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Review

Gap junctions synchronize vascular tone within the microcirculation

Volker J. Schmidt, Stephanie E. Wölfle, Markus Boettcher, Cor de Wit

Institut für Physiologie, Universität zu Lübeck, Ratzeburger Allee 160, 23538 Lübeck, Germany

Correspondence: Cor de Wit, e-mail: dewit@uni-luebeck.de

Abstract:
Gap junctions are formed in the cardiovascular system by connexin40 (Cx40), Cx37, Cx43, and Cx45. These low resistance channels allow the transfer of ions and small molecules between cells. The longitudinal coupling of endothelial and smooth muscle cells *via* gap junctions allows the spread of changes in membrane potential along the vascular wall and hence provides conduction pathways within the vessel itself. Functionally, this tight coupling is reflected by the spread of locally initiated vasomotor responses along the arteriole which are termed conducted responses. Conducted dilations are initiated by the application of endothelium-dependent stimuli which result in local hyperpolarization. This signal spreads along the wall, most likely along the endothelial cell layer, to elicit a coordinated dilation of the arteriole over a considerable distance. Likewise, the opposite signal (depolarization) spreads along the vessel giving rise to a conducted constriction. The latter response is however most likely transmitted along the smooth muscle cell layer. Thus, conducted responses reflect the synchronized behavior of the cells of the vascular wall. It is assumed that conducted responses are critical for the matching of oxygen delivery and tissue needs because they contribute to an ascending dilation which lowers resistance along the length of the arterioles and upstream vessels in a well-tuned fashion. Herein, Cx40 is of special importance because it is critically required for intact signal transduction along the endothelial cell layer. In addition, Cx40 mediates pressure feedback inhibition on renin synthesis in the kidney. Both, vascular and renal function of Cx40, may be involved in the hypertension that is observed in Cx40-deficient animals. In this review, we will summarize physiologic function of connexins in arterioles and briefly address their role in the kidney with respect to renin secretion.

Key words:
arterioles, endothelium, gap junctions, conducted response

Introduction

The delivery of sufficient amounts of oxygen to the tissues is a huge task that has to be met by the vascular system. It requires large variations in blood flow because tissue needs change substantially in relation to cellular function [32]. Blood flow is controlled by resistance and vascular diameter is therefore the most important parameter governing tissue perfusion. Consequently, prerequisites for the delivery of large increases in oxygen and for the manifold enhancements of blood flow are a considerable capacity of the vessels to increase their diameter and secondly coordinating mechanisms which serve to change vascular diameter simultaneously over large distances. The intrinsic myogenic tone creates an extensive capability to dilate, for example initiated by the release of autacoids from the endothelium including nitric oxide (NO), prostaglandins and an endothelium-derived hyperpolarizing factor (EDHF) [7]. However, a localized downstream dilation is not sufficient to create ex-

tensive blood flow increases because upstream vessels and their resistance becomes relatively larger and thus limit flow enhancements. The signals and mechanisms that lead to upstream dilation are still enigmatic although 'ascending' dilations have been observed nearly a century ago [26].

Flow-dependent dilation is certainly a mechanism that contributes to upstream dilation [36]. As a consequence of downstream dilation flow in upstream, conducting vessels increases which elicits a physical force on the endothelial cells thereby enhancing the release of dilator autacoids, mainly NO [33, 34, 47]. Recently, direct signalling between cells of the vascular wall through gap junctions has attracted attention because longitudinal signalling is in principle capable of concerting the activity of a large number of cells along the vascular wall [3, 38]. In addition, gap junctions may also provide a communication channel between endothelial cells and the adjacent smooth muscle cell (myoendothelial junctions) allowing the transfer of charge and dilator substances between these cells and is reviewed elsewhere [14, 17]. In this article, we focus on the role of gap junctions as a pathway that contributes to the tuning of vascular cell behavior along the length of the vessel wall.

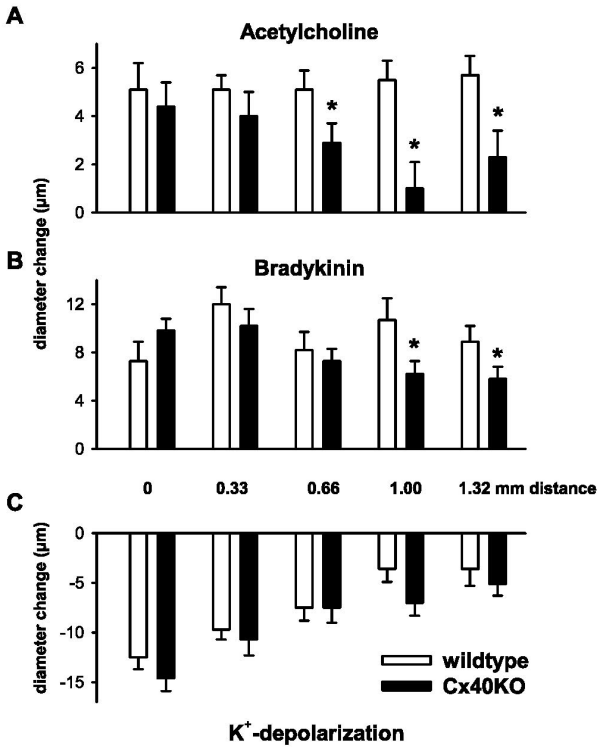

Fig. 1. Locally initiated dilations and constrictions conduct along arterioles. The stimulation of arterioles in the microcirculation in a locally confined manner using a micropipette initiates a dilation (**A**: acetylcholine, **B**: bradykinin) or constriction (**C**: K^+-depolarization) at the site of stimulation (0 mm distance). Dilations (**A**, **B**) conduct to remote, upstream sites as shown for varying distances from the site of stimulation (from 0.33 up to 1.32 mm) without significant attenuation in wildtype mice (open bars). In contrast, the amplitude of the constriction (**C**) decreases monotonically with distance in wildtype mice. The robust conduction of dilations requires connexin40, because the dilations in Cx40-deficient mice (Cx40KO, black bars in **A** and **B**) are significantly attenuated at remote sites * indicates $p < 0.05$ *vs.* wildtype). In contrast, vasoconstrictions conduct in Cx40KO mice with a similar amplitude as in wildtype (**C**). Further details see text. Diameter changes are given in µm, maximal diameters of the arterioles was 31 ±1 (**A**), 35 ± 1 (**B**), and 48 ± 2 (**C**) µm

Coordination through fast signalling mechanisms along the vascular wall

The synchronized behavior of arterioles in the microcirculation is easily studied and appreciated by stimulating an isolated vessel *in vitro* or an arteriole in the microcirculation *in vivo* in a localized manner because such a focal stimulation does not only induce a dilation or constriction at the site of stimulation but also at remote distant sites [5, 9, 12, 21, 39]. Such a response is termed conducted or ascending response although it spreads to up- as well as downstream sites. The distances covered by a conducted response varies between tissues and eliciting stimulus but can reach up to several millimetres (Fig. 1). However, not all vasoactive substances are able to initiate a conducted response. Dilators able to do so are mostly endothelium-dependet stimuli, such as acetylcholine or bradykinin [5, 21, 50]. In contrast, NO-donors such as sodium-nitroprusside elicit by the activation of the cGMP-cGKI pathway [24] a local dilation but fail to initiate a conducting response [10, 20]. This demonstrates that the local dilation per se does not initiate the conducting mechanisms. One might assume that a flow-dependent dilation underlies the dilation at upstream sites after downstream dilation and concomitant flow enhancement through the vessel under study. However, this is not the case because conducted dilations can be initiated in isolated vessels in the absence of flow [51]. Moreover, measurement of shear rate, the stimulus of flow-induced dilation, at distant locations have shown that shear rate did not increase before the dilation ensued at this upstream site [20, 40]. In addition, flow-induced dilations are in many cases NO-dependent, but NO has only a minor role (if any)

in conducting dilations [10, 20]. Finally, the onset of conducted responses is very rapid whereas flow-induced dilations are only developing slowly (15–30 s). All these observations clearly point to the fact that the conducted response is a mechanism which is different from flow-induced dilations. However, both may contribute to induce the required dilations in upstream vessels to provide maximal conductivity and hence blood flow to meet tissue needs.

The nearly instantaneous conducted response implies the contribution of very fast signalling mechanisms. Conduction through nerves has been excluded very early by the use of blockers of fast sodium channels [51], but nevertheless the signal depends on the electrotonic spread of membrane potential changes and is transmitted in the vascular wall itself. Evidence for this was provided by measurements of membrane potential in the cells of the vascular wall. In a number of *in vitro* studies the hyperpolarization initiated by acetylcholine was not only measured at the local site in endothelial and smooth muscle cells, but also at remote sites in these cells [9, 12, 13, 52]. In only a few studies the difficult task of measuring the membrane potential *in vivo* was accomplished, but these measurements also demonstrated hyperpolarizations at local and conducted sites [42, 48]. The hyperpolarization is initiated locally by the activation of calcium-dependent K^+-channels (K_{Ca}) which suggests that an EDHF is involved at least if acetylcholine is used as the stimulus [20–22, 41]. Whether EDHF is in fact a chemical factor which induces the smooth muscle hyperpolarization is questionable and reviewed elsewhere [17]. In any case, endothelial and smooth muscle cells are hyperpolarized and given that the vascular cells are coupled longitudinally (as outlined below) the membrane potential change can principally spread along the arteriolar wall. Whereas K_{Ca} activation is required at the site of initiation this is not the case at the remote site. In experiments in which these channels were blocked in a focal manner, we could show that an efficient blockade of K_{Ca} at conducted sites did not affect the dilation whereas K_{Ca} blockade at the local site abrogated the initiation of the response [20]. Together, these data suggest that in response to acetylcholine K_{Ca}-channels are activated (possibly through local rises in Ca^{2+} [9, 11, 31]) and induce a hyperpolarization. This is transmitted along the vascular wall and initiates a conducted response *per se*. Interestingly, electrical activation alone using a hyperpolarizing current likewise initiated a conducting response [13]. These assumptions are in agreement with the observation that only some substances induce conducted responses and suggests that a hyperpolarization is required which is not produced by every dilator substance.

Whereas conducted dilations are associated with a spreading hyperpolarization, conducted constrictions are conversely elicited by a local depolarization (Fig. 1). This can be induced by the application of a high K^+ solution [5, 21], which induces a strong depolarization according to the Nernst equation. Norepinephrine is also able to elicit such a response [51], but fails to do so in some tissues and species [21]. This might be related to the efficacy of the depolarization induced by norepinephrine which may or may not be sufficient to elicit these responses. Both, conducted dilations and constrictions, reflect fast signal transmission along the vascular wall although the signals are opposite in polarity. Interestingly, the distances through which constrictions conduct are attenuated by endogenous NO, implying that in vessels with intact NO production the efficacy of remote constrictions is limited [37].

Connexins form gap junctions in the vessel wall

The high conductivity which enables synchronous activity of vascular cells is due to gap junctions which interconnect the vascular cells by low-resistance channels. Gap junctions are composed of connexins. Six connexins form a channel (termed connexon) residing in the cell membrane [44]. Connexons from adjacent cells dock together and form a functional aequous pore which allows the exchange of ions and molecules up to a molecular weight of 1 kDa. The protein family of connexins consists of a family of about 20 members which are named according to their molecular size [49]. Of these connexin40 (Cx40), Cx37, Cx43, and Cx45 are expressed in the cardiovascular system [44]. The expression pattern of connexins in the vascular wall is dependent on vessel type and tissue. As a simplifying rule, Cx40 and Cx37 are abundantly expressed in endothelial cells, whereas Cx43 and possibly to a lesser extent Cx45 are expressed in smooth muscle [4, 45]. As a matter of fact the expression varies especially in arterioles and small arteries.

In these vessels depending on their origin, Cx43 has been found in the endothelium and Cx37 in smooth muscle cells. Interestingly, in some vascular beds Cx43 cannot be found at all. Having this in mind, it is required to study the expression pattern of connexins in the vessel of interest. Moreover, it suggests specific functions of different connexins within the vascular tree and possibly even within different organs.

The functional assessment of connexins is hampered by the fact that specific pharmacologic blockers are not available. Only recently, so called gap peptides have been developed and are supposedly able to block certain connexins specifically, because these small peptides are generated to interfere with a specific extracellular sequence of connexins, which may be a common sequence for all connexins or a sequence allowing to distinguish between them [2, 30]. However, it is difficult to obtain a sufficient peptide concentration at the site of interest. A different approach is the use of animals which are deficient for connexins. All connexins known to be expressed in the cardiovascular system have been deleted in mouse models but some of these deletions are lethal also highlighting the important role of connexins in embryogenesis and development. Animals deficient in Cx43 die perinatally due to an obstruction of the right ventricular outflow tract [35]. Cx45-deficient mice die during embryonic development exhibiting striking abnormalities of vascular development [27]. Thus, the functional study of these connexin deficiencies has to await the development of cell-specific deletion. In contrast, mice carrying a deletion of Cx37 or Cx40 are viable and can be studied to reveal connexin functions [23, 43].

The lack of Cx37 has not been reported to affect the conduction of vasomotor responses in arterioles or giving rise to a cardiovascular phenotype. However, functional data from our laboratory and others have demonstrated a critical role of Cx40 in the conduction of dilations along the arteriolar wall. The lack of Cx40 attenuated conducted dilations initiated by acetylcholine and bradykinin (Fig. 1). In contrast, the conduction of constrictions elicited by high K^+-solution remained unaffected [5]. These data were recently confirmed by other investigators who demonstrated an attenuated propagation of dilations (but not of constrictions) initiated by electrical stimulation in Cx40-deficient animals [15]. These functional data match the expression pattern of Cx40 as we have shown that Cx40 is mainly expressed in endothelial cells in the microcirculation [5]. The observation of an impaired conducted dilation, but a preserved conducted constriction combined with the fact that dilations and constrictions conduct for strikingly different distances along the vascular wall in mice suggests that different pathways conduct these signals along the wall. The endothelium may allow the spread of conducted dilations which travel further distances along the vessel than conducted constrictions that may rely on the smooth muscle as a conducting pathway. The endothelial cell layer may provide a more efficient pathway because of the anatomical shape and the length of a single cell that may serve as a distinct pathway to coordinate vascular behavior [18]. This assumption is also supported by modelling and simulation experiments demonstrating that changes of membrane potential propagate strikingly longer distances if initiated in endothelial cells [8]. However, it has to be kept in mind that the different polarity of the signals (hyper- *vs*. depolarization) could also explain the difference in distance covered by these signals because hyper- or depolarizations may be amplified in a distinct manner. This would result in different propagation distances for dilations or constrictons until the signal subsides. However, the data suggest that distinct pathways are involved, the endothelium conducting dilations and the smooth muscle cell layer constrictions.

The question whether this is indeed the case has been elegantly addressed by Segal et al. who have developed a technique to separately destroy the endothelial or smooth muscle cell layer by a light-dye treatment. Using this intervention to selectively destroy the endothelial cell layer along the conduction pathway they demonstrated that dilations conducted up to but not through the destructed vessel segment in the microcirculation of mice [29]. Similar observations were made in a larger feeding artery of the hamster which resides outside of the skeletal muscle [12]. However, in this latter vessel smooth muscle cells do not seem to be coupled at all and thus could not provide a second pathway. If such a second smooth muscle pathway exists (e.g. in the hamster cheek pouch microcirculation, arterioles residing within the organ) only the additional destruction of the smooth muscle cell layer prevented the conduction of dilations through the injured area [1]. Thus, it seems reasonable to assume that in principal both pathways, endothelium and smooth muscle cells, can provide a pathway for dilations. Up to date, it is unknown if these path-

ways exhibit divergent properties with respect to the distance the signal is able to propagate.

In contrast, conducted constrictions did not propagate through an area in which the smooth muscle cell layer was destroyed. This was independent of the stimulus used (K+-solution or norepinephrine) and also similarly observed in different tissues [1]. In summary, dilations initiated by acetylcholine or bradykinin conduct along the endothelial cell layer in a Cx40-dependent manner, but may also travel along the smooth muscle cell layer if this layer is coupled in the tissue under study. However, the properties may be distinct. In contrast, conducted constrictions propagate along the smooth muscle cell layer independent of Cx40. The connexins that are responsible for the coupling of the smooth muscle cell layer have not been characterized functionally up to now, but Cx43 and Cx45 are good candidates.

Hypertension in connexin40-deficient mice

Interestingly, Cx40-deficient mice are severely hypertensive. This was observed in anesthetised as well as awake animals [5, 6]. The mean blood pressure was increased by ~ 25 mmHg in Cx40-deficient mice and this was not associated with an alteration of NO release or efficacy because application of acetylcholine or an NO-donor induced comparable arterial pressure decreases. The hypertension was coincident with an altered vasomotion pattern in the microcirculation that was not observed in mice deficient for endothelial NO-synthase which are likewise hypertensive, although to a lesser degree. These irregular vasomotions consisted of a spontaneously appearing confined constriction which propagated slowly in the downstream direction along the vessel [6]. Currently, it is unknown if this is associated with an enhanced peripheral resistance. However, heart rate was not altered suggesting that sympathetic drive to the heart remained unaffected and did not contribute to hypertension.

Very recently, a renal phenotype was detected in these mice. Cx40 is also expressed in renin-secreting cells which form gap junctions with adjacent endothelial cells at the juxtaglomerular apparatus [19]. In Cx40-deficient mice, the negative feedback inhibition of renin synthesis and secretion by angiotensin II and pressure is abrogated. In contrast, the regulation by adrenergic stimulation and salt intake remained intact. The disturbed pressure feedback on renin secretion was reflected by strong elevations of plasma renin levels despite hypertension in these animals [46]. This suggests that hypertension in these animals is renin-dependent. However, inhibition of ACE [46] or a blocker of the AT-1 receptor [6] did not restore pressure of Cx40-deficient animals to the values of wildtype animals suggesting that increased pressure is not solely due to enhanced renin activity. In addition to its requirement for an efficient feedback inhibition of pressure and angiotensin II on renin secretion, Cx40 is also strikingly important for the maintenance of the architecture of the juxtaglomerular apparatus. In the absence of Cx40, the location and the identity of renin-producing cells was severely disturbed. Renin producing cells were relocated away from the terminal parts of the afferent arterioles, extending into the extraglomerular interstitium, and thereby losing contact to the endothelial cells of the afferent arterioles [28]. The mislocalisation of renin-producing cells may favor decoupling of renin secretion from the physiologic feedback suppressor (i.e. pressure and angiotensin II). However, it is also conceivable that the inhibitory effect of pressure requires intact gap junctional-coupling through Cx40 between the endothelium and renin-producing cells which would add endothelial cells to the pressure sensor machinery in the kidney. The abrogation of negative feedback inhibition on renin secretion in the kidney in conjuction with altered endothelial conduction in arterioles may lead to the severe hypertension observed in these animals. Very recently it was independently confirmed that Cx40-deficiency is associated with hypertension and an alteration of renin secretion [25]. Interestingly, a polymorphism within the Cx40 promotor has been demonstrated to be associated with an increased risk of hypertension in men [16]. Together with the evidence obtained in mice this suggests that defects in the expression and function of Cx40 may also account for hypertension in humans in a subpopulation of the hypertensive patients.

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