a cause for increased Ca²⁺ influx via these channels. Yet, the role of α₁δ-1 subunits in this process had not been established. Furthermore, the potential of targeting α₁δ-1 subunits to decrease expression of functional Caᵥ1.2 channels is a provocative finding.

As with any good study, the impact of the work Bannister et al is not limited to the questions that they answered but the questions that the study raised. What controls the expression of α₁δ-1 subunits in arterial myocytes? Is the transcription factor NFATc3, which is activated in smooth muscle in these cells during hypertension and regulates the expression of Caᵥ1.2 and voltage-gated K⁺ channels, involved in the regulation of α₁δ-1 transcript expression? Another question...
brought up by the work of Bannister et al⁵ is whether treatment of α₂δ-1 ligands, like pregabalin, would translate into lower blood pressure. In addition, because Ca²⁺ influx via CaV1.2 channel varies throughout the sarcolemma, does upregulation of α₂δ-1 alter the spatial distribution of functional CaV1.2 channels in arterial myocytes? Finally, future studies should investigate whether α₂δ-1 subunit upregulation is also a hallmark of human and animal models of hypertension.

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