Blood Pressure Reduction, Potassium Channels, and the Endothelium: Insights From L-Serine

Jorge E. Jalil

In this issue of Hypertension, Mishra et al.1 compared the in vitro effects of the amino acid L-serine, a precursor of central neurotransmitters, and acetylcholine in phenylephrine-constricted mesenteric arterioles in Nω-nitro-L-arginine methyl ester (L-NAME)—pretreated hypertensive rats, as well as in normotensive rats.1 L-Serine evoked concentration-dependent vasodilatation in endothelium-intact but not in endothelium-denuded vessels. This response to L-serine was abolished by a combination of apamin (a small conductance Ca2+-activated K+ channel inhibitor) and TRAM-34 (an intermediate conductance Ca2+-activated K+ channel inhibitor), ouabain (Na+ pump inhibitor) and barium chloride (an inward-rectifier K+ channel inhibitor), or when the vessels were constricted by potassium chloride.

In addition, the authors determined in vivo changes in mean arterial blood pressure and heart rate induced by acute intravenous infusion of either L-serine or acetylcholine in anesthetized rats. The maximal response to L-serine was higher in the L-NAME treatment group in contrast to the maximal response to acetylcholine. L-Serine evoked a rapid, reversible, dose-dependent fall in mean arterial pressure without increasing heart rate, which was more pronounced in L-NAME–treated hypertensive rats than in the control rats. This acute hypotensive effect of L-serine was significantly inhibited by apamin and charybdotoxin pretreatment, a combination that blocks Ca2+-activated K+ channels or endothelium-derived hyperpolarizing factor (EDHF).

The authors discussed that the acute dose-dependent response to L-serine may be because of activation of vascular/endothelial KCa channels (exaggerated when the NO system is blunted in the chronic L-NAME–pretreated rats). Based on their observations that the apamin+TRAM-34 combination abolished the vasodilator effect of L-serine and that the apamin+ChTX combination significantly reduced the acute hypotensive response to L-serine in L-NAME–treated rats, it is reasonable to state that the L-serine effect may be mediated by activation of the endothelial small conductance Ca2+-activated K+ channel.1 In addition, the lack of vasodilator response to L-serine in the presence of either a combination of ouabain and barium or in elevated K+ state suggests that, in these resistance arterioles, increased K+ concentration in the myoendothelial region contributes to L-serine–evoked vasodilatation.1

This is the first evidence that the administration of an amino acid has an antihypertensive effect in the NO-compromised state. Further studies will be necessary, mainly to determine the effects of L-serine in other arteries, in different models of experimental hypertension and also regarding the possibility of a chronic antihypertensive effect induced by this amino acid. The current findings from Mishra et al.1 also put into perspective the very interesting issue of the endothelium as a blood pressure regulator by paths independent from NO or prostacyclin.

The endothelium regulates the vascular tone through the release of a number of soluble mediators by releasing NO and prostacyclin and also by other pathways that cause hyperpolarization of the underlying vascular smooth muscle cells.2,3 Responses because of EDHF involve increased intracellular calcium, opening of calcium-activated potassium channels of small and intermediate conductance, and the hyperpolarization of the endothelial cells.2

Several substances or mechanisms have been proposed for the nature of the EDHF, including epoxyeicosatrienoic acids, K ions, electrical communications through myoendothelial gap junctions,3 endothelium-derived hydrogen peroxide,4 anandamide,5 and also the C-type natriuretic peptide.6 Despite this heterogeneity of proposed factors, it is unclear whether such a factor indeed exists in all of the vessels, because the hyperpolarization of vascular smooth muscle has been proposed to be induced by simple current transfer from the adjacent endothelium.5 For this to occur, the cells need to be electrically coupled, and this requirement is fulfilled by gap junctions, which are composed of connexins forming intercellular channels. Aside from myoendothelial coupling, gap junctions also interconnect endothelial cells, thus creating a functional unit, which synchronizes cellular behavior within the arteriolar tree of the microcirculation.5

In the human vasculature, EDHF involvement has been observed in the systemic, coronary, and visceral (gastrointestinal, renal, and reproductive) circulation. In these vascular systems, EDHF plays a role under physiological conditions either as another mechanism or as the “back-up” for NO.7 Altered EDHF function has been suggested in various pathological conditions, including heart diseases, atherosclerosis, hypertension, diabetes, eclampsia, glaucoma, chronic renal

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Voltage-gated \( \mathrm{K}^+ \) channels act as EDHF and regulate arterial tone. Other than regulating acid release from endothelial cells and arteries, thus, EETs are synthesized by the vascular endothelium and they function as EDHF. In arteries from experimental animals and humans, as well as the interaction between NO and EDHF-dependent mechanisms. A better understanding is needed to limit depolarization and prevent vasoconstriction. Kv and BKCa act in a negative feedback manner to limit depolarization and prevent vasoconstriction.

**Table 1. VSMC Potassium Channels**

<table>
<thead>
<tr>
<th>Potassium Channel</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inward-rectifier ( \mathrm{K}^+ ) channels</td>
<td>Dilation induced by elevated extracellular ( \mathrm{K}^+ ); may also be activated by C-type natriuretic peptide</td>
</tr>
<tr>
<td>ATP-sensitive ( \mathrm{K}^+ ) channels</td>
<td></td>
</tr>
<tr>
<td>KATP</td>
<td></td>
</tr>
<tr>
<td>Voltage-gated ( \mathrm{K}^+ ) channels</td>
<td></td>
</tr>
<tr>
<td>( \mathrm{K}_v )</td>
<td></td>
</tr>
<tr>
<td>Large conductance ( \mathrm{Ca}^{2+} )-activated ( \mathrm{K}^+ ) channels</td>
<td></td>
</tr>
<tr>
<td>( \mathrm{BK}_c )</td>
<td>May be activated by EETs</td>
</tr>
</tbody>
</table>

Vasodilators acting through cAMP or cGMP signaling pathways may open KATP, \( \mathrm{K}_v \), and \( \mathrm{BK}_c \), causing membrane hyperpolarization and vasodilatation. 

**Table 2. Microvascular Endothelial Cell Potassium Channels**

<table>
<thead>
<tr>
<th>Potassium Channel</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small conductance ( \mathrm{Ca}^{2+} )-activated ( \mathrm{K}^+ ) channels</td>
<td>Opened by endothelium-dependent vasodilators that increase intracellular ( \mathrm{Ca}^{2+} )-activated channels and cause membrane hyperpolarization that may be conducted through myoendothelial gap junctions to hyperpolarize and relax arteriolar vascular smooth muscle</td>
</tr>
<tr>
<td>Intermediate conductance ( \mathrm{Ca}^{2+} )-activated ( \mathrm{K}^+ ) channels</td>
<td>May serve to amplify ( \mathrm{SK}<em>{cd} ) and ( \mathrm{IK}</em>{ca} )-induced hyperpolarization and allow active transmission of hyperpolarization along endothelial cells through gap junctions</td>
</tr>
<tr>
<td>Inward-rectifier ( \mathrm{K}^+ ) channels</td>
<td>May provide a negative feedback mechanism to limit depolarization in some endothelial cells</td>
</tr>
</tbody>
</table>

Data are from Reference 10.

Potassium is a vasoactive substance. When potassium is infused into the arterial supply of a vascular bed, blood flow increases. The vasodilatation induced by potassium results from hyperpolarization of the vascular smooth muscle cells subsequent to potassium stimulation by the ion of the electrogenic \( \mathrm{Na}^+\)-\( \mathrm{K}^+ \) pump and/or by activating the inwardly rectifying inward-rectifier \( \mathrm{K}^+ \) channels. In the case of skeletal muscle and brain, the increased flow sustains the augmented metabolic needs of the tissues. Potassium ions are also released by the endothelial cells in response to neurohumoral mediators and physical forces (such as shear stress) and contribute to the endothelium-dependent relaxations, being a component of EDHF-mediated responses. Dietary supplementation of potassium can lower blood pressure in normal and in some hypertensive patients. The hypotensive response to potassium supplementation is slow to appear and takes \( \approx 4 \) weeks. Such supplementation may reduce the need for antihypertensive medication. “Salt-sensitive” hypertension responds particularly well, perhaps in part, because supplementation with potassium increases the urinary excretion of sodium chloride. Potassium supplementation may even reduce organ system complications (eg, stroke).

Vascular smooth muscle cells express \( \geq 4 \) different classes of \( \mathrm{K}^+ \) channels (Table 1), and endothelial microvascular cells express \( \geq 5 \) classes of \( \mathrm{K}^+ \) channels (Tables 1 and 2). From a clinical point of view and based on these preliminary experimental observations by Mishra et al., as well as on the results of necessary further experimental studies, \( L^{-} \)-serine might be investigated in clinical hypertension, especially when endothelium dysfunction corresponds with NO deficiency alone or by combining it with other antihypertensive drugs.
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References


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