Cell-to-Cell Communication Coordinates Blood Flow Control
Steven S. Segal

Abstract The control of tissue blood flow is a dynamic process exemplified by the interaction among physical, chemical, and electrical events occurring within the vessel wall and between the vasculature and tissue parenchyma. The range of blood flow control achieved in vivo is illustrated by functional hyperemia in exercising skeletal muscle: maximal flow can exceed resting values by more than 50-fold. Blood flow control is integrated among many vessel segments, beginning with resistance arteries external to the muscle and encompassing the arteriolar network within the muscle. As metabolic demand increases, the locus of blood flow control shifts from distal arterioles, which control capillary perfusion and blood flow distribution within the tissue, to the proximal arterioles and resistance arteries, which control the total volume of flow into the muscle. A fundamental question centers on how this vasomotor activity is actually coordinated throughout the resistance network. The interaction within and among vascular segments can be explained by chemical and electrical signals to smooth muscle cells (SMCs) and endothelial cells (ECs) in response to changes in transmural pressure as well as luminal shear stress. Increasing pressure results in SMC contraction via the myogenic response. Increasing flow stimulates ECs to release autacoids (eg, nitric oxide), which relax SMCs. Pressure and flow thereby provide opposing mechanical stimuli that interact in the maintenance of vasomotor tone throughout the resistance network. Vasomotor signals are also conducted along arterioles through cell-to-cell coupling between ECs and SMCs, thereby coordinating vasomotor activity of cells within a branch and among branches. Adrenergic innervation influences each of these relations, as do the metabolic and mechanical effects of muscle contraction. The contribution of respective mechanisms to the control of blood flow varies with location in the resistance network, yet the interaction between mechanisms results in tissue perfusion in accord with the local requirements of parenchymal cells. (Hypertension. 1994;23[part 2]:1113-1120.)

Key Words arteries arterioles vasodilation endothelium muscle, smooth, vascular exercise muscle contraction sympathetic nervous system

Blood flow control in the resistance vasculature is a dynamic process exemplified by the interaction among physical, chemical, and electrical events occurring within the vessel wall and originating from the tissue parenchyma. Resistance vessels begin with small (diameter, 100 to 500 μm) “feed” arteries external to the tissue and encompass the arteriolar network (10 to 100 μm) embedded within the tissue.1 Feed arteries and proximal arterioles (1A, 60 to 100 μm) control flow magnitude into the tissue; intermediate arterioles (2A and 3A, 15 to 60 μm) control flow distribution within the tissue; and terminal arterioles (4A, 8 to 15 μm) control capillary perfusion,2 ie, the surface area for exchange between parenchymal cells and the cardiovascular system (Fig 1).

The wall of resistance vessels consists primarily of smooth muscle cells (SMCs) wrapped around the vessel lumen, which is lined by a monolayer of endothelial cells (ECs) in contact with the blood.3,4 Vasoactive substances are produced by ECs, SMCs, and parenchymal cells and are released by autonomic nerve endings on the adventitial surface of SMCs. In addition, vessels are continually exposed to such physical forces as transmural pressure and luminal shear stress (Fig 2). These multiple stimuli interact to control the contractile activity of SMCs (either directly, or indirectly via the ECs) and thereby to change vessel diameter and regulate flow. At each level of the resistance network, the SMCs and ECs must act together to meet the changing requirements of the tissue parenchymal cells. The purpose of this review is to discuss the mechanisms whereby communication among SMCs and ECs, as well as autonomic nerves and parenchymal cells, results in the coordination of blood flow control within and among vascular segments. The influence of hypertension on these relations is also considered.

Functional Hyperemia
One of the most dramatic changes in tissue perfusion occurs in skeletal muscle. In response to exercise, the increase in blood flow to active muscle can exceed resting values by more than 50-fold.5 The traditional explanation of this “functional hyperemia” invokes the metabolic theory, which states that vasodilator substances (eg, potassium, adenosine, carbon dioxide) produced by active muscle fibers diffuse through the interstitial space to act on SMCs of arterioles, causing vasodilation in proportion to metabolic activity.6,7 This explanation implies that the action of vasodilator substances is confined to the vicinity of production and diffusion or to regions influenced by metabolites carried in (and diffusing from) the venous blood.12,13 However, such a view of local flow control does not adequately explain functional hyperemia.

Ascending Vasodilation
Vasodilation in response to muscle contraction is not confined to a particular segment of the vascular network.

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was thought to involve an axon reflex evoked in re-
first- and second-order arteriole and venule branches tend to run
the draining vein running parallel to the feed artery. Note that
flow can be appreciated by a simple model of resistors in
wall independently of any neural mechanism, l9-30-31 giv-
mediate arterioles (flow distribution) and into the proxi-
segments concomitant with downstream segments is
crease in perfusion is greatly enhanced. Thus, with
blood flow, but the magnitude of hyperemia would be
dilation of the arterioles alone would increase tissue
acetylcholine was shown to trigger the spread, or "prop-
agation," of arteriolar dilation in hamster cheek
nerves.28 Nearly 25 years ago, microiontophoresis of
activities in MF, which may induce ECs and SN to influence
transmission of electrical signals between ECs and SMCs
(s) as enabled by gap junctions) is illustrated as small
pores between adjacent cells. Numbered arrows indicate pro-
duction of vasodilator substances by MF that act on SMCs (1),
release of neurotransmitter from SN onto SMCs and ECs
(2), 5,14,15 release of autacoids from ECs that act on SMCs (3),16-18
transmission of electrical signals between ECs and SMCs
(4),19,20 and activation of motor nerve giving rise to electrical
activity in MF, which may induce ECs and SN to influence
contractile activity of SMCs (5).21
refers to direct coupling (eg, via gap junctions) between
ECs and SMCs rather than neural propagation.
Evidence for conducted vasodilation has also been
found in conduit arteries. Dilation of the cat femoral
artery was observed subsequent to contraction of the
gastrocnemius muscle, which was interpreted as the
transmission of an electrical signal along the SMCs of
the vessel media.32 However, in later studies dilation of
the femoral artery was ascribed to changes in flow
through the vessel lumen,33 a response subsequently
shown to be mediated via the ECs.34 In more recent
years this "flow-induced vasodilation" has been demon-
strated in arterioles both in situ35,36 and when isolated
from either skeletal37 or cardiac38 muscle. It is impor-
tant to recognize that neither flow-induced nor con-
ducted vasodilation depends on parenchymal cells; ie,
they reflect mechanisms of vasomotor control that are
intrinsic to the vessel wall (Fig 2).

Coordinating Vasomotor Activity
A fundamental question is how the demands of
parenchymal cells (eg, muscle fiber contraction) may
give rise to ascending vasodilation. The microcirculation
is virtually embedded in the tissue, separated from
parenchymal cells only by the interstitial space. There-
fore, vasoactive stimuli originating from the paren-

Fig 1. Schematic illustration shows resistance network supplying
skeletal muscle. Femoral artery and vein are shown running in
parallel; arrows indicate direction of blood flow. A feed
(resistance) artery (FA) originates from the femoral artery and
gives rise to the arteriolar network within the muscle. Primary
arterioles (1A) give rise to secondary (2A) branches, which
branch into third-order (3A) and fourth-order (4A) segments.
Capillary networks (caps) arise from 4A segments and converge
on fourth-order venules (4V), which lead into third (3V), second
(2V), and primary (1V) segments; venular effluent converges into
the draining vein running parallel to the feed artery. Note that
first- and second-order arteriole and venule branches tend to run
side by side and all microvessels are embedded in the muscle
parenchyma.

Fig 2. Schematic shows cell-to-cell communication in skeletal
muscle. Illustration (longitudinal section) depicts an arteriole
embedded between skeletal muscle fibers. Structural elements
include endothelial cells (EC) lining the vessel lumen,3-4 smooth
muscle cells (SMC) wrapped around ECs,3 sympathetic nerves (SN)
with varicosities containing neurotransmitter on adventitial
surface of SMCs,5 striated muscle fibers (MF) surrounding the
innervated arteriole, and neuromuscular junction (NMJ) of
a muscle fiber. Within the lumen are illustrated the physical forces
acting on the vessel wall: intravascular pressure (P), which
results in transmural pressure based on the difference between
intravascular and interstitial pressures6; and flow (F), shown as a
parabola, which translates into shear stress acting on the EC
surface.7 Direct coupling between ECs8,9 and between SMCs10-12 (as enabled by gap junctions) is illustrated as small
pores between adjacent cells. Numbered arrows indicate pro-
duction of vasodilator substances by MF that act on SMCs (1),
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The rapidity of arteriolar dilation in response to skeletal muscle contraction has suggested activation of dilator nerves intrinsic to the arteriolar network, although additional evidence is needed to support this hypothesis. Vasodilation triggered on terminal arterioles (eg, with acetylcholine microiontophoresis) can be rapidly (<1 second) conducted into proximal branches to increase capillary perfusion. Furthermore, conducted responses that are initiated on distal branches can be summed and integrated in parent vessels, which results in a graded increase in network perfusion. Thus, conducted vasodilation could explain the early portion of the hyperemic response, with flow-induced and metabolic dilation contributing thereafter. The mechanical action of skeletal muscle fibers associated with rhythmic movement (ie, the muscle pump) may also initiate the rapid onset of functional hyperemia. In the presence of a constant arterial pressure, time for substances to diffuse to the vicinity of arterioles (eg, with acetylcholine microiontophoresis) can be summed and integrated in parent vessels, which results in a graded increase in network perfusion. Thus, conducted vasodilation could explain the early portion of the hyperemic response, with flow-induced and metabolic dilation contributing thereafter.

Of all blood vessels, capillaries are most numerous and most closely associated with muscle fibers. Additionally, capillary ECs are most intimately associated with the parenchymal cells (there is no SMC layer in between). This raises the question of whether capillary ECs can be stimulated to trigger a response that travels upstream to influence the diameter and blood flow through parent arterioles. In the hamster cremaster muscle, acetylcholine microiontophoresis at the origin of capillary networks triggered a vasodilation that was conducted through the parent terminal arteriole, resulting in perfusion of capillary networks. Furthermore, epinephrine and norepinephrine applied from micropipettes onto capillaries in the rat mesentery were found to constrict the supplying arterioles. More recently, microapplication of acetylcholine or norepinephrine onto capillaries of the frog sartorius muscle was found to increase or decrease arteriolar diameter, respectively, with corresponding changes in capillary perfusion. These findings in capillary networks complement conducted vasodilation and vasoconstriction shown in arteriolar networks. Virtually any stimulus that changes flow through the vessel lumen can give rise to flow-induced responses. Similarly, myogenic responses can be triggered by relatively nonspecific stimuli; eg, changes in transmural pressure can be initiated either intravascularly or extravascularly. Although a number of agonists have been tested, it is clear that activation of muscarinic receptors consistently gives rise to conducted vasodilation, whereas activation of adrenergic receptors triggers conducted vasoconstriction. Although norepinephrine is clearly a physiological stimulus to resistance vessels, an endogenous source of vasoactive acetylcholine is less clear, particularly in tissues (eg, human and rodent skeletal muscle) devoid of cholinergic innervation of the vasculature. This seems remarkable in light of the established role of acetylcholine in defining cell-to-cell communication between ECs and SMCs. It is possible that acetylcholine released at the neuromuscular junction or from ECs may be vasoactive; however, these relations require further study.

In summary, a strong body of evidence now demonstrates that vasomotor activity is coordinated among the cells that comprise the blood vessel wall and among the vessel segments that comprise the resistance network. Conducted and myogenic responses are rapid enough to account for the onset of hyperemia, with metabolic and flow-induced dilation serving to maintain elevated flow. Each of these processes may be adjusted in accord with the local environment of a particular vessel segment and give rise to adjustments in adjacent segments. It is important to remember that the ultrastructure of the vessel wall changes as the resistance network branches into smaller segments, with a decrease in the thickness of the SMC layer and greater intimacy of contact between ECs and SMCs as vessel size is reduced. It appears that each regulatory mechanism (ie, metabolic, myogenic, flow-induced, and conducted responses) may predominate at different levels of the vascular network, whereas the role of a particular mechanism may vary throughout the network, as does the influence of sympathetic innervation. Nevertheless, cell-to-cell communication within the vessel wall, among vascular segments, and between parenchymal cells and the vasculature ensures that blood flow is matched to the prevailing requirements of the tissue.

Cell-to-Cell Communication and Vasomotor Responses

The purpose of this section is to summarize mechanisms by which SMCs and ECs communicate with each other in response to vasoactive stimuli. Respective mechanisms of signal transduction are only highlighted here; substantial research effort is currently aimed at elucidating these pathways.
The Myogenic Response

Myogenic response refers to the property of a vessel to respond to changes in transmural pressure. The underlying concept is that an increase in tangential wall stress is "sensed" by the SMCs, resulting in the activation of several transduction pathways. These include stretch-sensitive ion channels, phospholipase C, and perhaps the release of an EC-derived contracting factor. Together, these responses increase intracellular calcium in SMCs, thereby triggering contraction.

Thus, an increase in transmural pressure induces constriction, whereas reciprocal events result in relaxation. Myogenic responses occur independently of ECs or parenchymal cells, as does the development of spontaneous tone. Arterioles demonstrate maximal myogenic reactivity at physiological pressures, with relative responses increasing as vessel size decreases. Although each SMC experiences the physical stimulus, the coupling between SMCs coordinates contractile activity within the vessel wall.

Myogenic Adaptation

The myogenic response of arterioles is augmented with hypertension, which can explain the reduction in diameter and increased wall thickness observed in situ for arterioles of hypertensive rats. Hypertension is also associated with arteriolar rarefaction, although it is not necessarily attributable to elevated pressure per se. This confirms earlier findings of increased contractility of the femoral artery from hypertensive rats even when vessels were protected from elevated pressure.

Although a role for autacoids or neurohumoral mediators is thereby implicated in vascular adaptation to hypertension, the potential role of ECs in mediating these responses increasing as vessel size decreases. Although each SMC experiences the physical stimulus, the coupling between SMCs coordinates contractile activity within the vessel wall.

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Adaptation to elevated pressure also results in thickening of the arterial wall. Acutely, this may occur via the myogenic response, but over time SMC growth occurs either by hypertrophy or hyperplasia. This growth of the media offsets the increase in transmural pressure, thereby restoring wall stress toward control. Interestingly, endurance training has recently been found to increase both the myogenic response of resistance arteries and the thickness of the arterial media. Both responses may be attributable to the elevated arterial pressure that accompanies exercise. In contrast to hypertension, the increased arterial wall thickness with endurance training does not occur at the expense of the vessel lumen, indicating that this response to exercise is not pathological. Rather, endurance training may result in a vessel wall that is able to withstand greater hemodynamic stress without injury. The intercellular and intracellular mechanisms involved in stimulating cellular growth and proliferation in the vascular wall are the focus of substantial research effort.

Flow-Induced Vasodilation

The mechanism of flow-induced vasodilation centers on vasomotor responses to changes in flow through the vessel lumen. The EC monolayer sits at the interface between the vessel wall and blood flowing through the vessel lumen, essentially functioning as a signal transducer between the movement of blood and the contractile activity of the surrounding SMCs. In response to elevated shear stress, ECs release factors (ie, endothelium-derived relaxing factors [EDRFs]) that are transferred to the surrounding SMCs, causing vasodilation and returning wall shear stress toward control. The primary EDRFs released by ECs in response to shear stress are prostacyclin and nitric oxide.

ECs respond to both acute and long-term mechanical stress by a variety of signal transduction pathways, which evoke changes not only in the vasomotor activity of SMCs (acute) but also in vessel ultrastructure (long term). Mechanical deformation at the EC surface, perhaps via distortion of the glycocalyx or integrins within the cell membrane, can be transduced into electrical and biochemical signals at the cell surface (eg, production of EDRFs). In response to elevated flow, ECs hyperpolarize via mechanical activation of a potassium channel. This hyperpolarization could be transmitted directly to underlying SMCs via myoendothelial gap junctions and thereby induce vasodilation. However, these observations are limited in that the effect of flow on the membrane potential of ECs has been shown using only cultured ECs, which were not associated with SMCs. Furthermore, current evidence for such direct coupling between ECs and SMCs is controversial in both arteries and arterioles. Elevation of flow also increases the intracellular calcium of ECs, which may trigger the release of EDRFs and result in SMC relaxation. Note that only a single layer of SMCs surrounds ECs in arterioles, resulting in the direct action of EDRFs on SMCs. However, in arteries there are multiple SMC layers. Therefore, cell-to-cell coupling among SMCs may have an important role in evoking a coordinated response among SMCs of these larger vessels in response to flow.

In summary, mechanical perturbation directly elicits responses from both ECs and SMCs; however, the principal physical force responsible for stimulating respective cell types differs: tangential wall stress for SMCs and luminal shear stress for ECs. In contrast to the myogenic response intrinsic to SMCs, flow-induced dilation results from the interplay between ECs and SMCs. Mechanical signals can also be transmitted via the cytoskeleton directly into the cell interior, resulting in changes in gene expression and remodeling of the vascular wall. These findings demonstrate that the cells which comprise resistance vessels are highly sensitive to the physical forces prevailing in the vascular network. This points to the question of how pressure and flow may interact in the control of vasomotor tone.

Interaction Between Myogenic and Flow-Induced Responses

In excised resistance artery networks, elevation of perfusion pressure increased both transmural pressure and flow. After the initial passive dilation, vessels constricted myogenically, followed by a dilation that persisted with elevated flow. In paired segments exposed to elevated pressure but not flow, the myogenic constriction was sustained. Such responses indicate that myogenic constriction and flow-induced dilation interact to maintain vessels at an intermediate level of tone.
Similar interactions between pressure- and flow-induced responses have been observed in isolated coronary arteries. Furthermore, the prevailing level of transmural pressure dictated the magnitude of flow-induced dilation, whereas the prevailing level of flow determined the magnitude of myogenic constriction. In isolated segments of resistance arteries, flow was found to cause either constriction or dilation, depending on the initial level of tone; with intermediate tone, flow had a negligible effect. More recent work has found that flow caused depolarization when SMCs were hyperpolarized (eg, membrane potential more negative than -62 mV) and caused hyperpolarization when SMCs were depolarized (less negative than -49 mV). The balance of forces (ie, where flow had no effect on membrane potential) occurred at a resting potential of approximately -58 mV. However, the role of the ECs in mediating SMC responses to flow was not clear in these preparations. Recent studies of hamster arterioles in situ provide insight into this behavior. Jackson has proposed that resting tone is determined by the activity of ATP-sensitive potassium channels. At rest, with a portion of potassium channels open and another portion closed, membrane potential (and resting tone) would sit at an intermediate value. The opening of additional potassium channels would lead to hyperpolarization and vasodilation, whereas closure of these channels would lead to depolarization and vasoconstriction. The activity of a calcium-dependent potassium channel has also been implicated in the control of myogenic tone. Such findings indicate that the vaso-motor response of a vessel to a particular stimulus may vary in accord with the prevailing status of ion channels and therefore with the resting membrane potential. It is not yet apparent whether flow-induced dilation is altered with hypertension. Nevertheless, based on the preceding discussion, it is hypothesized that both conduit arteries and resistance vessels of hypertensive individuals would show impairment of this response. In contrast, recent evidence suggests that EC production of nitric oxide is augmented in response to exercise conditioning, with conduction occurring via “resistive connections” between contiguous SMCs. Observations of conducted vasodilation (described earlier) led to the hypothesis that acetylcholine-induced hyperpolarization, which was conducted along the arteriolar wall via cell-to-cell coupling, was related to the corresponding change in membrane potential. Recent findings have indicated that EC-EC (rather than SMC-EC) coupling could more readily serve as the pathway for conducted vasodilation. In a similar fashion, conducted vasoconstriction in response to nor-adrenaline was thought to reflect the spread of depolarization along the arteriolar wall, which could occur via SMC-SMC coupling. Thus, the intercellular pathway for conduction may vary with the nature of the stimulus as well as the location of the vessel in the resistance network. However, additional work is required to confirm such functional relations. Several studies have demonstrated functional gap-junctional coupling among both ECs and SMCs. Good morphological evidence exists for gap junctions in myoendothelial contacts between ECs and SMCs of arteries. Nevertheless, dye coupling (an index of gap junctions between cells) has not been found between ECs and SMCs in either arteries or arterioles. Spon-taneous slow waves (approximately two per minute) in membrane potential were recorded from ECs of arterioles in situ, which corresponded with spontaneous vasomotion. As pacemaker activity has not been reported for ECs, whereas arteriolar vasomotion has been attributed to SMC pacemakers, this observation raises the question of where such oscillations in EC membrane potential may originate. Based on dual recordings in coronary artery preparations, simultaneous oscillations in the membrane potential of ECs and SMCs have recently been reported, suggesting that electrical events originating in SMCs may be driving parallel changes in ECs. This may occur via unidirectional conduction through gap junctions, facilitated by differences in the input resistance between SMCs and ECs. Electrical coupling can also occur in the absence of dye cou-

Acetylcholine

Although various compounds have been used to investigate the interaction between ECs and SMCs, the present discussion will focus on acetylcholine. Physiologically, this molecule is a neurotransmitter that has also been widely used as a pharmacologic tool for the study of vasomotor properties of vascular wall. Through binding to a muscarinic receptor on the EC surface, acetylcholine causes hyperpolarization of ECs via activation of a calcium-sensitive potassium channel. In addition to this direct effect on ECs, acetylcholine stimulates the release of EDREs, which alter the contractile state of SMCs in arteries and arterioles. Furthermore, hyperpolarization of SMCs is induced by acetylcholine, which is abolished by the removal or impairment of ECs, giving rise to the recognition of an endothelium-derived hyperpolarizing factor (EDHF). Note that these responses of ECs to acetylcholine are similar to responses previously discussed above, pointing to a convergence of signal transduction pathways within ECs. The presence of an EDHF has been demonstrated in arteries, but it has not yet been shown in arterioles. Nevertheless, because acetylcholine results in hyperpolarization of both ECs and SMCs of arteries in situ, the question is raised as to how electrical (and vasomotor) activity may be communicated among cells that make up the arteriolar wall.

Cell-to-Cell Coupling

Electrical stimuli (either depolarization or hyperpolarization, produced via intracellular current injection) can travel over distances of several millimeters in arteriolar networks. Analysis of this behavior indicated that the arteriolar wall behaved in accord with the cable properties of excitable membranes, with conduction occurring via “resistive connections” between contiguous SMCs. Observations of conducted vasodilation (described earlier) led to the hypothesis that acetylcholine-induced hyperpolarization, which was conducted along the arteriolar wall via cell-to-cell coupling, the magnitude of dilation at each location was proposed to reflect the corresponding change in membrane potential.

Recent findings have indicated that EC-EC (rather than SMC-EC) coupling could more readily serve as the pathway for conducted vasodilation. In a similar fashion, conducted vasoconstriction in response to nor-adrenaline was thought to reflect the spread of depolarization along the arteriolar wall, which could occur via SMC-SMC coupling. Thus, the intercellular pathway for conduction may vary with the nature of the stimulus as well as the location of the vessel in the resistance network. However, additional work is required to confirm such functional relations. Several studies have demonstrated functional gap-junctional coupling among both ECs and SMCs. Good morphological evidence exists for gap junctions in myoendothelial contacts between ECs and SMCs of arteries. Nevertheless, dye coupling (an index of gap junctions between cells) has not been found between ECs and SMCs in either arteries or arterioles. Spon-taneous slow waves (approximately two per minute) in membrane potential were recorded from ECs of arterioles in situ, which corresponded with spontaneous vasomotion. As pacemaker activity has not been reported for ECs, whereas arteriolar vasomotion has been attributed to SMC pacemakers, this observation raises the question of where such oscillations in EC membrane potential may originate. Based on dual recordings in coronary artery preparations, simultaneous oscillations in the membrane potential of ECs and SMCs have recently been reported, suggesting that electrical events originating in SMCs may be driving parallel changes in ECs. This may occur via unidirectional conduction through gap junctions, facilitated by differences in the input resistance between SMCs and ECs. Electrical coupling can also occur in the absence of dye cou-
Adrenergic Interactions

A fundamental question with respect to flow control in vivo is whether the myogenic, EC-mediated, or conducted vasomotor responses are modulated by autonomic nerves. Activation of adrenergic receptors in rat cremaster arterioles enhanced the myogenic constriction in response to elevated pressure and myogenic dilation to a reduction in pressure. In hamster cremaster arterioles, adrenergic agonists have been found to attenuate conducted vasodilation, suggesting that sympathetic nerve activity can modulate the extent of intercellular coupling. Catecholamines have been found to impair the action of EDRFs on SMCs, as well as stimulate ECs to release substances that attenuate the magnitude of adrenergic constriction. Conversely, ECs have been found to metabolize norepinephrine, to inhibit norepinephrine release from adrenergic nerves (as previously shown for acetylcholine), and to act as a barrier to the overflow of norepinephrine into the bloodstream.

Thus, analogous to the interaction between myogenic constriction and flow-induced dilation (above), autonomic innervation on the adventitial surface of SMCs interacts with ECs on the luminal surface of SMCs in the control of vasomotor activity (Fig 2). In tissues that have low adrenergic tone at rest (eg, skeletal muscle), myogenic tone may be the predominant constrictor force, opposed by EC-mediated dilation. However, with the onset of exercise and the increased sympathetic outflow, the interaction between adrenergic constriction and EC-mediated dilation may become increasingly important in determining muscle blood flow.

Summary and Conclusion

The goal of this review has been to illustrate the importance of coordinating vasomotor activity both within and among the many vessel segments involved in blood flow control. It is apparent that cell-to-cell communication involves not only ECs and SMCs but autonomic nerves and the tissue parenchymal cells as well. Indeed, Mekata has recently reported that electrical activity of the myocardium can activate both perivascular nerves and ECs, thereby eliciting depolarization or hyperpolarization of coronary artery SMCs, respectively. Thus, activity in the surrounding tissue may invoke vasomotor responses independent of mechanical effects or the production of vasoactive metabolites. Such findings differ markedly from traditional explanations of blood flow control.

The interaction within and among vascular segments can be explained by mechanical, chemical, and electrical signals that are induced in ECs and/or SMCs in response to physical perturbations and receptor activation. Pressure and flow provide opposing stimuli that interact in the maintenance of vasomotor tone. In a similar fashion, adrenergic innervation and EDRF provide opposing inputs to the contractile status of SMCs. Vasodilation or vasoconstriction can also be conducted between ECs and SMCs independently of flow or pressure, yet the cell-to-cell coupling that underlies conduction may be modulated by a variety of factors. The contribution of respective processes to the control of blood flow appears to vary with location in the resistance network. Flow distribution is coordinated among distal branches and flow magnitude governed in proximal branches. The interaction among various mechanisms of flow control, together with the coordination of vasomotor activity among resistance segments, results in the perfusion of peripheral tissues in accord with the local requirements of the parenchymal cells.

Note added in proof: Mechanisms for coordinating the activity of ECs and SMCs in the vascular wall continue to unfold. Evidence is accumulating that SMCs are hyperpolarized by nitric oxide derived from ECs. In cell-free membrane patches of rabbit aortic SMCs, nitric oxide was recently reported to activate a calcium-sensitive potassium conductance. Further evidence for extensive gap-junctional coupling among cells in the arteriolar wall has been provided using intracellular microiontophoresis of bicocytin dye. When an EC was labelled, dye spread into adjacent ECs and SMCs. In contrast, labelling a SMC was followed by dye spread into adjacent SMCs but not into ECs. These findings also illustrate directionality in the nature of coupling between heterologous cells.

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