

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

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In this issue of *Hypertension*, Mishra et al¹ compared the *in vitro* effects of the amino acid L-serine, a precursor of central neurotransmitters, and acetylcholine in phenylephrine-constricted mesenteric arterioles in *N*^G-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 Ca-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 and the intermediate 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 al¹ 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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Table 1. VSMC Potassium Channels

Potassium Channel	Function
Inward-rectifier K ⁺ channels	
Kin	Dilation induced by elevated extracellular K ⁺ ; may also be activated by C-type natriuretic peptide
ATP-sensitive K ⁺ channels	
KATP	
Voltage-gated K ⁺ channels	
Kv	
Large conductance Ca ²⁺ -activated K ⁺ channels	
BKCa	May be activated by EETs

Vasodilators acting through cAMP or cGMP signaling pathways may open KATP, Kv, and BKCa, causing membrane hyperpolarization and vasodilatation. Vasoconstrictors may close KATP, Kv, and BKCa through protein kinase C, ρ -kinase, or c-Src pathways and contribute to vascular smooth muscle cell depolarization and vasoconstriction. Kv and BKCa act in a negative feedback manner to limit depolarization and prevent vasospasm.¹⁰

failure, erectile dysfunction, and the ischemia-reperfusion period during open heart surgery.⁷ Pharmacological agents such as potassium channel openers or cytochrome P450 metabolites have been used to either protect or recover EDHF-dependent mechanisms. A better understanding is essential with regard to the function of EDHF under pathophysiological conditions in humans, as well as the interaction between NO and EDHF.⁷

Epoxyeicosatrienoic acids (EETs) are generated in the endothelium from arachidonic acid by cytochrome P450 epoxygenases. The expression of cytochrome P450 epoxygenases in endothelial cells is determined by physical (fluid shear stress and cyclic stretch) and pharmacological stimuli, as well as by hypoxia.⁸ The activation of cytochrome P450 epoxygenases in endothelial cells is an important step in both the NO- and prostacyclin-independent vasodilatation of several vascular beds, and EETs have been identified as EDHFs. EETs are synthesized by the vascular endothelium and they open calcium-activated potassium channels, hyperpolarize the membrane, and relax the vascular smooth muscle.³

Endothelium-dependent relaxations to acetylcholine, bradykinin, and shear stress that are not inhibited by cyclooxygenase and NO synthase inhibitors are mediated by the EDHF.³ In arteries from experimental animals and humans, the non-NO, nonprostaglandin-mediated relaxations and endothelium-dependent hyperpolarizations are blocked by cytochrome P450 inhibitors, calcium-activated potassium channel blockers, and epoxyeicosatrienoic acid antagonists. Acetylcholine and bradykinin stimulate epoxyeicosatrienoic acid release from endothelial cells and arteries. Thus, EETs act as EDHF and regulate arterial tone.³ Other than regulating vascular tone, EETs modulate several signaling cascades and affect cell proliferation, cell migration, and angiogenesis. Signaling molecules modulated by EETs include tyrosine kinases and phosphatases, mitogen-activated protein kinases, protein kinase A, cyclooxygenase-2, and several transcription factors.⁸

Table 2. Microvascular Endothelial Cell Potassium Channels

Potassium Channel	Function
Small conductance Ca ²⁺ -activated K ⁺ channels	
SK _{Ca}	Opened by endothelium-dependent vasodilators that increase intracellular Ca ²⁺ -activated channels and cause membrane hyperpolarization that may be conducted through myoendothelial gap junctions to hyperpolarize and relax arteriolar vascular smooth muscle
Intermediate conductance Ca ²⁺ -activated K ⁺ channels	
IK _{Ca}	
Inward-rectifier K ⁺ channels	
Kin	May serve to amplify sK _{Ca} - and IK _{Ca} -induced hyperpolarization and allow active transmission of hyperpolarization along endothelial cells through gap junctions
ATP-sensitive K ⁺ channels	
KATP	May be activated by vasodilators
Voltage-gated K ⁺ channels	
Kv	May provide a negative feedback mechanism to limit depolarization in some endothelial cells

Data are from Reference 10.

Potassium is a vasoactive substance.⁹ When potassium is infused into the arterial supply of a vascular bed, blood flow increases.⁹ The vasodilatation induced by potassium results from hyperpolarization of the vascular smooth muscle cells subsequent to potassium stimulation by the ion of the electrogenic Na⁺-K⁺ pump and/or by activating the inwardly rectifying inward-rectifier K⁺ channels.⁹ 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.⁹ 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 ≈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 ≥4 different classes of K⁺ channels (Table 1), and endothelial microvascular cells express ≥5 classes of K⁺ channels (Tables 1 and 2).¹⁰ From a clinical point of view and based on these preliminary experimental observations by Mishra et al,¹ 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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