Editorial Commentary

Adding Accessories for Hypertension

α2δ-1 Subunits Upregulate CaV1.2 Channels in Arterial Myocytes in a Model of Genetic Hypertension

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See related article, pp 1006–1015

Hypertension is a major risk factor for the development of stroke, coronary artery disease, heart failure, and renal disease.1 Although the principal cause of hypertension is likely renal, vascular dysfunction is critical,2 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 human1 and hypertension models.3

In the current issue of Hypertension, a study from Bannister et al4 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 α, subunits and accessory β and α,δ-1 subunits.6 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.”7 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 activity in arterial myocytes is critical for the development of vascular dysfunction during hypertension.8,9

As noted above, Bannister et al4 addressed the missed molecular link of upregulation of CaV1.2 channel function in arterial myocytes during hypertension. Previous studies led Bannister et al5 to determine the potential answer to this important question. First, increased CaV1.2 channel function was associated with an increase in the expression of this channel during the development of hypertension.9 Second, the accessory α,δ-1 subunit increases trafficking of CaV1.2 channels to the sarcolemma of smooth muscle cells.6 On the basis of these findings, Bannister et al5 hypothesized that an increase in α,δ-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 al5 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 α,δ-1 subunits in CaV1.2 upregulation during hypertension.

Using these approaches, Banister et al5 elegantly demonstrated that upregulation of α,δ-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 α,δ-1 and CaV1.2 transcript and surface protein expression, which relates to an increase in arterial myocyte. Second, pregabalin, which binds to the α,δ-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 al5 are important because they establish α,δ-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 α,δ-1 subunits in this process had not been established. Furthermore, the potential of targeting α,δ-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 al5 is not limited to the questions that they answered but the questions that the study raised. What controls the expression of α,δ-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,11 involved in the regulation of α,δ-1 transcript expression? Another question...
brought up by the work of Bannister et al is whether treatment of $\alpha_2\delta$-1 ligands, like pregabalin, would translate into lower blood pressure. In addition, because Ca$^{2+}$ influx via CaV1.2 channel varies throughout the sarcolemma, does upregulation of $\alpha_2\delta$-1 alter the spatial distribution of functional CaV1.2 channels in arterial myocytes? Finally, future studies should investigate whether $\alpha_2\delta$-1 subunit upregulation is also a hallmark of human and animal models of hypertension.

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**References**


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