

Forum Review Article

Gap Junctions in the Control of Vascular Function

Xavier F. Figueroa¹ and Brian R. Duling²

Abstract

Direct intercellular communication *via* gap junctions is critical in the control and coordination of vascular function. In the cardiovascular system, gap junctions are made up of one or more of four connexin proteins: Cx37, Cx40, Cx43, and Cx45. The expression of more than one gap-junction protein in the vasculature is not redundant. Rather, vascular connexins work in concert, first during the development of the cardiovascular system, and then in integrating smooth muscle and endothelial cell function, and in coordinating cell function along the length of the vessel wall. In addition, connexin-based channels have emerged as an important signaling pathway in the astrocyte-mediated neurovascular coupling. Direct electrical communication between endothelial cells and vascular smooth muscle cells *via* gap junctions is thought to play a relevant role in the control of vasomotor tone, providing the signaling pathway known as endothelium-derived hyperpolarizing factor (EDHF). Consistent with the importance of gap junctions in the regulation of vasomotor tone and arterial blood pressure, the expression of connexins is altered in diseases associated with vascular complications. In this review, we discuss the participation of connexin-based channels in the control of vascular function in physiologic and pathologic conditions, with a special emphasis on hypertension and diabetes. *Antioxid. Redox Signal.* 11, 251–266.

Introduction

CELL-TO-CELL communication is fundamental in vascular function, as blood vessels are complex, multicellular structures that must work as an unit, and thus, control of vasomotor tone depends on the fine synchronization of the smooth muscle and endothelial cell function along the length of the vessel wall. Synchronization and coordination is accomplished by an intricate system of radial and longitudinal cell-to-cell communication (10, 55, 170, 175). In addition, in the microcirculation, small arteries and arterioles form a complex network whose elements must work in concert to regulate blood-flow distribution and peripheral vascular resistance by precise, well-integrated changes in the luminal diameter of the vessels (55, 171, 173, 174, 177).

One mode of communication that plays a critical role in controlling the function of the vessel wall is the release of paracrine molecules such as nitric oxide (NO) and prostaglandins. This signaling pathway is widely recognized, and its role in vascular physiology has been extensively studied. A complementary mechanism of communication that has

emerged as a key pathway to coordinate the vascular wall function is the direct cell-to-cell communication *via* gap junctions (Fig. 1). The expression of connexins has been reported to be altered in several animals models of pathologies associated with vascular complications (15), such as hypertension (56, 159) and diabetes (95, 215), which highlights the importance of the direct cell-to-cell interaction for vascular homeostasis.

Gap junctions are intercellular channels that directly connect the cytoplasm of adjacent cells, allowing the passage of current and small signaling molecules (molecular mass <1,000 Da), such as Ca^{2+} and IP_3 (49, 162) (Fig. 1). These intercellular channels comprise a protein family known as connexins (Cx), which are denoted according to their predicted molecular weight. Six connexins combine to make a connexon or hemichannel, and the association in the plasma membrane of two hemichannels provided by adjacent cells forms a functional gap-junction intercellular channel (49, 162) (Fig. 1). It is noteworthy that independent hemichannels may also remain unpaired and open to release paracrine signals such as ATP or NAD^+ (70, 163). Although it has been

¹Departamento de Ciencias Fisiológicas, Facultad de Ciencias Biológicas, Pontificia Universidad Católica de Chile, Santiago, Chile.

²Department of Molecular Physiology and Biological Physics, University of Virginia, Charlottesville, Virginia.

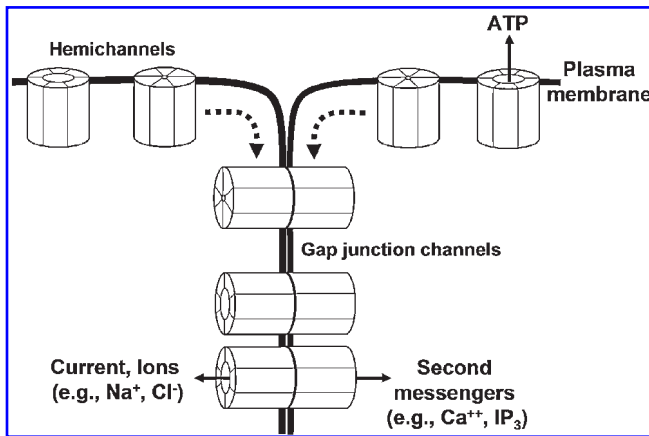


FIG. 1. Gap-junction channels in the plasma membrane. The family of proteins known as connexins constitutes the structural and functional unit of gap-junctional intercellular communication. Oligomerization of six connexin proteins forms a connexon or hemichannel (49, 162). In response to stimuli such as phosphorylation or Ca^{2+} , the associated six connexin subunits may coordinately change configuration to open the hemichannel and allow movement of paracrine signaling molecules such as ATP (70, 163). Hemichannels may diffuse laterally to the junctional membrane where they are in a position to dock with another hemichannel on the apposed membrane of the adjacent cell to complete a gap-junction channel (49, 162).

suggested that monocytes and macrophages expressed Cx37 hemichannels that regulate cell adhesion (207), this mode of connexin-based signaling has not yet been demonstrated to participate directly in the control of the vascular wall function (Fig. 1).

At least twenty connexin isoforms have been described in mammals, and one cell type often expresses more than one connexin (162). However, the expression of several connexins in one cell is not redundant. Gap junctions are not just simple channels that offer a low-resistance intercellular pathway for exchange of small solutes. Rather, the connexins mediate specific cell-to-cell signaling pathways, and the molecular selectivity as well as subcellular localization differs among connexin (55, 56, 129, 162, 203). Thus, although these proteins may have some overlap in function, they work in concert (55, 56, 79, 182, 183) and, in many cases, the function of one connexin cannot be replaced by other connexin isoform (79, 203, 206, 216). In addition, hemichannels can be composed of one (homomeric channels) or a mixture (heteromeric channels) of connexin proteins. Homomeric channels formed by different connexin isoforms typically differ in unitary conductance, permeability, and regulation and, as expected, the mixture of connexins in a heteromeric channel results in unique communication properties (28, 84, 131, 141), which provide an additional mechanism for fine regulation of gap junction-mediated signaling processes (12, 129, 204).

Connexin in the Vasculature

The vascular gap junctions are assembled from one or more of four connexin proteins: Cx37, Cx40, Cx43, and Cx45 (49, 55, 81, 178). The expression of connexins in the vessel wall is not uniform and seems to vary with vessel size, vas-

cular territory, and species (85, 191, 192). In most cases, Cx45 is observed only in the smooth muscle cells (109, 122, 158). Although Cx37 is typically confined to endothelial cells (64, 178, 191), it has also been detected in the smooth muscle cells (158). In contrast, Cx40 and Cx43 may be expressed in both cell types (64, 126, 178, 191), but Cx40 is located predominantly in the endothelial cells (64, 191), and Cx43 is the most prominent gap-junction protein found in the smooth muscle cells (191). It should be noted, however, that in the mouse, Cx40 has been detected exclusively in the endothelium (36, 57, 91, 115, 183).

Consistent with the importance of gap junctions for the vascular homeostasis, it has been found that selective ablation of connexin genes results in severe vascular malformations. Cx45 knockout mice die at early embryonic stages (E9.5 to E10.5) and exhibit major defects in remodeling and organization of blood vessels. In addition, these animals fail to form a smooth muscle layer surrounding the major arteries (109). Deletion of Cx43 modifies the expression of many genes known to be involved in the differentiation and function of vascular cells, and cell-signaling pathways important for the regulation of vasculogenesis and angiogenesis (197), which produces several alterations in the pattern of coronary artery development, and the embryos die at birth of blockage of the right ventricular outflow tract (25, 154). Although Cx40-deficient embryos exhibit small septational defects, deletion of one allele of Cx43 increases the cardiac malformations of Cx40-knockout mice and leads to neonatal death. In contrast, haploinsufficiency of Cx40 did not affect the Cx43-knockout phenotype (105). Deletion of Cx37 is not lethal and has not been shown to produce any particular vascular phenotype. However, simultaneous ablation of Cx37 and Cx40 results in severe vascular abnormalities in skin, testis, intestine, stomach, and lung, and the animals do not survive past the first postnatal day (183), which highlights the role of the endothelial cell-gap junction communication in the development of the vasculature. Taken together, these data indicate that individual connexin isoforms are differentially involved in vascular development and emphasize the notion that although these gap-junction proteins may be coexpressed, they basically work in concert.

Connexins in Vascular Physiology

Vascular smooth muscle

Synchronization of vasomotor tone among the smooth muscle cells is critical for the function of blood vessels. The contractile state of the smooth muscle cells is determined by the cytoplasmic Ca^{2+} concentration and the Ca^{2+} sensitivity of the contractile apparatus. Consequently, the smooth muscle cell-membrane potential plays a central role in the tonic control of intracellular Ca^{2+} concentration by modulating the influx of Ca^{2+} via L-type, voltage-dependent Ca^{2+} channels. Gap junctions play a central role integrating the smooth muscle cell function by coordinating changes in both membrane potential and intracellular Ca^{2+} between adjacent smooth muscle cells (22–24).

In addition, gap-junctional communication of vascular smooth muscle cells seems to be involved in the development of the myogenic vasomotor tone in resistance arteries (42, 118). Interestingly, the participation of the gap junction in this process is not related to synchronization of Ca^{2+} sig-

naling, but rather to earlier signaling events such as coordination of the smooth muscle cell depolarization or, directly, the mechanosensitivity of the vascular smooth muscle. This hypothesis is supported by the fact that the gap-junction inhibitory peptide Gap27 or the gap-junction inhibitor 18 α -glycyrrhetic acid, in addition to blocking Ca^{2+} influx and vasoconstriction in mesenteric resistance arteries, also prevented pressure-induced smooth muscle cell depolarization (42). However, a nonspecific effect of the gap-junction blockers on ion channels cannot be discounted. In any case, the involvement of gap junctions in the myogenic response may be consistent with the finding that tensile stretch increased Cx43 expression as well as gap-junctional intercellular communication in vascular smooth muscle cells. Interestingly, this response was mediated by the formation of reactive oxygen species (29, 30, 190), which has been reported to contribute to the initiation of the myogenic constriction in mouse-tail arterioles (146).

In addition, Cx43 seems to be essential for coordination of cell proliferation and migration in the vasculature (55, 116, 151, 214), which was recently confirmed by the specific deletion of the Cx43 gene in the smooth muscle cell (124). In these animals, the injury to the carotid artery by vascular occlusion or wire injury resulted in an increase in the neointima and the adventitia formation (124), suggesting an accelerated growth of the smooth muscle cell with the Cx43 deletion, which was further confirmed by using cultured cells. In contrast to these findings, Chadjichristos *et al.* (19) showed that in heterozygous Cx43-knockout mice, the neointimal formation was reduced. However, in those animals, Cx43 was deleted from all cell types expressing Cx43, and the experiments included a high-fat diet, which may have influenced the result by either vascular adaptive responses to the diet or complex interactions between different cell types. Although the participation of Cx43 in neointimal formation demands further investigation, these data highlight the relevance of Cx43 in the feedback-control pathways necessary for vascular morphogenesis.

Endothelium

The endothelium plays a key role in the tonic control of blood pressure, and deletion of vascular connexin genes has disclosed that gap-junctional communication is essential in the coordination and integration of microvascular function by the endothelial cells in a very complex manner. Vascular endothelial cells-specific deletion of Cx43 (VEC Cx43^{-/-}) results in hypotension (123) and, in contrast, ablation of Cx40 produces a hypertension associated with an irregular vasomotion (36, 37) and a dysregulation of renin production (107, 195, 196). Although deletion of Cx37 does not appear to alter vascular function or blood pressure, polymorphisms of this connexin have been associated with myocardial infarction, coronary artery disease, and atherosclerosis (13, 86, 211, 212). In mice, Cx40 and Cx37 are expressed primarily in the endothelium, which emphasizes the importance of the endothelial cell-gap junction communication in the control of cardiovascular homeostasis and the idea that vascular connexins work in concert coordinating specific signaling processes.

Although the mechanistic bases of the hypotension observed in VEC Cx43^{-/-} are still unknown, the plasma lev-

els of angiotensin I and II as well as NO were elevated in these animals (123), suggesting that a dysregulation of NO production may have been responsible for the hypotension, and the renin-angiotensin system was activated as a compensatory mechanism. It is interesting to note that shear stress upregulates the expression of Cx43 in cultured endothelial cells (6, 38) and in the endothelium of rat cardiac valves (93), which is consistent with the idea that Cx43 is involved in the sensitivity to mechanical stimuli.

Smooth muscle-endothelium communication via gap junction

The smooth muscle cells and the endothelial cells can also be electrically and metabolically connected by gap junctions located at discrete points of contact between the two cell types at the myoendothelial junction (MEJ) (11, 46, 127, 166, 179, 209). This heterocellular communication seems to play a pivotal role in the Ca^{2+} -mediated responses induced by endothelium-dependent vasodilators, such as ACh (Fig. 2). These vasodilator responses are typically paralleled by hyperpolarization of the underlying smooth muscle cells (46, 71, 75). The relaxant pathway associated with smooth muscle hyperpolarization is thought to be independent on NO and prostacyclin production by the endothelial cells and has

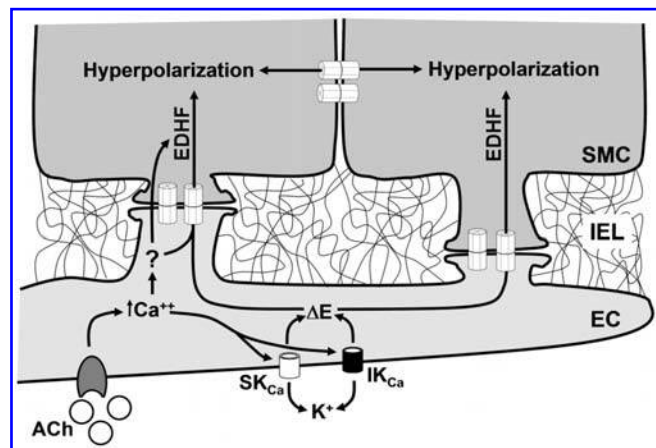


FIG. 2. Control of vasomotor tone by the endothelium-derived hyperpolarizing factor. Extensions derived from either the smooth muscle cells or endothelial cells may penetrate the internal elastic lamina (IEL) to make close contact with the other cell type. These points of contact, known as myoendothelial junctions (MEJs), provide the structural organization to achieve direct heterocellular coupling between the two cell types *via* gap junctions (40, 55, 166), and thus, one basis for endothelium-mediated smooth muscle hyperpolarization (often referred to as endothelium-derived hyperpolarizing factor, EDHF). Endothelium-dependent vasodilators such as acetylcholine (ACh) induce an increase in endothelial cell intracellular Ca^{2+} concentration, which, in turn, activates the Ca^{2+} -activated K^{+} channels (K_{Ca}) of small (SK_{Ca}) and intermediate conductance (IK_{Ca}). The endothelial cell hyperpolarization is transmitted electrotonically to the underlying smooth muscle cells *via* gap junctions located at the MEJ, contributing to the endothelium-dependent vasodilation (18, 44, 51). The question mark highlights that the participation of a diffusible EDHF has not been definitely discarded.

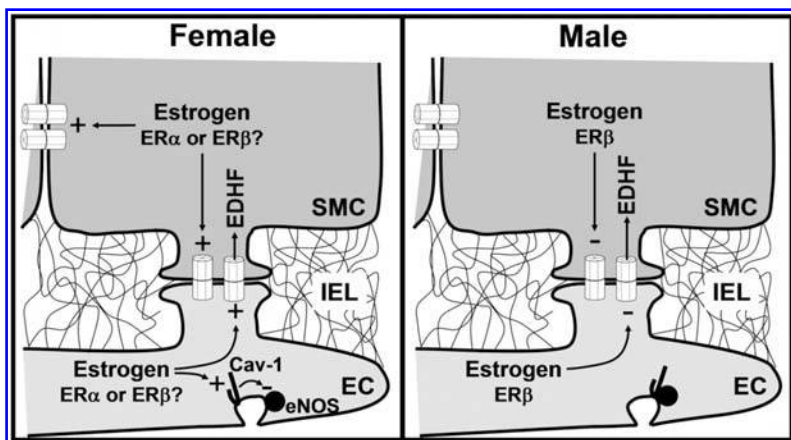


FIG. 3. Possible sex differences in the regulation of the endothelium-derived hyperpolarizing factor (EDHF). Nitric oxide (NO) and EDHF are the major endothelium-derived vasodilator signals in resistance vessels. The involvement of these two vasodilator signals differs between male and female animals. NO prevails over EDHF in males, and the contrary is observed in females (130, 169). This gender difference may be explained by the estrogen modulation of the myoendothelial gap junction-mediated smooth muscle hyperpolarization. In female animals, estrogen upregulates the expression of caveolin-1 (Cav-1) (128, 143), a structural protein of caveolae that, in turn, inhibits the activity of eNOS (52, 65, 100). In addition, this hormone enhances the expression

of Cx43 and Cx40 (128, 143), two gap-junction proteins found at the myoendothelial junctions (35, 97). As a result, the NO-dependent vasodilation is reduced, and the gap junction-mediated EDHF signaling is increased. The involvement of the estrogen receptor α (ER α) or β (ER β) remains to be determined. In contrast, in male animals, the activation of ER β reduces the gap junction-dependent smooth muscle hyperpolarization (130).

been attributed to the release of an endothelium-derived hyperpolarizing factor (EDHF) (50, 193). The identity of EDHF remains controversial, and several EDHF candidates have been proposed, such as K^+ ions (43), epoxyeicosatrienoic acids (EETs) (4, 62), hydrogen peroxide (180), and C-type natriuretic peptide (CNP) (1, 20). However, the direct electrotonic transmission of a hyperpolarizing current from the endothelial cells to the smooth muscle cells *via* myoendothelial gap junctions (Fig. 2) has emerged as a most attractive hypothesis to explain the EDHF pathway (18, 40, 74). In this context, the increase in endothelial cell intracellular Ca^{2+} concentration activates the Ca^{2+} -activated K^+ channels (K_{Ca}) of small (SK_{Ca}) and intermediate conductance (IK_{Ca}), leading to the endothelium-dependent hyperpolarization of the smooth muscle cells *via* gap junctions located at the MEJ (18, 32, 44, 51, 148) (Fig. 2). Consistent with this hypothesis, the EDHF-dependent vasodilation is prevented by the connexin-mimetic peptides that are thought to specifically block the gap junction (21, 35, 104), as well as endothelial cell-selective loading of antibodies directed against the carboxyl-terminal region of Cx40 (134).

In addition to NO, shear stress has been reported to activate an EDHF-dependent vasodilator response (198), and the contribution of the EDHF-mediated responses seems to increase as the vessel size decreases (165, 181), which suggests that an EDHF pathway may be involved in the tonic control of peripheral vascular resistance. Consistent with this idea, intrarenal infusion of connexin-mimetic peptides homologous to the second extracellular loop of Cx43 (^{43}Gap 27) or Cx40 (^{40}Gap 27) not only decreased basal renal blood flow, but also increased mean arterial blood pressure of female rats, either in the presence or the absence of NO synthase (NOS) and cyclooxygenase (COX) blockade (35), suggesting that the connexin-mimetic peptides induced vasoconstriction by disrupting a tonic vasodilator signal.

Interestingly, in male animals, NO is the major endothelium-dependent vasodilator signal, but in female animals, EDHF prevails over NO or PGI_2 (169), and estrogen appears to be responsible for this gender difference (90, 128, 143). The endothelial isoform of NOS (eNOS) is found in a inhibitory association with caveolin-1, a structural protein of caveolae

(52, 65, 100, 139, 140), and estrogen modulates the expression of this negative regulator of eNOS, and the EDHF-positive regulators, Cx43 and Cx40 (35, 97, 128, 143) (Fig. 3). Thus, in ovariectomized rats, the level of caveolin-1, Cx43, and Cx40 decreases in parallel with an increase in the NO-mediated vasodilation and a reduction in the EDHF-mediated vasodilation sensitive to the gap-junction blockers 18β and 18α -glycyrrhetic acid (128, 143). As expected, all the changes are recovered after estrogen replacement (128, 143).

Estrogen also enhances the EDHF-mediated vasodilation in response to flow (90), which suggests that the myoendothelial gap-junction-dependent signaling pathway may be more important in the control of blood pressure in female than in male animals. Recently, this idea was confirmed by using an eNOS/COX-1 double knockout. Deletion of eNOS and COX-1 did not alter the mean arterial blood pressure in female mice, whereas the double knockout resulted in hypertension in male mice (169). The endothelium-dependent relaxation was intact in resistance vessels of female mice and was mediated by the smooth muscle hyperpolarization (169), strongly indicating that EDHF plays a predominant role in the tonic control of blood pressure in female animals. These data suggest that EDHF rather than NO may underlie the higher resistance of premenopausal women to cardiovascular diseases such as hypertension.

Two estrogen receptor (ER) subtypes, ER α and ER β , are expressed in vascular endothelial cells as well as smooth muscle cells of both female and male animals (135, 136, 217). It is thought that ER α mediates most of the vascular effects of estrogen, but the importance of ER β is emerging, and ER β -deficient mice develop hypertension as they age (217). In addition, recently Luksha *et al.* (130) proposed that ER β contributes to the sex differences observed in the endothelium-dependent control of vasomotor tone by reducing the gap junction-mediated EDHF signaling in the male mouse (Fig. 3).

Conduction of vasomotor responses

Longitudinal conduction of vasomotor responses provides an essential means of coordinating changes in diameter and

flow distribution among vessels in a complex network. Vasomotor signals spread along the vessel length through gap junctions connecting cells of the vessel wall, and thereby, participate in the minute-to-minute coordination of vascular resistance by integrating function of proximal and distal vascular segments in the microcirculation (37, 55, 56). Although vasoconstrictor responses are thought to be conducted by the smooth muscle cells (8, 17, 202), the cellular pathway for conduction of vasodilator signals is more controversial and may be either exclusively the endothelium (47, 176) or both the smooth muscle and the endothelial cells (8, 17). The cellular pathway for conduction of vasomotor responses has been studied by selectively damaging a short segment of the endothelial cells or the smooth muscle cells with a light-dye (fluorescein-conjugated dextran) treatment. In feed arteries, selective damage of the endothelium completely blocked the ACh-induced conducted vasodilation (47, 176), but in arterioles, damage of either the endothelium or the smooth muscle did not affect the conduction of the response to ACh (8, 17), which led to the proposal that the cellular pathway for conducted vasodilations depends on the functional location of the vessel in the microvascular network (172). However, the cellular pathway of vasodilator signals may also depend on the stimulus that initiated the response, because, in contrast to ACh, selective damage of the endothelium blocked the vasodilation induced by bradykinin in arterioles (17, 202).

Direct measurements of membrane potential have shown that conducted vasomotor responses are associated with rapid propagation (milliseconds) of an electrical signal along the vessel length (47, 202, 208, 209). Because many observations have revealed an exponential decay of the conducted electrical signal, it was proposed that longitudinal spread of vasomotor responses reflects the passive, electrotonic conduction of changes in membrane potential *via* gap junctions connecting cells of the vessel wall (76, 150, 202). Therefore, the decay of the conducted vasomotor responses along the vessel length should be consistent with the length constant calculated from electrotonic potentials produced by current injection into the smooth muscle or endothelial cells of arterioles, which is between 0.9 and 1.6 mm (45, 87, 88).

Conduction of vasoconstrictor responses typically behaves as predicted by the electrotonic model. However, a simple electrotonic model often fails to predict conduction of vasodilator signals initiated by endothelium-dependent stimuli, such as ACh or bradykinin. These signals have been reported to propagate for many millimeters without showing noticeable decay in magnitude (36, 41, 47, 48) (Fig. 4). In addition, the electrical length constant of ACh-induced hyperpolarization has been shown to be longer than that measured for current injection (45), and the hyperpolarizing signal activated by ACh has been also reported to increase during the first 1,000 μm of longitudinal conduction (33). The lack of decay of these responses suggests that a regenerative, energy-dependent mechanism underlies the conduction process, similar to that described in neurons. Consistent with this idea, it was shown recently that electrical stimulation also activates a conducted, nondecremental endothelium-dependent vasodilation (Fig. 5) that is hypothesized to be mediated by a complex interplay between voltage-gated Na^+ channels (Na_v) and T-type, voltage-gated Ca^{2+} channels [T- Ca_v (54)], where Na_v underlies the conduction of the signal and T- Ca_v mediates the vasodilation (Fig. 6). Interestingly,

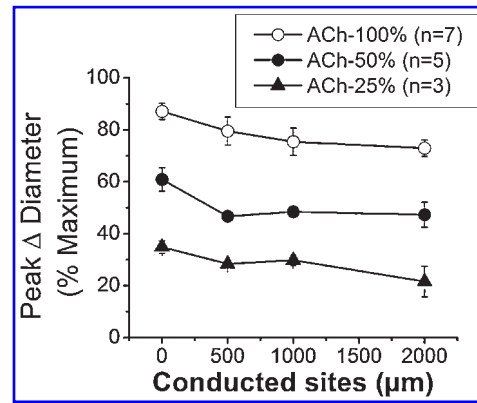


FIG. 4. Conduction of vasodilator responses induced by the stimulation of cremasteric arterioles with a pulse of ACh. The microcirculation of the cremaster muscle was prepared as described previously (54, 57), and arterioles were stimulated focally with the ejection of ACh (10 μM) by a pressure-pulse from a micropipette (inner diameter, 3–4 μm). The changes in diameter were measured first at the stimulation site (local), and then, at locations 500, 1,000, and 2,000 μm upstream in four separate stimuli. Variations in diameter were expressed as percentage of the maximal dilation possible (% maximum). The duration of the pulse (300–700 ms) and the ejection pressure (10–20 psi) were set to induce a local vasodilation of $\sim 100\%$, $\sim 50\%$, or $\sim 25\%$. Maximal diameter was estimated during superfusion of 1 mM adenosine. Note that the magnitude of the response decays only from the local site to the 500- μm conducted site and does not show a further reduction thereafter.

deletion of Cx40 selectively eliminates the regenerative component of the conducted vasodilation induced by ACh, bradykinin (36), or electrical stimulation (57), leaving a decaying component consistent with the electrotonic model, which demonstrates that gap junctions are the pathways for the intercellular propagation of these vasodilator signals and suggests that Cx40 may be functionally associated with the endothelial Na_v (Fig. 6). Deletion of Cx37 did not affect conduction of vasodilator responses (Figueroa and Duling, unpublished observations), and replacement of Cx40 by Cx45 did not restore the nondecremental component of the conducted vasodilation activated by ACh or bradykinin (206), supporting the idea that individual connexins have different functions, but leaving much to be explained as to how such selectivity is conferred.

The electrotonic and regenerative components of the conducted vasodilation activated by an endothelium-dependent vasodilator such as ACh are highlighted schematically in a hypothetical model shown in Fig. 6. The opening of inward-rectifier K^+ channels (K_{ir}) induced by the smooth muscle hyperpolarization may be an alternative hypothesis to explain the extended conduction of vasodilator responses. An intrinsic biophysical property of K_{ir} channels is that they increase their activity on cell hyperpolarization, and it has been proposed that the activation of these K^+ channels in the smooth muscle cells amplifies the hyperpolarizing current initiated by ACh, thereby facilitating the conduction of this signal (98). However, as mentioned earlier, current-induced hyperpolarization decays faster than the response induced by ACh (45), which argues against the participation of K_{ir}

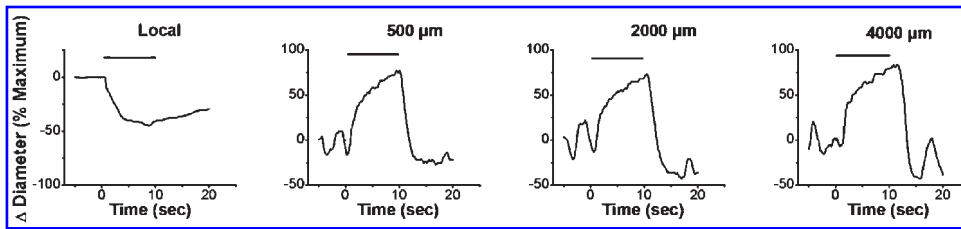


FIG. 5. Representative tracings of the conduction of the vasomotor responses induced by focal electrical stimulation of cremasteric arterioles. The microcirculation of the cremaster muscle was prepared as described previously (54, 57). An Ag/AgCl

reference electrode immersed in the superfusate was positioned symmetrically around the cremaster, and the arteriole was stimulated with a depolarizing train of pulses (30 Hz, 2 ms, 30 V) for 10 s by using a beveled micropipette (inner diameter, 3–4 μm) filled with 1 M NaCl. The stimulating pipette was inserted under the cremasteric mesothelium and positioned directly above the arteriole at a distance selected to evoke a local constriction of $\sim 50\%$ (54, 57). In separate stimuli, the changes in diameter were observed at the stimulation site (local), and at locations 500, 2,000, and 4,000 μm upstream. Variations in diameter were expressed as percentage of the maximal constriction or dilation possible (% maximum). Maximal diameter was estimated during superfusion of 1 mM adenosine. Focal electrical stimulation of the arteriole evoked a vasoconstriction that was restricted to a short vessel segment (~ 70 – 100 μm) at the stimulation site and, in addition, activated a rapid conducted vasodilation that spread along the length of the entire vessel without decay. Horizontal bars indicate the stimulation period.

alone in the nondecremental component of the conducted vasodilation and suggests that further investigation is needed to elucidate the mechanisms involved in the conduction of vasomotor responses.

Theoretic analysis of vascular adaptation to hemodynamic and metabolic stimuli indicate that conduction of vasodilator signals may also play a role in the long-term control of peripheral resistance by contributing to the maintenance of the structural homeostasis of the microvascular network (152). The vascular rarefaction observed during the development of hypertension may be an example of this. The phenomenon of rarefaction is manifested as a reduction in the number or density of microvessels, which occurs in two phases: a functional and an anatomic rarefaction (120). The functional rarefaction involves a reduction in the perfusion of microvessels that appears to reach a nadir at which they may then be disassembled, leading to the structural or anatomic rarefaction. Interestingly, mathematical simulations suggest that conduction of vasomotor responses induced by metabolic stimuli may be essential to preclude the disassembly of microvessels observed in the functional rarefaction (152, 153). Therefore, the functional longitudinal com-

munication from capillaries up to arterioles *via* gap junctions (9, 185) provides pathways for both short-term modulation of diameter and for long-term regulation of the microvascular network architecture in physiologic and pathologic conditions.

Neurovascular coupling

Conduction of vasomotor signals is also involved in the control of cerebral microcirculation by neuronal activity, referred to as neurovascular coupling (3, 83, 121). In this case, however, vasomotor signals seem to be conducted by astrocytes, as opposed to smooth muscle or endothelium (2, 106, 137, 142, 189, 218). Tight spatial and temporal coupling between neuronal activity and blood flow is essential for the brain function (2, 83, 121, 161), and astrocytes are found in a strategic location between neurons and the microvasculature, with the astrocytic endfeet ensheathing the vessels (Fig. 7). This spatial organization places the astrocytes in a key position to orchestrate the neurovascular coupling, and an increasing body of evidence shows that the astrocyte transduces and conducts neuron-generated vasomotor signals to

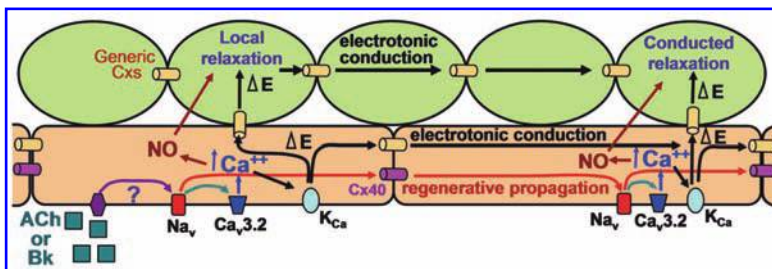


FIG. 6. Hypothetical model of conducted vasodilator responses activated by endothelium-dependent vasodilators [based on data from (36, 54, 57, 206)]. Stimulation of the endothelial cells with ACh or bradykinin triggers a regenerative, conducted vasodilator signal that is mediated by the activation of voltage-dependent Na^+ channels (Na_v) and rapidly propagated along the endothelium selectively *via* Cx40 gap junctions (red lines). The Na_v -mediated conducted electrical signal is transduced into vaso-

dilation by activation of the T-type, voltage-dependent Ca^{2+} channels $\text{Ca}_v3.2$ and the subsequent initiation of the production of Ca^{2+} -sensitive vasodilator signals such as NO and Ca^{2+} -activated K^+ channel (K_{Ca})-mediated smooth muscle hyperpolarization (black lines). The K_{Ca} -dependent hyperpolarization may be conducted electrotonically along the longitudinal axis of the vessel by either the smooth muscle cells or the endothelial cells *via* Cx40 or other connexins present in the vascular wall, which, in this schematic, we designated “generic” Cxs. This hypothetical model is compatible with the evidence showing that deletion of Cx40 completely eliminates the regenerative component of the conducted vasodilator response (36, 57, 206). The decremental conducted vasodilation that remains in the absence of Cx40 may correspond to the electrotonic conduction of the K_{Ca} -dependent hyperpolarizing signal. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article at www.liebertonline.com/ars)

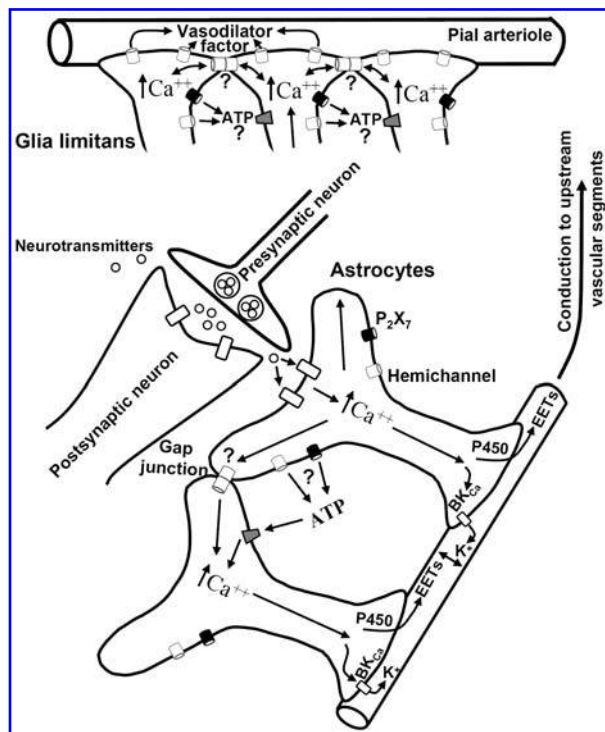


FIG. 7. Connexin-based channels likely to be involved in neurovascular coupling. Neurotransmitters released on an increase in neuronal activity may exit the synaptic cleft and activate receptors on astrocytes (2, 218). These receptors cause an increase in astrocyte intracellular Ca^{2+} concentration that leads to the activation of large conductance Ca^{2+} -activated K^+ channels (BK_{Ca}) and/or cytochrome P450 epoxygenase (P450) at the astrocytic endfeet. The efflux of K^+ through BK_{Ca} and/or production of epoxyeicosatrienoic acids (EETs) by P450 results in vasodilation of the parenchymal arterioles (2, 58, 59, 82, 187). The astrocyte-mediated vasodilation signal may be coordinated by the propagation of an interastrocyte Ca^{2+} signal *via* ATP release or directly by gap-junction communication. ATP may be released by either P_2X_7 receptors or unpaired hemichannels (70, 188). The potential role of interastrocyte Ca^{2+} waves in the coordination of the neurovascular coupling remains to be clearly defined. Local vasodilation of parenchymal cerebral arterioles must be communicated to upstream vascular segments to produce a functional increase of blood supply, and astrocytes may also communicate the vasodilator response to upstream vessels, such as the pial arterioles. These arterioles overlie a thick layer of astrocytic processes, called the glia limitans. The vasodilator signal triggered by neuronal activity reaches the glia limitans and induces a Cx43-based channel-dependent vasodilation (210). The mechanism by which Cx43 controls the astrocyte-mediated vasodilation has not been established, but coordination of the response between astrocytes, *via* gap-junction communication, or ATP release by hemichannels, is an interesting hypothesis that must be explored. An alternative hypothesis may be that a vasodilator factor is released at the endfeet *via* Cx43-based hemichannels.

the local microvasculature (2, 138, 142, 189, 218). As a result, astrocytes couple neuronal activation to vasodilation of local parenchymal arterioles (Fig. 7), which, in turn, leads to an increase in blood-borne oxygen and glucose supply to satisfy the enhanced metabolic demand rapidly (2, 83, 121, 161).

Calcium seems to be the intracellular vasomotor signal of the astrocyte-mediated neurovascular coupling. The increase in neuronal activity results in astrocytic calcium signaling that propagates through the astrocytic processes into the endfeet (2, 58, 142, 187, 218). The increase in cytosolic calcium concentration in the endfeet ultimately causes the release of vasoactive factors and arteriolar dilation (2, 58, 59, 187, 218) (Fig. 7). Interestingly, astrocytes express gap junctions (132, 133, 155, 162), and a calcium signal may propagate between neighboring astrocytes in a wavelike manner (27, 144, 145), coordinating the neurovascular coupling in the local cerebral microcirculation (2, 58, 142, 187, 218). However, the possible participation of gap junctions in the coordination of the astrocyte-mediated vasomotor signals remains to be established.

As described in the peripheral microcirculation (171, 177), local vasodilation of cerebral arterioles must be communicated to upstream vascular segments to produce a functional increase of blood-flow supply and to match the local metabolic demand (31, 92). Although vasomotor responses have been observed to be conducted in cerebral arterioles (39, 89), recently Xu *et al.* (210) demonstrated *in vivo* that astrocytes also play a central role in integrating the function of local arterioles with upstream cerebral vessels involved in the neurovascular coupling. Pial arterioles are important upstream vessels of the parenchymal cerebral arterioles. It is important to note that pial arterioles overlie a thick layer of astrocytic processes, known as the glia limitans, which isolate these arterioles from the neurons that are located right below (Fig. 7). Vasodilation of pial arterioles associated with neuronal activation was blocked by the selective elimination of astrocytes through treatment with L- α -aminoadipic acid, and, interestingly, this response was also sensitive to the inhibition of Cx43-based channels with the specific connexin-mimetic peptide gap-27 (161, 210). The selectivity of the Cx43 inhibition was confirmed by using two connexin-blocking peptides: gap-27, which targets Cx43/37-based channels, and gap-26, which is a Cx40/37-selective peptide (210). Taken together, these data suggest that Cx43 is essential in the astrocytic signaling that mediates the neurovascular coupling. In astrocytes, Cx43 may be found forming unpaired hemichannels or gap-junction intercellular channels (155, 162, 186). Thus, astrocytic, Cx43-based channels could be involved in the coordination of calcium waves between astrocytes or in the release of vasoactive factors (Fig. 7), which is an interesting scientific challenge that requires further investigations.

Vascular Connexins in Pathology

Hypertension

Consistent with the participation of gap junctions in the control of vasomotor tone, the expression of vascular connexins is altered in hypertension (56). However, changes in several parameters associated with this pathology, such as mechanical load (30), bioavailability of NO (80, 101, 156, 213), shear stress (93, 99, 117), or angiotensin II (78, 103), may modulate the expression of connexins. In addition, gap junctions are involved in different and sometimes antagonistic (vasodilation *vs.* vasoconstriction) functions in the control of vascular function, and changes in connexin expression vary depending on the experimental model of hypertension or

vascular territory studied (72, 77, 78, 80, 103, 157, 160, 199, 213). Therefore, a simple analysis of connexin expression does not allow one to determine whether connexins play a role in the genesis of hypertension or whether the changes observed are a consequence of the development of the pathology. Also, it is important to note that the heterocellular coupling between the smooth muscle and endothelial cells has been shown to be enhanced in spontaneously hypertensive rats (SHRs). However, in these animals, the vasodilation induced by ACh and the gap junction-mediated smooth muscle hyperpolarization were reduced, which was assumed to be the result of structural changes in the media, and that the greater heterocellular coupling was a compensatory mechanism to maintain the EDHF signaling in this model of hypertension (164). A recent review describes in detail the alterations of gap junctions in hypertension (56), and therefore, in this section of the review, we focus on the genetic manipulations of connexin expression that result in an altered control of arterial blood pressure.

Probably the clearest participation of gap junctions in hypertension is through the control of renin secretion. Cx37, -40, and -43 are expressed in the kidney and link the cells of the juxtaglomerular apparatus (JGA) (5, 114, 215). These three gap-junction proteins are expressed in the endothelial cells of afferent arterioles. In addition, Cx37 and Cx40 are found in renin-secreting cells and mesangial cells (5, 114, 215). Interestingly, endothelial cell communication *via* Cx43 appears to be a key in the control of renin secretion, because replacement of Cx43 by Cx32 (Cx43KI32) disrupted the regulation of renin synthesis and secretion (79). In Cx43KI32 mice, expression of renin was reduced, and the levels of this hormone were not downregulated by a high-salt diet or increased by clipping a renal artery in the two-kidney, one-clip (2K1C) model of renin-dependent renovascular hypertension (79).

In contrast to the inhibition of renin secretion observed in Cx43KI32 mice, deletion of Cx40 resulted in increased renin production and plasma renin concentration (Fig. 8), leading to the proposal that this connexin plays an essential role in the tonic inhibition of the renin system in the kidney (107, 196). Consistent with this idea, intrarenal pressure and angiotensin II failed to attenuate renin secretion in Cx40-deficient mice (196). Although Cx40 is the dominant gap-junction protein in renin-secreting cells, the dysregulation of the renin system observed in Cx40-knockout mice may depend, not on direct cell-to-cell signaling *via* Cx40 gap junctions, but on structural changes in the JGA architecture, as shown by Kurtz *et al.* (114). Ablation of Cx40 seems to affect the JGA development and, in the absence of Cx40, renin-expressing cells were not present in the terminal part of the afferent arteriole wall; instead, renin was found in cells of the extraglomerular mesangium and periglomerular interstitium (114). Taken together, these studies highlight the importance of gap-junction communication in the control of JGA development and renin secretion. It is important to remember that Cx37 is also expressed in the JGA, and although deletion of Cx37 does not affect arterial blood pressure, the participation of this connexin in JGA development and control of the renin system remains to be determined.

Although it may be controversial (107), the increase in renin secretion does not fully account for the hypertension observed in Cx40-knockout mice because blockade of the an-

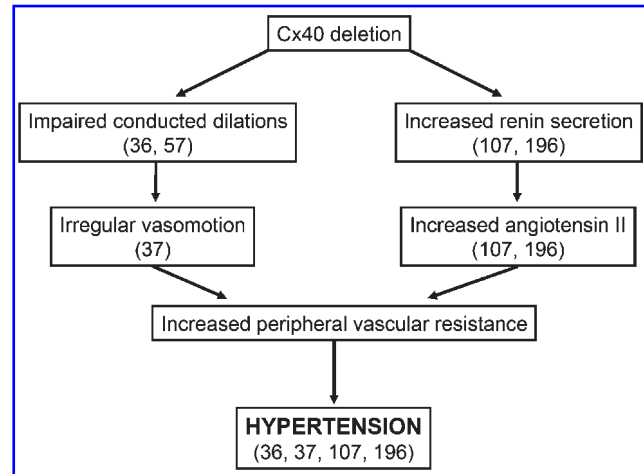


FIG. 8. Mechanisms of the control of arterial blood pressure by Cx40. Cx40 seems to play a central role in the control of arterial blood pressure by the parallel coordination of the vasomotor tone of resistance vessels and by renin secretion in the juxtaglomerular apparatus (JGA). Deletion of Cx40 affects the endothelial cell-dependent longitudinal synchronization of the vessel wall function, which results in an impaired conduction of vasodilator responses (36, 57), an irregular vasomotion and segmental constrictions (37). At the same time, the absence of Cx40 in the renin-secreting cells at the JGA disrupts the tonic inhibition of renin system, leading to an increase in renin secretion with the consequent increase in angiotensin II levels (107, 196). The dysregulation in the longitudinal communication of microvessels and renin secretion converges to increase the peripheral vascular resistance and produce the hypertension observed in Cx40-knockout animals (36, 37, 107, 196).

giotensin II receptor AT1 with candesartan (37) or the angiotensin I-converting enzyme (ACE) with enalapril (196) reduced, but did not revert the blood pressure of these animals to the normal values (Fig. 8). As mentioned earlier, deletion of Cx40 is also associated with an irregular vasomotion of microvessels and an impaired conduction of vasodilator signals (37). Therefore, the renin/angiotensin II-independent component of the hypertension triggered by the absence of Cx40 probably is caused by an interruption of the control and coordination of the cells of the vessel wall (Fig. 8). In support of the importance of coordination and integration of vasomotor tone in the control of arterial blood pressure (37, 55, 56) and structural adaptation of the microvascular network (152, 153), conduction of vasodilator responses has been found to be impaired in spontaneously hypertensive hamsters (110, 111) and SHRs (72).

The potential importance of endothelial cell Cx40 in the development of hypertension has also been noted in SHRs (103, 160). In the caudal artery of these animals, Rummery *et al.* (160) found decreased endothelial cell size and a reduction in the density of endothelial gap-junction plaques containing Cx40. Again, the heterogeneity in connexin participation arises because, in these experiments, no changes were found in the expression of Cx37 or Cx43.

Consistent with the key role played by Cx40 in the control of renin secretion and coordination of vasomotor tone, two closely related polymorphisms (−44A and +71G) within

the regulatory region of the human Cx40 gene have been associated with increased risk of hypertension in men (61, 73). As expected, these polymorphisms seem to alter the activity of the Cx40 promoter, because *in vitro* reporter assays revealed that the Cx40 haplotype -44A/+71G reduced the expression of luciferase by 50%, and the -44A polymorphism negatively affects the promoter regulation by the transcription factors Sp1 and GATA4 (60, 61, 73).

Diabetes

As observed in hypertension, control and coordination of vasomotor tone play a critical role during the development of diabetes, and vascular complications are the leading causes of mortality in this pathology. Diabetes and hyperglycemia may lead to vascular dysfunction by several mechanisms, such as nonenzymatic glycosylation (16, 194), oxidative stress (69), polyol-myoinositol alteration (63), and activation of diacylglycerol (DAG)-protein kinase C (PKC) pathways (119, 205).

A large body of evidence shows that PKC-dependent phosphorylation of Cx43 affects the gap-junction intercellular communication (125, 162), and, in the vasculature, the direct activation of PKC with phorbol myristate acetate (PMA) reduces the Cx43-mediated dye coupling in primary cultures of human tonsil high endothelial cells (53). In accordance with these findings, high glucose concentrations inhibited gap-junction dye transfer through the activation of a PKC-dependent signaling pathway in cultured bovine aortic endothelial cells (94, 95). In addition, exposure to a high-glucose medium reduced gap-junction activity in rat microvascular endothelial cells (167), and the reduction in dye coupling observed in these cells was correlated with a decrease in Cx43 mRNA and protein levels (Fig. 9), whereas the expression of Cx37 and Cx40 was not affected (167). Together, these data suggest that inhibition of gap junction-endothelial cell communication by an increase in glucose concentration may be involved in the endothelial cell dysfunction typically observed in diabetes (Fig. 9).

Glucose and diabetes may also alter vascular function by affecting gap-junction activity in vascular smooth muscle cells (102). In this regard, Kuroki *et al.* (95, 113) showed that high glucose levels reduce gap-junction intercellular communication of cultured aortic smooth muscle cells through the activation of a PKC-dependent pathway and the subsequent Cx43 phosphorylation (Fig. 9). In view of the importance of Cx43 gap junctions in smooth muscle cell proliferation and migration, as well as in vascular morphogenesis (55, 112, 124, 151, 214), the effect of high glucose on Cx43 gap-junction activity may contribute to the development of the diabetes-associated angiopathy. In addition, the permeability properties of the Cx43-derived gap-junction channel were reported to be altered in corporeal vascular smooth muscle cells isolated from streptozotocin-induced diabetic rats (14) (Fig. 9). As Cx43 appears to play a central role in the development of myogenic vasoconstriction, the alteration in the selectivity filter observed in the gap-junction communication of corporeal vascular myocytes may be involved in the diabetes-related erectile dysfunction.

The retina is a particularly sensitive tissue to be damaged by diabetes. Chronic hyperglycemia in diabetes is associated with the development and progression of pathologic changes

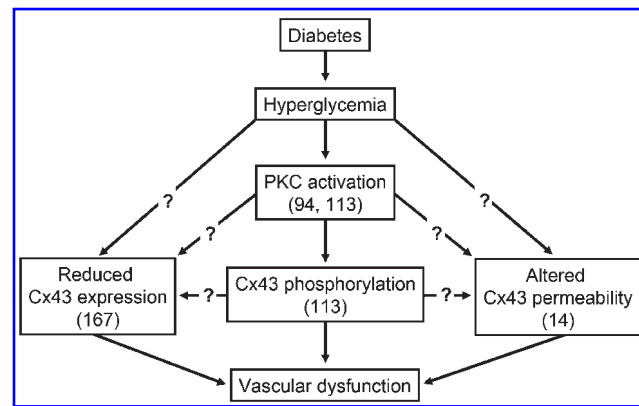


FIG. 9. Diabetes affects the Cx43-mediated communication in the vascular wall. The hyperglycemia associated with diabetes leads to a reduction in the gap-junction intercellular communication in the endothelial cells and smooth muscle cells through the activation of PKC (94, 113). The reduction in gap-junction communication induced by hyperglycemia is associated with a decrease in Cx43 expression (167), Cx43 phosphorylation (113), and changes in the permeability properties of the Cx43-based channels (14). Although the phosphorylation of Cx43 is mediated by PKC, the participation of this protein kinase in the changes of Cx43 expression and permeability remains to be established. Cx43 is an important gap-junction protein in the vasculature, and the disruption of Cx43-mediated gap-junction communication induced by hyperglycemia may contribute to the vascular dysfunction typically observed in diabetes.

in the retinal vasculature, and diabetic retinopathy is the leading cause of blindness in the working population (26). Retinal microvessels are well coupled *via* gap-junction channels, and, as may be expected, soon after the onset of streptozotocin-induced diabetes, the intercellular communication of the retinal microvascular network is disrupted (149). Therefore, the breakdown in the cell-to-cell organization *via* gap junctions may contribute to the early vascular dysfunction typically observed in diabetes (Fig. 9).

Concluding Remarks

Gap junctions play a multifaceted role in the vasculature that is essential in the control of gene expression, vascular development, and vascular function. However, the function of gap junctions in the vasculature does not depend only on the molecular selectivity or permeability of the different vascular connexin isoforms. It is now evident that connexins work in concert, and thus, the same connexin isoform may have distinct and sometimes antagonistic functions, depending on organization of the connexins and the cell type of the vessel wall in which they are expressed (*e.g.*, the endothelial cells or the smooth muscle cells). In addition, the function of gap junctions may be influenced by the subcellular localization of the connexin-based channels. Gap junctions may be targeted to signaling microdomains such as tight junction, lipid raft, and caveolae (55, 147, 168). In accordance with that localization, connexins have been reported to be associated with cytoskeletal proteins and caveolin-1 (7, 56, 66–68, 147, 168). Such targeting positions the connexins in a strategic spatial relation with a variety of cell-

signaling cascades in which they may participate in cell-cell signaling both by direct protein-to-protein interactions and by coordination of signaling pathways between two neighboring cells (34, 55, 147, 200, 201). Therefore, simple analysis of the level of connexin expression is not sufficient to understand fully the participation of the gap junction in cardiovascular function in normal and pathologic conditions. In addition, the cell-type distribution and, if it is possible, the subcellular localization of the specific connexin isoforms must be determined.

The apparent co-regulation of the connexin expression is another potentially important point in the study of vascular gap junctions. That is, deletion of one connexin isoform may affect the expression of another isoform (96, 108, 123, 184). Interestingly, this interaction may traverse the cell boundaries, and connexins present in one cell of the vascular wall may be linked to the expression of connexins in the functional associated cell type, as observed by Liao *et al.* (123), who reported a reduction in the Cx43 levels in the smooth muscle cells of VEC Cx43^{-/-} mice. Consequently, changes in one connexin may be secondary to the alteration of a different connexin, which leads to a demand for parallel analysis of multiple connexin isoforms, especially during the study of gap junctions in chronic vascular diseases.

Although the participation of the gap junction in vascular function seems to be very complex, the development of connexin-knockout animals has been a great contribution to our understanding of how these proteins work in the vasculature. In addition, connexin-mimetic peptides have demonstrated to be an effective tool to dissect the participation of gap junctions in vascular function. However, the potential manipulation of connexin function and/or expression in therapeutic interventions must await the expected future development of selective pharmacologic tools that allow targeting gap junctions in a connexin-isoform and cell type-specific manner.

Acknowledgments

This work was supported by NIH grant HL53318 (to B.R.D.), grant BM14/2007 from Vicerrectoría Adjunta de Investigación y Doctorado-VRAID de la Pontificia Universidad Católica de Chile, and grant 11060289 from Fondo Nacional de Desarrollo Científico y Tecnológico-FONDECYT (to X.F.F.).

Abbreviations

ACE, angiotensin I-converting enzyme; Ach, acetylcholine; ATP, adenosine 5'-triphosphate; COX, cyclooxygenase; Cx, connexin; Cx43KI32, replacement of Cx43 by Cx32; DAG, diacylglycerol; EDHF, endothelium-derived hyperpolarizing factor; eNOS, endothelial nitric oxide synthase; ER, estrogen receptor; ER α , estrogen receptor alpha; ER β , estrogen receptor beta; IK_{Ca}, Ca²⁺-activated K⁺ channels of intermediate conductance; IP₃, inositol 1, 4, 5-triphosphate; JGA, juxtaglomerular apparatus; K_{Ca}, Ca²⁺-activated K⁺ channels; 2K1C, two-kidney, one-clip model of hypertension; MEJ, myoendothelial junction; NAD⁺, nicotinamide adenine dinucleotide; Na_v, voltage-gated Na⁺ channel; NO, nitric oxide; NOS, nitric oxide synthase; PGI₂, prostacyclin; PKC, protein kinase C; PMA, phorbol 12-myristate 13-acetate; SHR,

spontaneously hypertensive rat; SK_{Ca}, Ca²⁺-activated K⁺ channels of small conductance; T-Ca_v, T-type, voltage-gated Ca²⁺ channels; VEC Cx43^{-/-}, vascular endothelial cell-specific deletion of Cx43.

References

1. Ahluwalia A and Hobbs AJ. Endothelium-derived C-type natriuretic peptide: more than just a hyperpolarizing factor. *Trends Pharmacol Sci* 26: 162–167, 2005.
2. Anderson CM and Nedergaard M. Astrocyte-mediated control of cerebral microcirculation. *Trends Neurosci* 26: 340–344, 2003.
3. Andresen J, Shafi NI, and Bryan RM Jr. Endothelial influences on cerebrovascular tone. *J Appl Physiol* 100: 318–327, 2006.
4. Archer SL, Gragasin FS, Wu X, Wang S, McMurtry S, Kim DH, Platonov M, Koshal A, Hashimoto K, Campbell WB, Falck JR, and Michelakis ED. Endothelium-derived hyperpolarizing factor in human internal mammary artery is 11,12-epoxyeicosatrienoic acid and causes relaxation by activating smooth muscle BK(Ca) channels. *Circulation* 107: 769–776, 2003.
5. Arensbak B, Mikkelsen HB, Gustafsson F, Christensen T, and Holstein-Rathlou NH. Expression of connexin 37, 40, and 43 mRNA and protein in renal preglomerular arterioles. *Histochem Cell Biol* 115: 479–487, 2001.
6. Bao X, Clark CB, and Frangos JA. Temporal gradient in shear-induced signaling pathway: involvement of MAP kinase, c-fos, and connexin43. *Am J Physiol Heart Circ Physiol* 278: H1598–H1605, 2000.
7. Barth K, Gentsch M, Blasche R, Pfuller A, Parshyna I, Koslowski R, Barth G, and Kasper M. Distribution of caveolin-1 and connexin43 in normal and injured alveolar epithelial R3/1 cells. *Histochem Cell Biol* 123: 239–247, 2005.
8. Bartlett IS and Segal SS. Resolution of smooth muscle and endothelial pathways for conduction along hamster cheek pouch arterioles. *Am J Physiol Heart Circ Physiol* 278: H604–H612, 2000.
9. Beach JM, McGahren ED, and Duling BR. Capillaries and arterioles are electrically coupled in hamster cheek pouch. *Am J Physiol Heart Circ Physiol* 44: H1489–H1496, 1998.
10. Beny JL. Information networks in the arterial wall. *News Physiol Sci* 14: 68–73, 1999.
11. Beny JL and Pacicca C. Bidirectional electrical communication between smooth muscle and endothelial cells in the pig coronary artery. *Am J Physiol* 266: H1465–H1472, 1994.
12. Beyer EC, Gemel J, Seul KH, Larson DM, Banach K, and Brink PR. Modulation of intercellular communication by differential regulation and heteromeric mixing of co-expressed connexins. *Braz J Med Biol Res* 33: 391–397, 2000.
13. Boerma M, Forsberg L, Van Zeijl L, Morgenstern R, De Faire U, Lemne C, Erlinge D, Thulin T, Hong Y, and Cotgreave IA. A genetic polymorphism in connexin 37 as a prognostic marker for atherosclerotic plaque development. *J Intern Med* 246: 211–218, 1999.
14. Brink PR, Valiunas V, Wang HZ, Zhao W, Davies K, and Christ GJ. Experimental diabetes alters connexin43 derived gap junction permeability in short-term cultures of rat corporeal vascular smooth muscle cells. *J Urol* 175: 381–386, 2006.
15. Brisset AC, Isakson BE, and Kwak BR. Connexin in vascular physiology and pathology. *Antioxid Redox Signal* 2008.
16. Bucala R, Tracey KJ, and Cerami A. Advanced glycosylation products quench nitric oxide and mediate defective en-

- dothelium-dependent vasodilatation in experimental diabetes. *J Clin Invest* 87: 432–438, 1991.
17. Budel S, Bartlett IS, and Segal SS. Homocellular conduction along endothelium and smooth muscle of arterioles in hamster cheek pouch: unmasking an NO wave. *Circ Res* 93: 61–68, 2003.
 18. Busse R, Edwards G, Feletou M, Fleming I, Vanhoutte PM, and Weston AH. EDHF: bringing the concepts together. *Trends Pharmacol Sci* 23: 374–380, 2002.
 19. Chadjichristos CE, Matter CM, Roth I, Sutter E, Pelli G, Luscher TF, Chanson M, and Kwak BR. Reduced connexin43 expression limits neointima formation after balloon distension injury in hypercholesterolemic mice. *Circulation* 113: 2835–2843, 2006.
 20. Chauhan SD, Nilsson H, Ahluwalia A, and Hobbs AJ. Release of C-type natriuretic peptide accounts for the biological activity of endothelium-derived hyperpolarizing factor. *Proc Natl Acad Sci U S A* 100: 1426–1431, 2003.
 21. Chaytor AT, Bakker LM, Edwards DH, and Griffith TM. Connexin-mimetic peptides dissociate electrotonic EDHF-type signalling via myoendothelial and smooth muscle gap junctions in the rabbit iliac artery. *Br J Pharmacol* 144: 108–114, 2005.
 22. Christ GJ, Moreno AP, Melman A, and Spray DC. Gap junction-mediated intercellular diffusion of Ca^{2+} in cultured human corporal smooth muscle cells. *Am J Physiol* 263: C373–C383, 1992.
 23. Christ GJ, Moreno AP, Parker M, Gondre CM, Valcic M, Melman A, and Spray DC. Intercellular communication through gap junctions: a potential role in pharmacomechanical coupling and syncytial tissue contraction in vascular smooth muscle isolated from the human corpus cavernosum. *Life Sci* 49: PL195–PL200, 1991.
 24. Christ GJ, Spray DC, el-Sabban M, Moore LK, and Brink PR. Gap junctions in vascular tissues: evaluating the role of intercellular communication in the modulation of vasomotor tone. *Circ Res* 79: 631–646, 1996.
 25. Clauss SB, Walker DL, Kirby ML, Schimel D, and Lo CW. Patterning of coronary arteries in wildtype and connexin43 knockout mice. *Dev Dyn* 235: 2786–2794, 2006.
 26. Congdon NG, Friedman DS, and Lietman T. Important causes of visual impairment in the world today. *JAMA* 290: 2057–2060, 2003.
 27. Cornell-Bell AH, Finkbeiner SM, Cooper MS, and Smith SJ. Glutamate induces calcium waves in cultured astrocytes: long-range glial signaling. *Science* 247: 470–473, 1990.
 28. Cottrell GT, Wu Y, and Burt JM. Cx40 and Cx43 expression ratio influences heteromeric/ heterotypic gap junction channel properties. *Am J Physiol Cell Physiol* 282: C1469–C1482, 2002.
 29. Cowan DB, Jones M, Garcia LM, Noria S, del Nido PJ, and McGowan FX, Jr. Hypoxia and stretch regulate intercellular communication in vascular smooth muscle cells through reactive oxygen species formation. *Arterioscler Thromb Vasc Biol* 23: 1754–1760, 2003.
 30. Cowan DB, Lye SJ, and Langille BL. Regulation of vascular connexin43 gene expression by mechanical loads. *Circ Res* 82: 786–793, 1998.
 31. Cox SB, Woolsey TA, and Rovainen CM. Localized dynamic changes in cortical blood flow with whisker stimulation corresponds to matched vascular and neuronal architecture of rat barrels. *J Cereb Blood Flow Metab* 13: 899–913, 1993.
 32. Crane GJ, Gallagher N, Dora KA, and Garland CJ. Small- and intermediate-conductance calcium-activated K^{+} channels provide different facets of endothelium-dependent hyperpolarization in rat mesenteric artery. *J Physiol* 553: 183–189, 2003.
 33. Crane GJ, Neild TO, and Segal SS. Contribution of active membrane processes to conducted hyperpolarization in arterioles of hamster cheek pouch. *Microcirculation* 11: 425–433, 2004.
 34. Dang X, Doble BW, and Kardami E. The carboxy-tail of connexin-43 localizes to the nucleus and inhibits cell growth. *Mol Cell Biochem* 242: 35–38, 2003.
 35. De Vriese AS, Van de Voorde J, and Lameire NH. Effects of connexin-mimetic peptides on nitric oxide synthase- and cyclooxygenase-independent renal vasodilation. *Kidney Int* 61: 177–185, 2002.
 36. de Wit C, Roos F, Bolz SS, Kirchhoff S, Kruger O, Willecke K, and Pohl U. Impaired conduction of vasodilation along arterioles in connexin40-deficient mice. *Circ Res* 86: 649–655, 2000.
 37. de Wit C, Roos F, Bolz SS, and Pohl U. Lack of vascular connexin 40 is associated with hypertension and irregular arteriolar vasomotion. *Physiol Genom* 13: 169–177, 2003.
 38. dePaola N, Davies PF, Pritchard WF Jr, Florez L, Harbeck N, and Polacek DC. Spatial and temporal regulation of gap junction connexin43 in vascular endothelial cells exposed to controlled disturbed flows in vitro. *Proc Natl Acad Sci U S A* 96: 3154–3159, 1999.
 39. Dietrich HH, Kajita Y, and Dacey RG Jr. Local and conducted vasomotor responses in isolated rat cerebral arterioles. *Am J Physiol* 271: H1109–H1116, 1996.
 40. Dora KA, Sandow SL, Gallagher NT, Takano H, Rummery NM, Hill CE, and Garland CJ. Myoendothelial gap junctions may provide the pathway for EDHF in mouse mesenteric artery. *J Vasc Res* 40: 480–490, 2003.
 41. Doyle MP and Duling BR. Acetylcholine induces conducted vasodilation by nitric oxide-dependent and -independent mechanisms. *Am J Physiol Heart Circ Physiol* 41: H1364–H1371, 1997.
 42. Earley S, Resta TC, and Walker BR. Disruption of smooth muscle gap junctions attenuates myogenic vasoconstriction of mesenteric resistance arteries. *Am J Physiol Heart Circ Physiol* 287: H2677–H2686, 2004.
 43. Edwards G, Dora KA, Gardener MJ, Garland CJ, and Weston AH. K^{+} is an endothelium-derived hyperpolarizing factor in rat arteries. *Nature* 396: 269–272, 1998.
 44. Eichler I, Wibawa J, Grgic I, Knorr A, Brakemeier S, Pries AR, Hoyer J, and Kohler R. Selective blockade of endothelial Ca^{2+} -activated small- and intermediate-conductance K^{+} -channels suppresses EDHF-mediated vasodilation. *Br J Pharmacol* 138: 594–601, 2003.
 45. Emerson GG, Neild TO, and Segal SS. Conduction of hyperpolarization along hamster feed arteries: augmentation by acetylcholine. *Am J Physiol Heart Circ Physiol* 283: H102–H109, 2002.
 46. Emerson GG and Segal SS. Electrical coupling between endothelial cells and smooth muscle cells in hamster feed arteries: role in vasomotor control. *Circ Res* 87: 474–479, 2000.
 47. Emerson GG and Segal SS. Endothelial cell pathway for conduction of hyperpolarization and vasodilation along hamster feed artery. *Circ Res* 86: 94–100, 2000.
 48. Emerson GG and Segal SS. Electrical activation of endothelium evokes vasodilation and hyperpolarization along hamster feed arteries. *Am J Physiol Heart Circ Physiol* 280: H160–H167, 2001.
 49. Evans WH and Martin PE. Gap junctions: structure and function (review). *Mol Membr Biol* 19: 121–136, 2002.

50. Feletou M and Vanhoutte PM. Endothelium-derived hyperpolarizing factor. *Clin Exp Pharmacol Physiol* 23: 1082–1090, 1996.
51. Feletou M, Vanhoutte PM, Weston AH, and Edwards G. EDHF and endothelial potassium channels: IKCa and SKCa. *Br J Pharmacol* 140: 225, 2003.
52. Feron O, Belhassen L, Kobzik L, Smith TW, Kelly RA, and Michel T. Endothelial nitric oxide synthase targeting to caveolae: specific interactions with caveolin isoforms in cardiac myocytes and endothelial cells. *J Biol Chem* 271: 22810–22814, 1996.
53. Figueroa XF, Alvina K, Martinez AD, Garces G, Roseblatt M, Boric MP, and Saez JC. Histamine reduces gap junctional communication of human tonsil high endothelial cells in culture. *Microvasc Res* 68: 247–257, 2004.
54. Figueroa XF, Chen CC, Campbell KP, Damon DN, Day KH, Ramos S, and Duling BR. Are voltage-dependent ion channels involved in the endothelial cell control of vasomotor tone? *Am J Physiol Heart Circ Physiol* 293: H1371–H1383, 2007.
55. Figueroa XF, Isakson BE, and Duling BR. Connexins: gaps in our knowledge of vascular function. *Physiology (Bethesda)* 19: 277–284, 2004.
56. Figueroa XF, Isakson BE, and Duling BR. Vascular gap junctions in hypertension. *Hypertension* 48: 804–811, 2006.
57. Figueroa XF, Paul DL, Simon AM, Goodenough DA, Day KH, Damon DN, and Duling BR. Central role of connexin40 in the propagation of electrically activated vasodilation in mouse cremasteric arterioles in vivo. *Circ Res* 92: 793–800, 2003.
58. Filosa JA, Bonev AD, and Nelson MT. Calcium dynamics in cortical astrocytes and arterioles during neurovascular coupling. *Circ Res* 95: e73–e81, 2004.
59. Filosa JA, Bonev AD, Straub SV, Meredith AL, Wilkerson MK, Aldrich RW, and Nelson MT. Local potassium signaling couples neuronal activity to vasodilation in the brain. *Nat Neurosci* 9: 1397–1403, 2006.
60. Firouzi M, Bierhuizen MF, Kok B, Teunissen BE, Jansen AT, Jongsma HJ, and Groenewegen WA. The human Cx40 promoter polymorphism –44G→A differentially affects transcriptional regulation by Sp1 and GATA4. *Biochim Biophys Acta* 1759: 491–496, 2006.
61. Firouzi M, Kok B, Spiering W, Busjahn A, Bezzina CR, Ruijter JM, Koeleman BP, Schipper M, Groenewegen WA, Jongsma HJ, and de Leeuw PW. Polymorphisms in human connexin40 gene promoter are associated with increased risk of hypertension in men. *J Hypertens* 24: 325–330, 2006.
62. Fleming I. Cytochrome P450 epoxygenases as EDHF synthase(s). *Pharmacol Res* 49: 525–533, 2004.
63. Gabbay KH. The sorbitol pathway and the complications of diabetes. *N Engl J Med* 288: 831–836, 1973.
64. Gabriels JE and Paul DL. Connexin43 is highly localized to sites of disturbed flow in rat aortic endothelium but connexin37 and connexin40 are more uniformly distributed. *Circ Res* 83: 636–643, 1998.
65. Garcia-Cardena G, Martasek P, Masters BS, Skidd PM, Couet J, Li S, Lisanti MP, and Sessa WC. Dissecting the interaction between nitric oxide synthase (NOS) and caveolin: functional significance of the nos caveolin binding domain in vivo. *J Biol Chem* 272: 25437–25440, 1997.
66. Giepmans BN and Moolenaar WH. The gap junction protein connexin43 interacts with the second PDZ domain of the zona occludens-1 protein. *Curr Biol* 8: 931–934, 1998.
67. Giepmans BN, Verlaan I, Hengeveld T, Janssen H, Calafat J, Falk MM, and Moolenaar WH. Gap junction protein connexin-43 interacts directly with microtubules. *Curr Biol* 11: 1364–1368, 2001.
68. Giepmans BN, Verlaan I, and Moolenaar WH. Connexin-43 interactions with ZO-1 and alpha- and beta-tubulin. *Cell Commun Adhes* 8: 219–223, 2001.
69. Giugliano D, Ceriello A, and Paolisso G. Oxidative stress and diabetic vascular complications. *Diabetes Care* 19: 257–267, 1996.
70. Goodenough DA and Paul DL. Beyond the gap: functions of unpaired connexon channels. *Nat Rev Mol Cell Biol* 4: 285–294, 2003.
71. Goto K, Fujii K, Kansui Y, Abe I, and Iida M. Critical role of gap junctions in endothelium-dependent hyperpolarization in rat mesenteric arteries. *Clin Exp Pharmacol Physiol* 29: 595–602, 2002.
72. Goto K, Rummery NM, Grayson TH, and Hill CE. Attenuation of conducted vasodilatation in rat mesenteric arteries during hypertension: role of inwardly rectifying potassium channels. *J Physiol* 561: 215–231, 2004.
73. Grayson TH. Is Cx40 a marker for hypertension? *J Hypertens* 24: 279–280, 2006.
74. Griffith TM. Endothelium-dependent smooth muscle hyperpolarization: do gap junctions provide a unifying hypothesis? *Br J Pharmacol* 141: 881–903, 2004.
75. Griffith TM, Chaytor AT, and Edwards DH. The obligatory link: role of gap junctional communication in endothelium-dependent smooth muscle hyperpolarization. *Pharmacol Res* 49: 551–564, 2004.
76. Gustafsson F and Holstein-Rathlou N. Conducted vasomotor responses in arterioles: characteristics, mechanisms and physiological significance. *Acta Physiol Scand* 167: 11–21, 1999.
77. Haefliger JA, Castillo E, Waeber G, Bergonzelli GE, Aubert JF, Sutter E, Nicod P, Waeber B, and Meda P. Hypertension increases connexin43 in a tissue-specific manner. *Circulation* 95: 1007–1014, 1997.
78. Haefliger JA, Demotz S, Braissant O, Suter E, Waeber B, Nicod P, and Meda P. Connexins 40 and 43 are differentially regulated within the kidneys of rats with renovascular hypertension. *Kidney Int* 60: 190–201, 2001.
79. Haefliger JA, Krattinger N, Martin D, Pedrazzini T, Capponi A, Doring B, Plum A, Charollais A, Willecke K, and Meda P. Connexin43-dependent mechanism modulates renin secretion and hypertension. *J Clin Invest* 116: 405–413, 2006.
80. Haefliger JA, Meda P, Formenton A, Wiesel P, Zanchi A, Brunner HR, Nicod P, and Hayoz D. Aortic connexin43 is decreased during hypertension induced by inhibition of nitric oxide synthase. *Arterioscler Thromb Vasc Biol* 19: 1615–1622, 1999.
81. Haefliger JA, Nicod P, and Meda P. Contribution of connexins to the function of the vascular wall. *Cardiovasc Res* 62: 345–356, 2004.
82. Harder DR, Alkayed NJ, Lange AR, Gebremedhin D, and Roman RJ. Functional hyperemia in the brain: hypothesis for astrocyte-derived vasodilator metabolites. *Stroke* 29: 229–234, 1998.
83. Hawkins BT and Davis TP. The blood-brain barrier/neurovascular unit in health and disease. *Pharmacol Rev* 57: 173–185, 2005.
84. He DS, Jiang JX, Taffet SM, and Burt JM. Formation of heteromeric gap junction channels by connexins 40 and 43 in vascular smooth muscle cells. *Proc Natl Acad Sci U S A* 96: 6495–6500, 1999.
85. Hill CE, Rummery N, Hickey H, and Sandow SL. Heterogeneity in the distribution of vascular gap junctions and

- connexins: implications for function. *Clin Exp Pharmacol Physiol* 29: 620–625, 2002.
86. Hirashiki A, Yamada Y, Murase Y, Suzuki Y, Kataoka H, Morimoto Y, Tajika T, Murohara T, and Yokota M. Association of gene polymorphisms with coronary artery disease in low- or high-risk subjects defined by conventional risk factors. *J Am Coll Cardiol* 42: 1429–1437, 2003.
 87. Hirst GD, Edwards FR, Gould DJ, Sandow SL, and Hill CE. Electrical properties of iridial arterioles of the rat. *Am J Physiol* 273: H2465–H2472, 1997.
 88. Hirst GD and Neild TO. An analysis of excitatory junctional potentials recorded from arterioles. *J Physiol* 280: 87–104, 1978.
 89. Horiuchi T, Dietrich HH, Hongo K, and Dacey RG Jr. Mechanism of extracellular K⁺-induced local and conducted responses in cerebral penetrating arterioles. *Stroke* 33: 2692–2699, 2002.
 90. Huang A, Wu Y, Sun D, Koller A, and Kaley G. Effect of estrogen on flow-induced dilation in NO deficiency: role of prostaglandins and EDHF. *J Appl Physiol* 91: 2561–2566, 2001.
 91. Hwan SK and Beyer EC. Heterogeneous localization of connexin40 in the renal vasculature. *Microvasc Res* 59: 140–148, 2000.
 92. Iadecola C, Yang G, Ebner TJ, and Chen G. Local and propagated vascular responses evoked by focal synaptic activity in cerebellar cortex. *J Neurophysiol* 78: 651–659, 1997.
 93. Inai T, Mancuso MR, McDonald DM, Kobayashi J, Nakamura K, and Shibata Y. Shear stress-induced upregulation of connexin 43 expression in endothelial cells on upstream surfaces of rat cardiac valves. *Histochem Cell Biol* 122: 477–483, 2004.
 94. Inoguchi T, Ueda F, Umeda F, Yamashita T, and Nawata H. Inhibition of intercellular communication via gap junction in cultured aortic endothelial cells by elevated. *Biochem Biophys Res Commun* 208: 492–497, 1995.
 95. Inoguchi T, Yu HY, Imamura M, Kakimoto M, Kuroki T, Maruyama T, and Nawata H. Altered gap junction activity in cardiovascular tissues of diabetes. *Med Electron Microsc* 34: 86–91, 2001.
 96. Isakson BE, Damon DN, Day KH, Liao Y, and Duling BR. Connexin40 and connexin43 in mouse aortic endothelium: evidence for coordinated regulation. *Am J Physiol Heart Circ Physiol* 290: H1199–H1205, 2006.
 97. Isakson BE and Duling BR. Heterocellular contact at the myoendothelial junction influences gap junction organization. *Circ Res* 97: 44–51, 2005.
 98. Jantzi MC, Brett SE, Jackson WF, Corteling R, Vigmond EJ, and Welsh DG. Inward rectifying potassium channels facilitate cell-to-cell communication in hamster retractor muscle feed arteries. *Am J Physiol Heart Circ Physiol* 291: H1319–H1328, 2006.
 99. Johnson TL and Nerem RM. Endothelial connexin 37, connexin 40, and connexin 43 respond uniquely to substrate and shear stress. *Endothelium* 14: 215–226, 2007.
 100. Ju H, Zou R, Venema VJ, and Venema RC. Direct interaction of endothelial nitric-oxide synthase and caveolin-1 inhibits synthase activity. *J Biol Chem* 272: 18522–18525, 1997.
 101. Kameritsch P, Hoffmann A, and Pohl U. Opposing effects of nitric oxide on different connexins expressed in the vascular system. *Cell Commun Adhes* 10: 305–309, 2003.
 102. Kang N, Alexander G, Park JK, Maasch C, Buchwalow I, Luft FC, and Haller H. Differential expression of protein kinase C isoforms in streptozotocin-induced diabetic rats. *Kidney Int* 56: 1737–1750, 1999.
 103. Kansui Y, Fujii K, Nakamura K, Goto K, Oniki H, Abe I, Shibata Y, and Iida M. Angiotensin II receptor blockade corrects altered expression of gap junctions in vascular endothelial cells from hypertensive rats. *Am J Physiol Heart Circ Physiol* 287: H216–H224, 2004.
 104. Karagiannis J, Rand M, and Li CG. Role of gap junctions in endothelium-derived hyperpolarizing factor-mediated vasodilatation in rat renal artery. *Acta Pharmacol Sin* 25: 1031–1037, 2004.
 105. Kirchhoff S, Kim JS, Hagedorff A, Thonnissen E, Kruger O, Lamers WH, and Willecke K. Abnormal cardiac conduction and morphogenesis in connexin40 and connexin43 double-deficient mice. [see comments]. *Circulation Research* 87: 399–405, 2000.
 106. Koehler RC, Gebremedhin D, and Harder DR. Role of astrocytes in cerebrovascular regulation. *J Appl Physiol* 100: 307–317, 2006.
 107. Krattinger N, Capponi A, Mazzolai L, Aubert JF, Caille D, Nicod P, Waeber G, Meda P, and Haefliger JA. Connexin40 regulates renin production and blood pressure. *Kidney Int* 72: 814–822, 2007.
 108. Kruger O, Beny JL, Chabaud F, Traub O, Theis M, Brix K, Kirchhoff S, and Willecke K. Altered dye diffusion and up-regulation of connexin37 in mouse aortic endothelium deficient in connexin40. *J Vasc Res* 39: 160–172, 2002.
 109. Kruger O, Plum A, Kim JS, Winterhager E, Maxeiner S, Hallas G, Kirchhoff S, Traub O, Lamers WH, and Willecke K. Defective vascular development in connexin 45-deficient mice. *Development* 127: 4179–4193, 2000.
 110. Kurjiaka DT. The conduction of dilation along an arteriole is diminished in the cremaster muscle of hypertensive hamsters. *J Vasc Res* 41: 517–524, 2004.
 111. Kurjiaka DT, Bender SB, Nye DD, Wiehler WB, and Welsh DG. Hypertension attenuates cell-to-cell communication in hamster retractor muscle feed arteries. *Am J Physiol Heart Circ Physiol* 288: H861–H870, 2005.
 112. Kurjiaka DT, Steele TD, Olsen MV, and Burt JM. Gap junction permeability is diminished in proliferating vascular smooth muscle cells. *Am J Physiol* 275: C1674–C1682, 1998.
 113. Kuroki T, Inoguchi T, Umeda F, Ueda F, and Nawata H. High glucose induces alteration of gap junction permeability and phosphorylation of connexin-43 in cultured aortic smooth muscle cells. *Diabetes* 47: 931–936, 1998.
 114. Kurtz L, Schweda F, de Wit C, Kriz W, Witzgall R, Warth R, Sauter A, Kurtz A, and Wagner C. Lack of connexin 40 causes displacement of renin-producing cells from afferent arterioles to the extraglomerular mesangium. *J Am Soc Nephrol* 18: 1103–1111, 2007.
 115. Kwak BR, Mulhaupt F, Veillard N, Gros DB, and Mach F. Altered pattern of vascular connexin expression in atherosclerotic plaques. *Arterioscler Thromb Vasc Biol* 22: 225–230, 2002.
 116. Kwak BR, Pepper MS, Gros DB, and Meda P. Inhibition of endothelial wound repair by dominant negative connexin inhibitors. *Mol Biol Cell* 12: 831–845, 2001.
 117. Kwak BR, Silacci P, Stergiopoulos N, Hayoz D, and Meda P. Shear stress and cyclic circumferential stretch, but not pressure, alter connexin43 expression in endothelial cells. *Cell Commun Adhes* 12: 261–270, 2005.
 118. Lagaud G, Karicheti V, Knot HJ, Christ GJ, and Laher I. Inhibitors of gap junctions attenuate myogenic tone in cerebral arteries. *Am J Physiol Heart Circ Physiol* 283: H2177–H2186, 2002.
 119. Lee TS, Saltsman KA, Ohashi H, and King GL. Activation of protein kinase C by elevation of glucose concentration:

- proposal for a mechanism in the development of diabetic vascular complications. *Proc Natl Acad Sci U S A* 86: 5141–5145, 1989.
120. Levy BI, Ambrosio G, Pries AR, and Struijker-Boudier HA. Microcirculation in hypertension: a new target for treatment? *Circulation* 104: 735–740, 2001.
 121. Leybaert L. Neurobarrier coupling in the brain: a partner of neurovascular and neurometabolic coupling? *J Cereb Blood Flow Metab* 25: 2–16, 2005.
 122. Li X and Simard JM. Connexin45 gap junction channels in rat cerebral vascular smooth muscle cells. *Am J Physiol Heart Circ Physiol* 281: H1890–H1898, 2001.
 123. Liao Y, Day KH, Damon DN, and Duling BR. Endothelial cell-specific knockout of connexin 43 causes hypotension and bradycardia in mice. *Proc Natl Acad Sci U S A* 98: 9989–9994, 2001.
 124. Liao Y, Regan CP, Manabe I, Owens GK, Day KH, Damon DN, and Duling BR. Smooth muscle-targeted knockout of connexin43 enhances neointimal formation in response to vascular injury. *Arterioscler Thromb Vasc Biol* 27: 1037–1042, 2007.
 125. Lin D and Takemoto DJ. Oxidative activation of protein kinase Cgamma through the C1 domain: effects on gap junctions. *J Biol Chem* 280: 13682–13693, 2005.
 126. Little TL, Beyer EC, and Duling BR. Connexin-43 and connexin-40 gap junctional proteins are present in arteriolar smooth-muscle and endothelium in-vivo. *Am J Physiol* 37: H729–H739, 1995.
 127. Little TL, Xia J, and Duling BR. Dye tracers define differential endothelial and smooth-muscle coupling patterns within the arteriolar wall. *Circ Res* 76: 498–504, 1995.
 128. Liu MY, Hattori Y, Sato A, Ichikawa R, Zhang XH, and Sakuma I. Ovariectomy attenuates hyperpolarization and relaxation mediated by endothelium-derived hyperpolarizing factor in female rat mesenteric artery: a concomitant decrease in connexin-43 expression. *J Cardiovasc Pharmacol* 40: 938–948, 2002.
 129. Locke D, Liu J, and Harris AL. Lipid rafts prepared by different methods contain different connexin channels, but gap junctions are not lipid rafts. *Biochemistry* 44: 13027–13042, 2005.
 130. Luksha L, Poston L, Gustafsson JA, Hultenby K, and Kublickiene K. The oestrogen receptor beta contributes to sex related differences in endothelial function of murine small arteries via EDHF. *J Physiol* 577: 945–955, 2006.
 131. Martinez AD, Hayrapetyan V, Moreno AP, and Beyer EC. Connexin43 and connexin45 form heteromeric gap junction channels in which individual components determine permeability and regulation. *Circ Res* 90: 1100–1107, 2002.
 132. Martinez AD and Saez JC. Arachidonic acid-induced dye uncoupling in rat cortical astrocytes is mediated by arachidonic acid byproducts. *Brain Res* 816: 411–423, 1999.
 133. Martinez AD and Saez JC. Regulation of astrocyte gap junctions by hypoxia-reoxygenation. *Brain Res Brain Res Rev* 32: 250–258, 2000.
 134. Mather S, Dora KA, Sandow SL, Winter P, and Garland CJ. Rapid endothelial cell-selective loading of connexin 40 antibody blocks endothelium-derived hyperpolarizing factor dilation in rat small mesenteric arteries. *Circ Res* 97: 399–407, 2005.
 135. McDonnell DP. The molecular pharmacology of SERMs. *Trends Endocrinol Metab* 10: 301–311, 1999.
 136. Mendelsohn ME and Karas RH. The protective effects of estrogen on the cardiovascular system. *N Engl J Med* 340: 1801–1811, 1999.
 137. Metea MR and Newman EA. Calcium signaling in specialized glial cells. *Glia* 54: 650–655, 2006.
 138. Metea MR and Newman EA. Glial cells dilate and constrict blood vessels: a mechanism of neurovascular coupling. *J Neurosci* 26: 2862–2870, 2006.
 139. Michel JB, Feron O, Sacks D, and Michel T. Reciprocal regulation of endothelial nitric-oxide synthase by Ca²⁺-calmodulin and caveolin. *J Biol Chem* 272: 15583–15586, 1997.
 140. Michel JB, Feron O, Sase K, Prabhakar P, and Michel T. Caveolin versus calmodulin. Counterbalancing allosteric modulators of endothelial nitric oxide synthase. *J Biol Chem* 272: 25907–25912, 1997.
 141. Moreno AP. Biophysical properties of homomeric and heteromultimeric channels formed by cardiac connexins. *Cardiovasc Res* 62: 276–286, 2004.
 142. Mulligan SJ and MacVicar BA. Calcium transients in astrocyte endfeet cause cerebrovascular constrictions. *Nature* 431: 195–199, 2004.
 143. Nawate S, Fukao M, Sakuma I, Soma T, Nagai K, Takikawa O, Miwa S, and Kitabatake A. Reciprocal changes in endothelium-derived hyperpolarizing factor and nitric oxide system in the mesenteric artery of adult female rats following ovariectomy. *Br J Pharmacol* 144: 178–189, 2005.
 144. Nedergaard M. Direct signaling from astrocytes to neurons in cultures of mammalian brain cells. *Science* 263: 1768–1771, 1994.
 145. Nedergaard M, Ransom B, and Goldman SA. New roles for astrocytes: redefining the functional architecture of the brain. *Trends Neurosci* 26: 523–530, 2003.
 146. Nowicki PT, Flavahan S, Hassanain H, Mitra S, Holland S, Goldschmidt-Clermont PJ, and Flavahan NA. Redox signaling of the arteriolar myogenic response. *Circ Res* 89: 114–116, 2001.
 147. Nusrat A, Parkos CA, Verkade P, Foley CS, Liang TW, Innis-Whitehouse W, Eastburn KK, and Madara JL. Tight junctions are membrane microdomains. *J Cell Sci* 113: 1771–1781, 2000.
 148. Ohashi M, Satoh K, and Itoh T. Acetylcholine-induced membrane potential changes in endothelial cells of rabbit aortic valve. *Br J Pharmacol* 126: 19–26, 1999.
 149. Oku H, Kodama T, Sakagami K, and Puro DG. Diabetes-induced disruption of gap junction pathways within the retinal microvasculature. *Invest Ophthalmol Vis Sci* 42: 1915–1920, 2001.
 150. Pacicca C, Schaad O, and Beny JL. Electrotonic propagation of kinin-induced, endothelium-dependent hyperpolarizations in pig coronary smooth muscles. *J Vasc Res* 33: 380–385, 1996.
 151. Polacek D, Bech F, McKinsey JF, and Davies PF. Connexin43 gene expression in the rabbit arterial wall: effects of hypercholesterolemia, balloon injury and their combination. *J Vasc Res* 34: 19–30, 1997.
 152. Pries AR, Secomb TW, and Gaetgens P. Structural adaptation and stability of microvascular networks: theory and simulations. *Am J Physiol* 275: H349–H360, 1998.
 153. Pries AR, Secomb TW, and Gaetgens P. Structural autoregulation of terminal vascular beds: vascular adaptation and development of hypertension. *Hypertension* 33: 153–161, 1999.
 154. Reaume AG, de Sousa PA, Kulkarni S, Langille BL, Zhu D, Davies TC, Juneja SC, Kidder GM, and Rossant J. Cardiac malformation in neonatal mice lacking connexin43. *Science* 267: 1831–1834, 1995.
 155. Retamal MA, Cortes CJ, Reuss L, Bennett MV, and Saez JC. S-nitrosylation and permeation through connexin 43

- hemichannels in astrocytes: induction by oxidant stress and reversal by reducing agents. *Proc Natl Acad Sci U S A* 103: 4475–4480, 2006.
156. Roh CR, Heo JH, Yang SH, and Bae DS. Regulation of connexin 43 by nitric oxide in primary uterine myocytes from term pregnant women. *Am J Obstet Gynecol* 187: 434–440, 2002.
 157. Rummery NM, Grayson TH, and Hill CE. Angiotensin-converting enzyme inhibition restores endothelial but not medial connexin expression in hypertensive rats. *J Hypertens* 23: 317–328, 2005.
 158. Rummery NM, Hickey H, McGurk G, and Hill CE. Connexin37 is the major connexin expressed in the media of caudal artery. *Arterioscler Thromb Vasc Biol* 22: 1427–1432, 2002.
 159. Rummery NM and Hill CE. Vascular gap junctions and implications for hypertension. *Clin Exp Pharmacol Physiol* 31: 659–667, 2004.
 160. Rummery NM, McKenzie KU, Whitworth JA, and Hill CE. Decreased endothelial size and connexin expression in rat caudal arteries during hypertension. *J Hypertens* 20: 247–253, 2002.
 161. Saez JC. Astrocytes as connexin-dependent signaling cells for local blood flow regulation. *Am J Physiol Heart Circ Physiol* 294: H586–H587, 2008.
 162. Saez JC, Berthoud VM, Branes MC, Martinez AD, and Beyer EC. Plasma membrane channels formed by connexins: their regulation and functions. *Physiol Rev* 83: 1359–1400, 2003.
 163. Saez JC, Retamal MA, Basilio D, Bukauskas FF, and Bennett MV. Connexin-based gap junction hemichannels: gating mechanisms. *Biochim Biophys Acta* 1711: 215–224, 2005.
 164. Sandow SL, Bramich NJ, Bandi HP, Rummery NM, and Hill CE. Structure, function, and endothelium-derived hyperpolarizing factor in the caudal artery of the SHR and WKY rat. *Arterioscler Thromb Vasc Biol* 23: 822–828, 2003.
 165. Sandow SL and Hill CE. Incidence of myoendothelial gap junctions in the proximal and distal mesenteric arteries of the rat is suggestive of a role in endothelium-derived hyperpolarizing factor-mediated responses. *Circ Res* 86: 341–346, 2000.
 166. Sandow SL, Looft-Wilson R, Doran B, Grayson TH, Segal SS, and Hill CE. Expression of homocellular and heterocellular gap junctions in hamster arterioles and feed arteries. *Cardiovasc Res* 60: 643–653, 2003.
 167. Sato T, Haimovici R, Kao R, Li AF, and Roy S. Downregulation of connexin 43 expression by high glucose reduces gap junction activity in microvascular endothelial cells. *Diabetes* 51: 1565–1571, 2002.
 168. Schubert AL, Schubert W, Spray DC, and Lisanti MP. Connexin family members target to lipid raft domains and interact with caveolin-1. *Biochemistry* 41: 5754–5764, 2002.
 169. Scotland RS, Madhani M, Chauhan S, Moncada S, Andersen J, Nilsson H, Hobbs AJ, and Ahluwalia A. Investigation of vascular responses in endothelial nitric oxide synthase/cyclooxygenase-1 double-knockout mice: key role for endothelium-derived hyperpolarizing factor in the regulation of blood pressure in vivo. *Circulation* 111: 796–803, 2005.
 170. Segal SS. Cell-to-cell communication coordinates blood flow control. *Hypertension* 23: 1113–1120, 1994.
 171. Segal SS. Integration of blood flow control to skeletal muscle: key role of feed arteries. *Acta Physiol Scand* 168: 511–518, 2000.
 172. Segal SS. Regulation of blood flow in the microcirculation. *Microcirculation* 12: 33–45, 2005.
 173. Segal SS, Damon DN, and Duling BR. Propagation of vasomotor responses coordinates arteriolar resistances. *Am J Physiol* 256: H832–H837, 1989.
 174. Segal SS and Duling BR. Communication between feed arteries and microvessels in hamster striated muscle: segmental vascular responses are functionally coordinated. *Circ Res* 59: 283–290, 1986.
 175. Segal SS and Duling BR. Conduction of vasomotor responses in arterioles: a role for cell-to-cell coupling. *Am J Physiol* 256: H838–H845, 1989.
 176. Segal SS and Jacobs TL. Role for endothelial cell conduction in ascending vasodilatation and exercise hyperaemia in hamster skeletal muscle. *J Physiol* 536: 937–946, 2001.
 177. Segal SS and Kurjiaka DT. Coordination of blood flow control in the resistance vasculature of skeletal muscle. *Med Sci Sports Exerc* 27: 1158–1164, 1995.
 178. Severs NJ, Rothery S, Dupont E, Coppen SR, Yeh HI, Ko YS, Matsushita T, Kaba R, and Halliday D. Immunocytochemical analysis of connexin expression in the healthy and diseased cardiovascular system. *Microsc Res Tech* 52: 301–322, 2001.
 179. Sheridan JD. Dye transfer in small vessels from rat omentum: homologous and heterologous junctions. *J Cell Biol* 87: 61a, 1980.
 180. Shimokawa H and Morikawa K. Hydrogen peroxide is an endothelium-derived hyperpolarizing factor in animals and humans. *J Mol Cell Cardiol* 39: 725–732, 2005.
 181. Shimokawa H, Yasutake H, Fujii K, Owada MK, Nakaike R, Fukumoto Y, Takayanagi T, Nagao T, Egashira K, Fujishima M, and Takeshita A. The importance of the hyperpolarizing mechanism increases as the vessel size decreases in endothelium-dependent relaxations in rat mesenteric circulation. *J Cardiovasc Pharmacol* 28: 703–711, 1996.
 182. Simon AM and Goodenough DA. Diverse functions of vertebrate gap junctions. *Trends Cell Biol* 8: 477–483, 1998.
 183. Simon AM and McWhorter AR. Vascular abnormalities in mice lacking the endothelial gap junction proteins connexin37 and connexin40. *Dev Biol* 251: 206–220, 2002.
 184. Simon AM and McWhorter AR. Decreased intercellular dye-transfer and downregulation of non-ablated connexins in aortic endothelium deficient in connexin37 or connexin40. *J Cell Sci* 116: 2223–2236, 2003.
 185. Song H and Timpl K. Evidence for sensing and integration of biological signals by the capillary network. *Am J Physiol* 265: H1235–H1242, 1993.
 186. Stout CE, Costantin JL, Naus CC, and Charles AC. Intercellular calcium signaling in astrocytes via ATP release through connexin hemichannels. *J Biol Chem* 277: 10482–10488, 2002.
 187. Straub SV, Bonev AD, Wilkerson MK, and Nelson MT. Dynamic inositol trisphosphate-mediated calcium signals within astrocytic endfeet underlie vasodilation of cerebral arterioles. *J Gen Physiol* 128: 659–669, 2006.
 188. Suadicani SO, Brosnan CF, and Scemes E. P2X7 receptors mediate ATP release and amplification of astrocytic intercellular Ca²⁺ signaling. *J Neurosci* 26: 1378–1385, 2006.
 189. Takano T, Tian GF, Peng W, Lou N, Libionka W, Han X, and Nedergaard M. Astrocyte-mediated control of cerebral blood flow. *Nat Neurosci* 9: 260–267, 2006.
 190. Tulenko TN. Regulating cross-talk between vascular smooth muscle cells. *Arterioscler Thromb Vasc Biol* 23: 1707–1709, 2003.
 191. van Kempen MJ and Jongsma HJ. Distribution of connexin37, connexin40 and connexin43 in the aorta and coro-

- nary artery of several mammals. *Histochem Cell Biol* 112: 479–486, 1999.
192. van Kempen MJ, ten Velde I, Wessels A, Oosthoek PW, Gros D, Jongsma HJ, Moorman AF, and Lamers WH. Differential connexin distribution accommodates cardiac function in different species. *Microsc Res Tech* 31: 420–436, 1995.
 193. Vanhoutte PM. Endothelium-dependent hyperpolarizations: the history. *Pharmacol Res* 49: 503–508, 2004.
 194. Vlassara H, Fuh H, Makita Z, Krungkrai S, Cerami A, and Bucala R. Exogenous advanced glycosylation end products induce complex vascular dysfunction in normal animals: a model for diabetic and aging complications. *Proc Natl Acad Sci U S A* 89: 12043–12047, 1992.
 195. Wagner C, de Wit C, Gerl M, Kurtz A, and Hoehnerl K. Increased expression of cyclooxygenase 2 contributes to aberrant renin production in connexin 40-deficient kidneys. *Am J Physiol Regul Integr Comp Physiol* 293: R1781–R1786, 2007.
 196. Wagner C, de Wit C, Kurtz L, Grunberger C, Kurtz A, and Schweda F. Connexin40 is essential for the pressure control of renin synthesis and secretion. *Circ Res* 100: 556–563, 2007.
 197. Walker DL, Vacha SJ, Kirby ML, and Lo CW. Connexin43 deficiency causes dysregulation of coronary vasculogenesis. *Dev Biol* 284: 479–498, 2005.
 198. Watanabe S, Yashiro Y, Mizuno R, and Ohhashi T. Involvement of NO and EDHF in flow-induced vasodilation in isolated hamster cremasteric arterioles. *J Vasc Res* 42: 137–147, 2005.
 199. Watts SW and Webb RC. Vascular gap junctional communication is increased in mineralocorticoid-salt hypertension. *Hypertension* 28: 888–893, 1996.
 200. Wei CJ, Francis R, Xu X, and Lo CW. Connexin43 associated with an N-cadherin-containing multiprotein complex is required for gap junction formation in NIH3T3 cells. *J Biol Chem* 280: 19925–19936, 2005.
 201. Wei CJ, Xu X, and Lo CW. Connexins and cell signaling in development and disease. *Annu Rev Cell Dev Biol* 20: 811–838, 2004.
 202. Welsh DG and Segal SS. Endothelial and smooth muscle cell conduction in arterioles controlling blood flow. *Am J Physiol* 274: H178–H186, 1998.
 203. White TW. Nonredundant gap junction functions. *News Physiol Sci* 18: 95–99, 2003.
 204. White TW and Bruzzone R. Multiple connexin proteins in single intercellular channels: connexin compatibility and functional consequences. *J Bioenerg Biomembr* 28: 339–350, 1996.
 205. Williams B and Schrier RW. Glucose-induced protein kinase C activity regulates arachidonic acid release and eicosanoid production by cultured glomerular mesangial cells. *J Clin Invest* 92: 2889–2896, 1993.
 206. Wolfle SE, Schmidt VJ, Hoepfl B, Gebert A, Alcolea S, Gros D, and de Wit C. Connexin45 cannot replace the function of connexin40 in conducting endothelium-dependent dilations along arterioles. *Circ Res* 101: 1292–1299, 2007.
 207. Wong CW, Christen T, Roth I, Chadjichristos CE, Derouette JP, Foglia BF, Chanson M, Goodenough DA, and Kwak BR. Connexin37 protects against atherosclerosis by regulating monocyte adhesion. *Nat Med* 12: 950–954, 2006.
 208. Xia J and Duling BR. Electromechanical coupling and the conducted vasomotor response. *Am J Physiol* 38: H2022–H2030, 1995.
 209. Xia J, Little TL, and Duling BR. Cellular pathways of the conducted electrical response in arterioles of hamster cheek pouch in vitro. *Am J Physiol Heart Circ Physiol* 38: H2031–H2038, 1995.
 210. Xu HL, Mao L, Ye S, Paisansathan C, Vetri F, and Pelligrino DA. Astrocytes are a key conduit for upstream signaling of vasodilation during cerebral cortical neuronal activation in vivo. *Am J Physiol Heart Circ Physiol* 294: H622–H632, 2007.
 211. Yamada Y, Ichihara S, Izawa H, Tanaka M, and Yokota M. Genetic risk for coronary artery disease in individuals with or without type 2 diabetes. *Mol Genet Metab* 81: 282–290, 2004.
 212. Yamada Y, Izawa H, Ichihara S, Takatsu F, Ishihara H, Hirayama H, Sone T, Tanaka M, and Yokota M. Prediction of the risk of myocardial infarction from polymorphisms in candidate genes. *N Engl J Med* 347: 1916–1923, 2002.
 213. Yeh HI, Lee PY, Su CH, Tian TY, Ko YS, and Tsai CH. Reduced expression of endothelial connexins 43 and 37 in hypertensive rats is rectified after 7-day carvedilol treatment. *Am J Hypertens* 19: 129–135, 2006.
 214. Yeh HI, Lupu F, Dupont E, and Severs NJ. Upregulation of connexin43 gap junctions between smooth muscle cells after balloon catheter injury in the rat carotid artery. *Arterioscler Thromb Vasc Biol* 17: 3174–3184, 1997.
 215. Zhang J and Hill CE. Differential connexin expression in preglomerular and postglomerular vasculature: accentuation during diabetes. *Kidney Int* 68: 1171–1185, 2005.
 216. Zheng-Fischhofer Q, Ghanem A, Kim JS, Kibschull M, Schwarz G, Schwab JO, Nagy J, Winterhager E, Tiemann K, and Willecke K. Connexin31 cannot functionally replace connexin43 during cardiac morphogenesis in mice. *J Cell Sci* 119: 693–701, 2006.
 217. Zhu Y, Bian Z, Lu P, Karas RH, Bao L, Cox D, Hodgins J, Shaul PW, Thoren P, Smithies O, Gustafsson JA, and Mendelsohn ME. Abnormal vascular function and hypertension in mice deficient in estrogen receptor beta. *Science* 295: 505–508, 2002.
 218. Zonta M, Angulo MC, Gobbo S, Rosengarten B, Hossmann KA, Pozzan T, and Carmignoto G. Neuron-to-astrocyte signaling is central to the dynamic control of brain microcirculation. *Nat Neurosci* 6: 43–50, 2003.

Address reprint requests to:

Dr. Xavier F. Figueroa
Departamento de Ciencias Fisiológicas
Facultad de Ciencias Biológicas
Pontificia Universidad Católica de Chile
Casilla 114-D
Santiago, Chile

E-mail: xfigueroa@bio.puc.cl

Date of first submission to ARS Central, May 12, 2008; date of final revised submission, July 21, 2008; date of acceptance, July 21, 2008.

This article has been cited by:

1. Lula L. Hilenski, Kathy K. Griendling Vascular Smooth Muscle 25-42. [[CrossRef](#)]
2. Anatoly I. Soloviev, Alexander I. Bondarenko, Igor V. Kizub. 2012. Selective glycolysis blockade in guinea pig pulmonary artery and aorta reverses contractile and electrical responses to acute hypoxia. *Vascular Pharmacology* **57**:2-4, 119-123. [[CrossRef](#)]
3. Claude Colomer, Agnès O. Martin, Michel G. Desarménien, Nathalie C. Guérineau. 2012. Gap junction-mediated intercellular communication in the adrenal medulla: An additional ingredient of stimulus–secretion coupling regulation. *Biochimica et Biophysica Acta (BBA) - Biomembranes* **1818**:8, 1937-1951. [[CrossRef](#)]
4. Peter Bedner, Christian Steinhäuser, Martin Theis. 2012. Functional redundancy and compensation among members of gap junction protein families?. *Biochimica et Biophysica Acta (BBA) - Biomembranes* **1818**:8, 1971-1984. [[CrossRef](#)]
5. M. A. Shaikh, D. J. N. Wall, T. David. 2012. Macro-scale phenomena of arterial coupled cells: a massively parallel simulation. *Journal of The Royal Society Interface* **9**:70, 972-987. [[CrossRef](#)]
6. Keith D. Barlow, Anne M. Sanders, Shay Soker, Suleyman Ergun, Linda J. Metheny-Barlow. 2012. Pericytes on the Tumor Vasculature: Jekyll or Hyde?. *Cancer Microenvironment* . [[CrossRef](#)]
7. Rekha Kar, Nidhi Batra, Manuel A. Riquelme, Jean X. Jiang. 2012. Biological role of connexin intercellular channels and hemichannels. *Archives of Biochemistry and Biophysics* . [[CrossRef](#)]
8. Jennifer S. Fang, Stoyan N. Angelov, Alexander M. Simon, Janis M. Burt. 2012. Cx40 Is Required for, and Cx37 Limits, Postischemic Hindlimb Perfusion, Survival and Recovery. *Journal of Vascular Research* **49**:1, 2-12. [[CrossRef](#)]
9. Thomas L. Pallone, Aurélie Edwards, David L. Mattson Renal Medullary Circulation . [[CrossRef](#)]
10. Belén Climent, Rudolf Schubert, Edgaras Stankevicius, Albino García-Sacristán, Ulf Simonsen, Luis Rivera. 2011. Large conductance Ca²⁺-activated K⁺ channels modulate endothelial cell outward currents and nitric oxide release in the intact rat superior mesenteric artery. *Biochemical and Biophysical Research Communications* . [[CrossRef](#)]
11. Pablo S. Gaete, Mauricio A. Lillo, Nicolás M. Ardiles, Francisco R. Pérez, Xavier F. Figueroa. 2011. Ca²⁺-activated K⁺ channels of small and intermediate conductance control eNOS activation through NAD(P)H oxidase. *Free Radical Biology and Medicine* . [[CrossRef](#)]
12. Helén Andersson, Eva Brittebo. 2011. Proangiogenic effects of environmentally relevant levels of bisphenol A in human primary endothelial cells. *Archives of Toxicology* . [[CrossRef](#)]
13. Marcela A. Avila , Stacy L. Sell , Bridget E. Hawkins , Helen L. Hellmich , Debbie R. Boone , Jeanna M. Crookshanks , Donald S. Prough , Douglas S. DeWitt . 2011. Cerebrovascular Connexin Expression: Effects of Traumatic Brain Injury. *Journal of Neurotrauma* **28**:9, 1803-1811. [[Abstract](#)] [[Full Text HTML](#)] [[Full Text PDF](#)] [[Full Text PDF with Links](#)]
14. H. Glenn Bohlen. 2011. Rapid and Slow Nitric Oxide Responses During Conducted Vasodilation in the In Vivo Intestine and Brain Cortex Microvasculatures. *Microcirculation* no-no. [[CrossRef](#)]
15. P. Bagher, S. S. Segal. 2011. Regulation of blood flow in the microcirculation: role of conducted vasodilation. *Acta Physiologica* **202**:3, 271-284. [[CrossRef](#)]
16. Natalia Tkachuk, Sergey Tkachuk, Margret Patecki, Angelika Kusch, Elena Korenbaum, Hermann Haller, Inna Dumler. 2011. The tight junction protein ZO-2 and Janus kinase 1 mediate intercellular communications in vascular smooth muscle cells. *Biochemical and Biophysical Research Communications* **410**:3, 531-536. [[CrossRef](#)]
17. Belén Climent, Emese Zsiros, Edgaras Stankevicius, Pedro de la Villa, György Panyi, Ulf Simonsen, Albino García-Sacristán, Luis Rivera. 2011. Intact rat superior mesenteric artery endothelium is an electrical syncytium and expresses strong inward rectifier K⁺ conductance. *Biochemical and Biophysical Research Communications* **410**:3, 501-507. [[CrossRef](#)]
18. Massimo Bolognesi, Francesca Zampieri, Marco Di Pascoli, Alberto Verardo, Cristian Turato, Fiorella Calabrese, Francesca Lunardi, Patrizia Pontisso, Paolo Angeli, Carlo Merkel, Angelo Gatta, David Sacerdoti. 2011. Increased myoendothelial gap junctions mediate the enhanced response to epoxyeicosatrienoic acid and acetylcholine in mesenteric arterial vessels of cirrhotic rats. *Liver International* **31**:6, 881-890. [[CrossRef](#)]
19. Michel Félétou. 2011. The Endothelium, Part I: Multiple Functions of the Endothelial Cells -- Focus on Endothelium-Derived Vasoactive Mediators. *Colloquium Series on Integrated Systems Physiology: From Molecule to Function* **3**:4, 1-306. [[CrossRef](#)]
20. Michel Félétou. 2011. The Endothelium, Part II: EDHF-Mediated Responses "The Classical Pathway". *Colloquium Series on Integrated Systems Physiology: From Molecule to Function* **3**:4, 1-306. [[CrossRef](#)]

21. John D. Kanady, Michael T. Dellinger, Stephanie J. Munger, Marlys H. Witte, Alexander M. Simon. 2011. Connexin37 and Connexin43 deficiencies in mice disrupt lymphatic valve development and result in lymphatic disorders including lymphedema and chylothorax. *Developmental Biology* **354**:2, 253-266. [[CrossRef](#)]
22. Jeffrey W. Kiel. 2011. The Ocular Circulation. *Colloquium Series on Integrated Systems Physiology: From Molecule to Function* **3**:1, 1-81. [[CrossRef](#)]
23. Axel R. Pries, Michael Höpfner, Ferdinand le Noble, Mark W. Dewhirst, Timothy W. Secomb. 2010. The shunt problem: control of functional shunting in normal and tumour vasculature. *Nature Reviews Cancer* **10**:8, 587-593. [[CrossRef](#)]
24. F. Alonso, N. Krattinger, L. Mazzolai, A. Simon, G. Waeber, P. Meda, J.-A. Haefliger. 2010. An angiotensin II- and NF- B- dependent mechanism increases connexin 43 in murine arteries targeted by renin-dependent hypertension. *Cardiovascular Research* **87**:1, 166-176. [[CrossRef](#)]
25. Gautam K Gandhi, Kelly K Ball, Nancy F Cruz, Gerald A Dienel. 2010. Hyperglycaemia and diabetes impair gap junctional communication among astrocytes. *ASN NEURO* **2**:2, 57-73. [[CrossRef](#)]
26. D. Begandt, W. Bintig, K. Oberheide, S. Schlie, A. Ngezahayo. 2010. Dipyridamole increases gap junction coupling in bovine GM-7373 aortic endothelial cells by a cAMP-protein kinase A dependent pathway. *Journal of Bioenergetics and Biomembranes* **42**:1, 79-84. [[CrossRef](#)]
27. Katarína Dlugošová, Peter Weismann, Iveta Bernátová, Ružena Sotníková, Ján Slezák, Ľudmila Okruhlicová. 2009. Omega-3 fatty acids and atorvastatin affect connexin 43 expression in the aorta of hereditary hypertriglyceridemic rats This article is one of a selection of papers published in a special issue on Advances in Cardiovascular Research. *Canadian Journal of Physiology and Pharmacology* **87**:12, 1074-1082. [[CrossRef](#)]
28. Sandrine Morel, Laurent Burnier, Brenda R. Kwak. 2009. Connexins participate in the initiation and progression of atherosclerosis. *Seminars in Immunopathology* **31**:1, 49-61. [[CrossRef](#)]
29. Juan A. Orellana , Pablo J. Sáez , Kenji F. Shoji , Kurt A. Schalper , Nicolás Palacios-Prado , Victoria Velarde , Christian Giaume , Michael V.L. Bennett , Juan C. Sáez . 2009. Modulation of Brain Hemichannels and Gap Junction Channels by Pro-Inflammatory Agents and Their Possible Role in Neurodegeneration. *Antioxidants & Redox Signaling* **11**:2, 369-399. [[Abstract](#)] [[Full Text HTML](#)] [[Full Text PDF](#)] [[Full Text PDF with Links](#)]