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REVIEW

Vasomotion: cellular background for the oscillator and for the synchronization of smooth muscle cells

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1 Vasomotion is the oscillation of vascular tone with frequencies in the range from 1 to 20 min^{-1} seen in most vascular beds. The oscillation originates in the vessel wall and is seen both *in vivo* and *in vitro*.

2 Recently, our ideas on the cellular mechanisms responsible for vasomotion have improved. Three different types of cellular oscillations have been suggested. One model has suggested that oscillatory release of Ca^{2+} from intracellular stores is important (the oscillation is based on a cytosolic oscillator). A second proposed mechanism is an oscillation originating in the sarcolemma (a membrane oscillator). A third mechanism is based on an oscillation of glycolysis (metabolic oscillator). For the two latter mechanisms, only limited experimental evidence is available.

3 To understand vasomotion, it is important to understand how the cells synchronize. For the cytosolic oscillators synchronization may occur *via* activation of Ca^{2+}-sensitive ion channels by oscillatory Ca^{2+} release. The ensuing membrane potential oscillation feeds back on the intracellular Ca^{2+} stores and causes synchronization of the Ca^{2+} release. While membrane oscillators in adjacent smooth muscle cells could be synchronized through the same mechanism that sets up the oscillation in the individual cells, a mechanism to synchronize the metabolic-based oscillators has not been suggested.

4 The interpretation of the experimental observations is supported by theoretical modelling of smooth muscle cells behaviour, and the new insight into the mechanisms of vasomotion has the potential to provide tools to investigate the physiological role of vasomotion.
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Abbreviations: CICR, Ca^{2+}-induced Ca^{2+} release; CPA, cyclopiazonic acid; NAADP, nicotinic acid adenine dinucleotide phosphate; SERCA, sarcoplasmic reticulum Ca^{2+} pump; SMC, smooth muscle cells; SR, sarcoplasmic reticulum; TEA, tetraethylammonium

Introduction

Vasomotion is the oscillation of vascular tone or vascular diameter that can be seen in many, if not all, vascular segments. It occurs both *in vivo* (Figure 1) and *in vitro* (Figure 2) and is generated from within the vascular wall, that is, it is not a consequence of the heart beat, respiration or neuronal input (although neuronal input may in some instances synchronize vasomotion in vascular beds, which are far apart; Schechner & Braverman, 1992; Porret *et al*., 1995). The first detailed report of vasomotion was made more than 150 years ago in the bat wing (Jones, 1852). In spite of this relatively long history, the two main questions are still incompletely understood: (1) What is the cellular background for vasomotion? and (2) what is the physiological consequence of vasomotion? One of the reasons for the lack of understanding of the cellular background is undoubtedly that there is more than one mechanism that will cause vasomotion, and that the mechanisms involved are complex and interacting in ways that are difficult to address experimentally. One of the reasons why the physiological and pathophysiological roles (if any) for vasomotion are not understood is that there is still no consistent way of inducing or inhibiting vasomotion in experimental settings.

This review will focus on the cellular background for vasomotion, but to enhance the reader's interest in the subject we will briefly mention the ideas on the physiological role of vasomotion, which have been suggested. The physiological importance of vasomotion is not well understood (Nilsson & Aalkjaer, 2003), although several suggestions have been made. For the same average diameter vasomotion ensures an increased flow conductance. An intriguing idea is that vasomotion and the ensuing slow oscillation of flow into a capillary bed – that is, flowmotion – provides an oscillation of oxygen tension (Misrahy *et al*., 1962), which ensures a better tissue oxygenation than that obtained with a steady oxygen delivery. Although theoretical evidence for this has been presented, the experimental evidence is scarce (Nilsson & Aalkjaer, 2003). There is, thus, a great need for experimental approaches that can address the relevance of vasomotion. To do this, it is important to understand the cellular background for vasomotion. Such an understanding may provide means of selectively interfering with steps in the cellular chain of events leading to vasomotion and thus specifically switch on or turn

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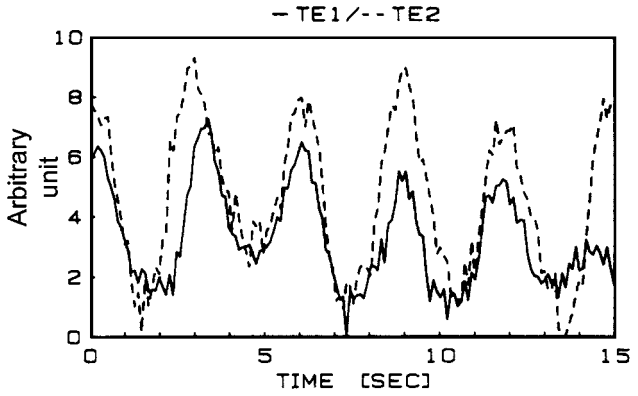

Figure 1 Synchronized oscillations of diameter (vasomotion) in two daughter branches in a rabbit skeletal muscle assessed under *in vivo* conditions. Data from Meyer *et al*. (1987).

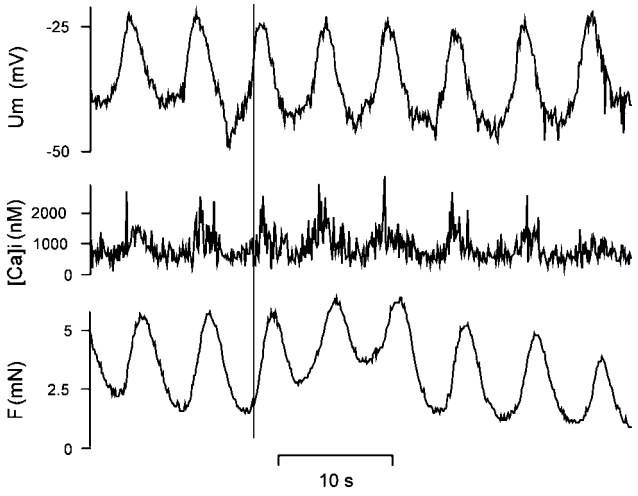

Figure 2 Simultaneous measurements of isometric force, SMC membrane potential and SMC $[Ca^{2+}]_i$ in an isolated rat mesenteric small artery. Note that membrane potential oscillations precede oscillations in $[Ca^{2+}]_i$, which again precede oscillations in tension.

off vasomotion. When this becomes possible, the physiological relevance of the phenomenon will be much more accessible to investigation.

Cellular background for vasomotion

For vasomotion to occur, a cellular oscillator must be present, which can be modelled as a string of events forming a feedback loop, where inertia in one or more of the steps in the loop ensures oscillation. In order to get macroscopic oscillations of a blood vessel, the oscillations in individual smooth muscle cells (SMCs) must be synchronized. Therefore, some means of synchronization must be present. We will discuss these two essential elements of vasomotion separately. With respect to the oscillator, we will discuss the three different types of oscillators that have been suggested, viz. a cytosolic oscillator, a membrane oscillator and a metabolic oscillator. Of these, the cytosolic oscillator is probably the most relevant and we will consequently discuss in some detail the source of Ca^{2+} and the regulation that sets up the cytosolic oscillator. With respect to synchronization we will discuss the role of membrane potential

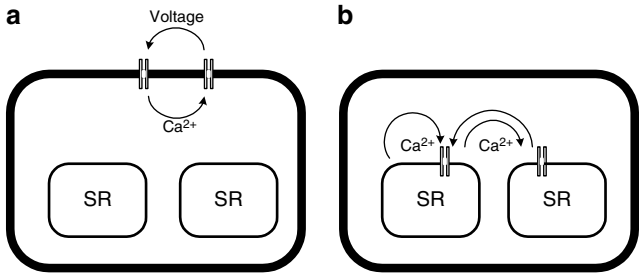

Figure 3 Model illustrating the differences between (a) a membrane oscillator and (b) a cytosolic oscillator.

and its reciprocal interaction with the sarcoplasmic reticulum (SR). In particular, we will discuss which sarcolemmal ion channels might be relevant for synchronization and also include a brief section on gap junctions. Since the role of the endothelium for vasomotion varies between different vascular beds, we will discuss the potential role of the endothelium in a separate section. In the last section, we discuss the theoretical models that have been developed for vasomotion.

The oscillator

A classification of cellular oscillators into two main types, membrane oscillators and cytosolic (or cytoplasmic) oscillators, was introduced by Berridge & Rapp (1979) (Figure 3). A membrane oscillator is considered to be one where the rhythm is generated at the membrane by oscillations in transporter activity or permeability. In contrast, a cytosolic oscillator does not depend on the cell membrane, but here oscillations arise from an intracellular instability in, for example, calcium release or energy production (the latter has also been called a metabolic oscillator).

A cytosolic oscillator in SMC

Ca^{2+} waves originating from intracellular Ca^{2+} stores Oscillations of SMC $[Ca^{2+}]_i$ have been reported for a long time (Weissberg *et al*., 1989), and, as will be discussed in some detail later, may form the basis for vasomotion even though these are often asynchronous. Blatter & Wier (1992) demonstrated that oscillations of $[Ca^{2+}]_i$ take the form of waves of Ca^{2+} running parallel to the long axis of the cells in an SMC line (A7r5) and Iino *et al*. (1994) reported a similar behaviour of SMCs in the intact vascular wall. Following these initial observations, oscillating Ca^{2+} waves have been demonstrated in SMCs from many different vessels (see, e.g. Lee *et al*., 2002). It is very likely that vascular SMCs from all vascular beds can exhibit this behaviour. An example from rat mesenteric small arteries is shown in Figure 4. Much work has gone into defining the mechanism(s) responsible for this oscillating $[Ca^{2+}]_i$. Most detailed work has been carried out with regard to isolated SMCs, but information is also available from SMCs in the intact vascular wall and much of the background has come from studies of similar behaviour in many other cell systems.

Blocking of the SR Ca^{2+} pump (SERCA) strongly inhibits the Ca^{2+} waves, suggesting that they are caused by release of Ca^{2+} from the SR. This is supported by the observation that the waves are present in the absence of extracellular Ca^{2+}, although they disappear eventually (Iino *et al*., 1994;

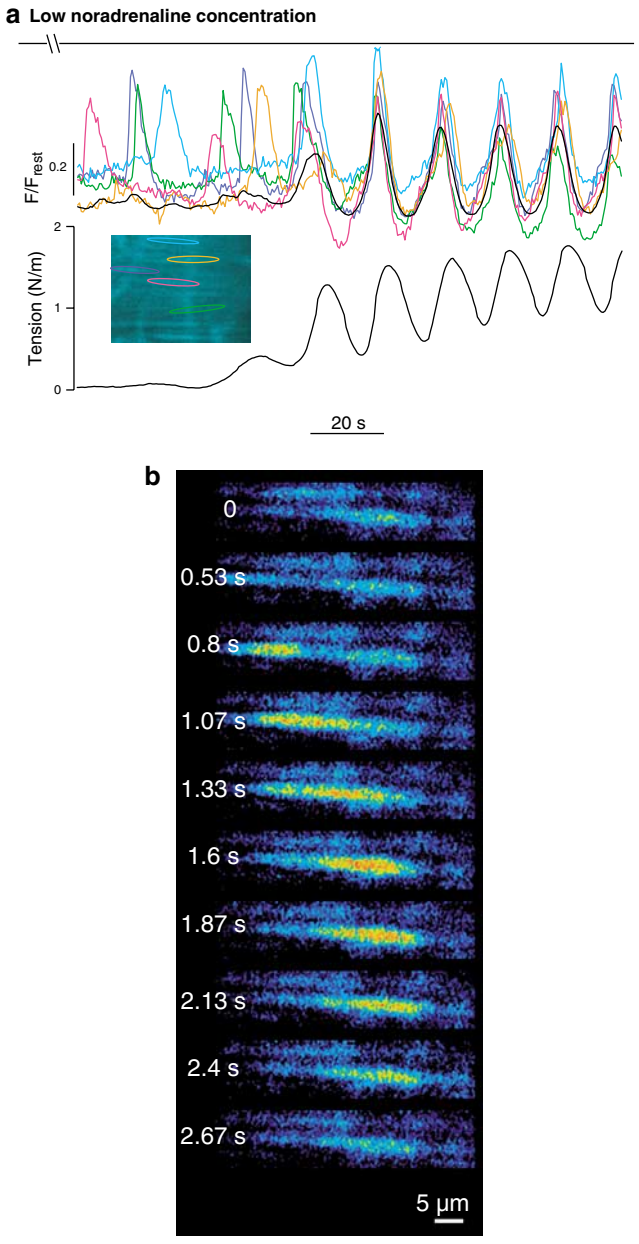

Figure 4 (a) Confocal imaging of $[Ca^{2+}]_i$ in SMCs (upper traces) and isometric tension (lower trace) of an isolated rat mesenteric small artery. The black graph in the upper trace shows the average $[Ca^{2+}]$. The different colours in the upper trace represent $[Ca^{2+}]$ in individual SMCs. The artery was activated with a low concentration of noradrenaline. The oscillations of SMC $[Ca^{2+}]_i$ are first seen to be unsynchronized but then synchronize and vasomotion starts. (b) Confocal images of $[Ca^{2+}]_i$ in a single SMC detailing the unsynchronized oscillations shown in (a). Note how the increase of $[Ca^{2+}]_i$ runs as a wave along the axis of the SMC, which is typical for the unsynchronized activity. Data from Peng *et al.* (2001).

Ruehlmann *et al.*, 2000; Peng *et al.*, 2001). The reason for this is thought to be that some of the Ca^{2+} released from the SR during a Ca^{2+} wave is being pumped out of the cells, and some influx of Ca^{2+} is consequently necessary to refill the SR (Iino *et al.*, 1994; Ruehlmann *et al.*, 2000). In the rabbit portal vein both voltage-gated Ca^{2+} channels, nonselective cation channels and the Na^+,Ca^{2+}-exchanger have been suggested to be of importance for providing this influx maintaining the

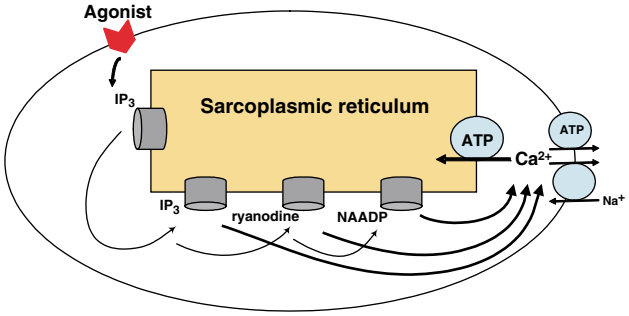

Figure 5 Model illustrating the basic elements in a cytosolic oscillator in an SMC. An IP_3-producing agonist causes release of Ca^{2+} from the SR. This Ca^{2+} release is reinforced through Ca^{2+}-induced Ca^{2+} release from different Ca^{2+} release channels. Ca^{2+} is taken up into the SR again or extruded from the cells *via* Ca^{2+}-ATPases.

Ca^{2+} waves (Lee *et al.*, 2001). A consistent characteristic of the Ca^{2+} waves is that they do not represent simple diffusion of released Ca^{2+}, but involve a regenerative release of Ca^{2+} mediated by Ca^{2+}-induced Ca^{2+} release (CICR). In vascular SMC, Ca^{2+} can be released *via* an IP_3-sensitive channel *via* a caffeine- and ryanodine-sensitive channel and possibly *via* a nicotinic acid adenine dinucleotide phosphate (NAADP)-sensitive channel. When agonists are used to induce Ca^{2+} waves IP_3 is always involved. In isolated vascular and intestinal SMCs, uncaging of caged IP_3 leads to generation of Ca^{2+} waves (Boittin *et al.*, 1999; McCarron *et al.*, 2003). Furthermore, blocking the IP_3 receptor with heparin (Blatter & Wier, 1992; Boittin *et al.*, 1999) and with 2-aminoethoxydiphenyl borate (Lee *et al.*, 2001) blocks agonist-induced Ca^{2+} waves in A7r5 cells and in rabbit inferior vena cava, respectively. There is thus little doubt that the Ca^{2+} waves are caused by release from and subsequent uptake by the SR of Ca^{2+}, and that several release channels are likely to be involved in the release (Figure 5).

The next question is whether a primary release from the IP_3 receptor leads to CICR *via* receptors for IP_3 or ryanodine receptors. There is little doubt that acute blockade of the ryanodine receptor blocks Ca^{2+} waves (Blatter & Wier, 1992; Iino *et al.*, 1994; Boittin *et al.*, 1999; Ruehlmann *et al.*, 2000; Peng *et al.*, 2001), indicating a role for the ryanodine receptor. Further evidence that CICR *via* the ryanodine receptor is important for the IP_3-initiated Ca^{2+} waves was obtained by Boittin *et al.* (1999) in the rat portal vein using IP_3- and ryanodine-receptor-specific antibodies. In these experiments, care was taken to demonstrate that the inhibition of agonist-induced Ca^{2+} waves was not due to depletion of SR Ca^{2+} caused by ryanodine or ryanodine-receptor antibodies. On the other hand, chronic downregulation of the ryanodine receptors in the intact rat tail artery did not affect Ca^{2+} waves elicited by noradrenaline (Dreja *et al.*, 2001) even though acute exposure to ryanodine inhibited Ca^{2+} release. This suggests that CICR *via* the IP_3 receptor under some circumstances is sufficient to produce Ca^{2+} waves. In line with this, McCarron *et al.* (2003) recently showed that in isolated intestinal SMCs, IP_3-induced Ca^{2+} waves are dependent on CICR, yet they are mediated only *via* the IP_3 receptor and not *via* the ryanodine receptor (whether this also occurs in vascular smooth muscle is currently not known). It therefore seems that a primary Ca^{2+} release mediated *via* IP_3 release can induce Ca^{2+} waves

in SMCs through CICR mediated either *via* IP_3 receptors or ryanodine receptors or a combination. Whether one or the other mechanism is important may depend on the relative concentration of the receptors (Boittin *et al*., 1999) or on the distribution of receptor subtypes or by luminal Ca^{2+} (McCarron *et al*., 2003) or perhaps a number of other parameters that determine the Ca^{2+} sensitivity of the two receptors.

The functional consequence – if any – of the different modes of Ca^{2+} waves is unknown, although it has been suggested that IP_3-mediated Ca^{2+} release and ryanodine-receptor-mediated release may affect different ion channels in SMCs (Haddock & Hill, 2002). Based on this background, it is tempting to ask whether Ca^{2+} waves in smooth muscle can also be elicited completely independent of IP_3. The answer to this is yes. Ca^{2+} waves elicited by high pH_i in isolated VSMC from rat cerebral arteries are not inhibited by blockers of IP_3 receptors (Heppner *et al*., 2002), but here as in the portal vein (Ruehlmann *et al*., 2000) and in rat mesenteric small arteries (A. Rahman, H. Nilsson, C. Aalkjær, unpublished observation), caffeine can induce Ca^{2+} waves. Whether pure ryanodine-receptor-mediated Ca^{2+} waves have functional consequences different from those seen with IP_3 is unknown. It is also unclear whether cADP-ribose, which is a known endogenous agonist for the ryanodine receptor, is involved in these ryanodine-receptor-mediated Ca^{2+} waves in SMCs, but it has been suggested that cADP-ribose might instead lower $[Ca^{2+}]_i$ through activation of the calcium-activated potassium channel (Boittin *et al*., 2003).

A third Ca^{2+} release channel activated by NAADP is also suggested to play a potential role. In this respect, it is of substantial interest that Boittin *et al*. (2002) recently showed that NAADP can induce a Ca^{2+} wave in VSMC from pulmonary arteries that is blocked by ryanodine but unaffected by inhibition of the IP_3 receptor. The authors suggest that Ca^{2+} is released through an intracellular NAADP-sensitive channel, which initiates the wave through CICR from the ryanodine receptor. The importance of this mechanism in other VSMCs needs to be investigated.

Removal of Ca^{2+} from the cytosol Following the increase of $[Ca^{2+}]_i$ caused by release of Ca^{2+} from the SR, $[Ca^{2+}]_i$ decreases again. This declining phase of the wave can be seen as the combination of a decrease of the Ca^{2+} release and the active removal of Ca^{2+} from the cytosol. The reason for the reduction of Ca^{2+} release could be a refractoriness of the Ca^{2+} release channels and evidence that it could be refractoriness to IP_3 consequent to the high $[Ca^{2+}]_i$ was recently reviewed (McCarron *et al*., 2004). The mechanisms responsible for the active removal of Ca^{2+} from the cytosol has been less intensely investigated compared to the release mechanism, and the likely candidates are the plasmalemmal and SR Ca^{2+}-ATPases and the Na^+, Ca^{2+}-exchanger (Lee *et al*., 2001).

What causes the phase shift necessary for the oscillation? As indicated above, inertia in one of the steps in the feedback loop ensures that the feedback signal is out of phase with the initiating event. This phase shift is essential for creating an oscillation. Several of the steps discussed above have been suggested to provide this relative 'slowness' of the feedback loop. Possible candidates are a slow refilling of the SR after Ca^{2+} release, inactivation of the IP_3 receptor or the ryanodine receptor either time-dependently or consequent to high $[Ca^{2+}]_i$ or high receptor substrate concentration. In a recent detailed analysis of intestinal SMCs, a $[Ca^{2+}]_i$-induced inactivation of the IP_3 receptor was shown to be important (McCarron *et al*., 2003), but the issue is not clarified in vascular smooth muscles yet.

Functional consequences of Ca^{2+} waves Several functional consequences of Ca^{2+} waves have been suggested. From the point of view of this review, it is relevant that an oscillatory Ca^{2+} release has been suggested to be responsible for vasomotion (Peng *et al*., 2001). In general, the amplitude and frequency information contained in the Ca^{2+} waves has been suggested to be decoded rather acutely by transcriptional factors so that different types of oscillations lead to expression of different proteins (Dolmetsch *et al*., 1998; Li *et al*., 1998; and see recent review by Lewis, 2003). The role of this for VSM cell phenotype has not been investigated at all. Specifically for vascular smooth muscle, the force production has been shown to be graded by both recruitment of cells producing Ca^{2+} waves and by modulation of the frequency of Ca^{2+} waves in the individual cells (Iino *et al*., 1994; Kasai *et al*., 1997; Ruehlmann *et al*., 2000; Zang *et al*., 2001). This was suggested to be the background for the relation between the global intracellular calcium concentration in the vascular wall and force development. However, this may not always be the case because in mesenteric small arteries, the occurrence of Ca^{2+} waves seems not always to be tightly associated with force (Miriel *et al*., 1999; Peng *et al*., 2001). Interestingly, Swärd *et al*. (2002) have taken these observations further and suggested that even for a constant global $[Ca^{2+}]_i$, different combinations of frequency and amplitudes give rise to different mechanical responses. The background for this suggestion is that mitochondrial inhibition leads to higher frequency, lower amplitude Ca^{2+} waves and a reduced force development despite an unchanged time-averaged $[Ca^{2+}]_i$. These observations could be explained on the basis of a nonlinear and time-dependent relationship between $[Ca^{2+}]_i$ myosin light-chain phosphorylation and force (Swärd *et al*., 2002).

Oscillations that appear independent of Ca^{2+} release from stores or a membrane oscillator Another type of SMC oscillation appears to be present after blockade of the SR Ca^{2+}-ATPase or inhibition of release of Ca^{2+} from ryanodine-sensitive Ca^{2+} channels. Such oscillations have been demonstrated by Omote and Mizusawa in a series of papers (Omote *et al*., 1992; 1993; Omote & Mizusawa, 1993), where they found oscillations in isometric tension of different isolated rabbit arteries after the SR Ca^{2+}-ATPase was inhibited with cyclopiazonic acid (CPA) or Ca^{2+}-induced Ca^{2+} release was inhibited with ryanodine. The oscillations were inhibited by charybdotoxin and iberiotoxin and it was suggested that the oscillations were due to an interaction between the large-conductance calcium-activated potassium channel and the voltage-dependent calcium channel. In a rabbit ear small artery, perfused *in situ* oscillations with a low but complex frequency were induced by low concentrations of CPA. Modelling suggested that this could represent the presence of membrane oscillator. With higher concentrations of CPA, all oscillations were inhibited (Griffith & Edwards, 1997), emphasizing the importance of the SR. Also in rat mesenteric small arteries, CPA could induce an oscillation of tone (Huang

& Cheung, 1997) that similarly was abolished by charybdotoxin and by a moderate increase of extracellular potassium consistent with an important role for potassium channels. The endothelium-dependence of these oscillations differed, being endothelium-independent in the rabbit arteries but endothelium-dependent in the rat. In A7r5 cells, Ca^{2+} oscillations in response to low physiological concentrations of vasopressin have been demonstrated by Byron & Taylor (1993); these are present even after treatment with CPA and ryanodine, suggesting an independence from release of Ca^{2+} from stores sensitive to CPA and ryanodine. Furthermore, it has been suggested that this type of oscillation is dependent on activation of phospholipase D (Li *et al*., 2001) but the electrophysiological background has not been addressed.

Although there is some evidence for a membrane oscillator as just described, this has not been subject to as detailed an analysis as has the cytosolic-oscillator-based vasomotion. For example, it is not known to what extent the oscillations are caused by mechanisms, which are fully independent from Ca^{2+} release from the SR. As discussed above, the different Ca^{2+} stores in vascular SMCs are complex and may differ from preparation to preparation, and it is not clear from the studies with CPA and thapsigargin whether all stores have been completely blocked by the drugs (Griffith & Edwards, 1997). It therefore appears that membrane oscillators can indeed drive vasomotion under certain conditions or in certain vascular beds. However, in the majority of cases, a cytosolic oscillator seems more important. On the other hand, as discussed below, the cytosolic oscillator interacts importantly with the membrane to induce synchronization, that is, even in the cytosolic-oscillator-based oscillation, the membrane oscillates. It may therefore not be fruitful to maintain a strong distinction between the two types of oscillation.

A metabolic oscillator?

A third type of oscillator that could be responsible for vasomotion has been suggested by Siegel in a series of papers (Siegel *et al*., 1980; 1991; Siegel, 1983). It was suggested that oscillations in glycolysis could lead to oscillations in ATP concentrations, which then might cause oscillations in the activity of the electrogenic Na,K-pump, leading to oscillations in membrane potential. Experimental evidence for the two latter suggestions was provided. Based on modelling and experimental evidence from other tissues, Siegel and co-workers suggested that oscillations in the activity of the enzyme phosphofructokinase might be responsible. A pre-requisite for this is allosteric regulation of phosphofructokinase activity by substrates, products and ATP on the regulatory control point of the glycolytic system (Siegel, 1983). Although this is an interesting possibility, nobody has followed up on this suggestion and the hypothesis is still waiting to be tested thoroughly. It should be noted that the Ca^{2+} oscillations discussed above could also potentially explain the oscillations of the Na,K-pump activity reported by Siegel (i.e. oscillation of the Na,K-pump may be consequent to the Ca^{2+} oscillation). A primary metabolic oscillation is therefore not necessary to explain this oscillation, although it is an intriguing idea. It could be added that, as pointed out by Siegel (1983), the mechanism for intercellular coupling that is necessary for vasomotion to occur is not known for this type of oscillation.

Endothelial cell oscillations

Interestingly, Ca^{2+} oscillations have been shown repeatedly in isolated endothelial cells (Jacob *et al*., 1988; Sage *et al*., 1989; Laskey *et al*., 1992; Paltauf-Doburzynska *et al*., 2000). Also in intact arteries, oscillations of endothelial $[Ca^{2+}]_i$ (Schuster *et al*., 2001) and membrane potential (Segal & Beny, 1992; Muraki *et al*., 2000) have been reported in association with vasomotion. The role of these oscillations for vasomotion has not been investigated, and it is not known whether a primary endothelial oscillation can drive vasomotion. Undoubtedly, the interaction between endothelial oscillations and vascular smooth muscle oscillations is a potentially interesting area to investigate.

Synchronization

The importance of the membrane potential for synchronization

Whenever SMC membrane potential has been measured during vasomotion, a slow oscillation corresponding to the vasomotion has been reported (Mulvany *et al*., 1982; Hayashida *et al*., 1986; Garland, 1989; Segal & Beny, 1992; der Weid & Beny, 1993; Gustafsson *et al*., 1993; Hill *et al*., 1999; Peng *et al*., 2001; Haddock & Hill, 2002; Haddock *et al*., 2002; Oishi *et al*., 2002). The oscillation has the same frequency as the vasomotion and the oscillation in potential precedes the oscillation in smooth muscle tension (Figure 2). It should be pointed out that in human pial arteries, action potentials have been reported, which were associated with vasomotion (Gokina *et al*., 1996). During high-frequency oscillation of the action potentials, the associated contractions fused to a tonic contraction. Most authors have consequently suggested that vasomotion is caused by an oscillation in membrane potential. An electrical signal is also likely to be the only signal fast enough to synchronize SMC activity over several millimetres. However, it is interesting that Haddock *et al*. (2002) suggested that the tone of isolated irideal arterioles may oscillate independent of oscillations in membrane potential. The signal causing synchronization in this case is unknown.

Reciprocal interaction between the SR and the sarcolemma is important for synchronization in many situations

In most cases where the role of the endoplasmic reticulum has been investigated, vasomotion seems to be prevented when either release or uptake of Ca^{2+} into the SR is inhibited. This occurs in rabbit ear artery (Griffith & Edwards, 1993; 1997), and rat mesenteric (Gustafsson & Nilsson, 1993; Peng *et al*., 2001), cerebral (Haddock & Hill, 2002) and irideal (Hill *et al*., 1999; Haddock *et al*., 2002) arteries. Based on this observation, it has been suggested (Gustafsson, 1993; Griffith & Edwards, 1994; Peng *et al*., 2001; Haddock & Hill, 2002) that the unsynchronized Ca^{2+} oscillations caused by release of Ca^{2+} from the SR (discussed above) may entrain to initiate vasomotion (Figure 4). By entrainment, we understand that individual oscillators become phase-locked into the same phase. This is believed to occur through interaction between

the oscillators (Strogatz & Stewart, 1993). In this suggestion, the Ca^{2+} released from the SR will activate an inward current in the membrane, leading to depolarization. As discussed above, several release channels potentially releasing Ca^{2+} from different stores may contribute to this. Although it has been suggested (Haddock & Hill, 2002) that release of Ca^{2+} from different Ca^{2+} stores may affect different ion channels, this problem is not easy to address experimentally. The extent to which a potentially very interesting functional coupling between specific Ca^{2+} stores and specific sarcolemmal ion channels is physiologically relevant therefore is still largely unknown. The vascular SMCs are electrically coupled and the current generated in one cell will run into the neighbouring SMCs. The ensuing synchronized depolarization will enhance the likelihood of Ca^{2+} release from the SR. This may occur either due to enhanced influx of Ca^{2+} through L-type Ca^{2+} channels leading to Ca^{2+}-induced Ca^{2+} release (Peng *et al*., 2001) or due to depolarization-induced potentiation of IP_3 production as it has been suggested for slow oscillations in the guinea-pig gastric pylorus (van Helden *et al*., 2000; van Helden & Imtiaz, 2003). In rat mesenteric small arteries, the former possibility seems more likely because nifedipine inhibits synchronization (Peng *et al*., 2001). This would not be expected if membrane-potential-induced oscillations of IP_3 concentrations were causing the synchronization unless the IP_3 oscillations were partly dependent on an oscillating Ca^{2+}. An important distinction in this model (van Helden & Imtiaz, 2003) is whether the individual SMCs (or the SR in the cells) are sequentially activated following the primary activation of one cell or through entrainment of cells that all are active initially. In rat mesenteric small arteries most, possibly all, cells are active although unsynchronized and the synchronization may therefore predominantly reflect an entrainment. In the initial phase, it is possible that there is an element of sequential activation. Another implication of this model is that the release of Ca^{2+} from the SR is determining the Ca^{2+} concentration in a restricted space between the superficial SR and the sarcolemma, which, on the other hand, is not substantially affected by the Ca^{2+} influx through the L-type Ca^{2+} channels. Alternatively, the Ca^{2+} influx would provide a positive feedback on the depolarizing current, which would prevent the hyperpolarizing phase of the vasomotion. It is not easy to test this experimentally since it is difficult with the current techniques to detect Ca^{2+} in the restricted space on top of bulk Ca^{2+} caused by Ca^{2+} influx. A diagram of this model is shown in Figure 6.

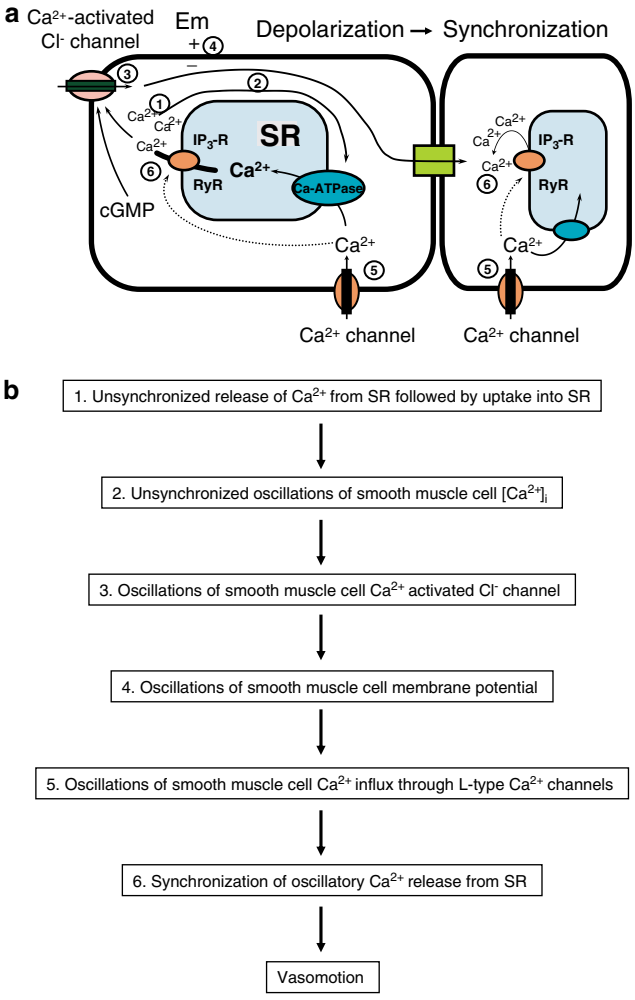

Figure 6 (a) Model indicating one proposed mechanism for initiation of vasomotion. The mechanism is based on a cytosolic oscillator, which interacts reciprocally with the membrane and which we consider an important mechanism for vasomotion (from Peng *et al*., 2001). (b) Diagram showing the proposed sequence of events in the model shown in (a).

Which sarcolemmal ion channel is important for vasomotion?

Several authors have implied models involving the mentioned elements, with the cytosolic oscillator interacting reciprocally with the membrane (Gustafsson, 1993; Parthimos *et al*., 1999; Peng *et al*., 2001; Haddock & Hill, 2002) to ensure entrainment of the SR. A similar mechanism has been suggested for the rhythmic contractions of the gastric pylorus (van Helden *et al*., 2000; van Helden & Imtiaz, 2003) and lymphatic vasomotion (Ferrusi *et al*., 2004) by van Helden's group. It becomes of interest to characterize the channel(s) responsible for the depolarizing current(s) induced by the Ca^{2+} release, which is responsible for the entrainment of the SR in this model. A likely candidate would be a Ca^{2+}-activated Cl^- current. Coupling of oscillatory Ca^{2+} release to activation of a Cl^- channel has been shown in several smooth muscle preparations (Bakhramov *et al*., 1996; Liu & Farley, 1996b; Hyvelin *et al*., 1998), and in swine tracheal SMCs, it was shown that a tonic increase of IP_3 could induce such oscillations (Liu & Farley, 1996a). The Ca^{2+}-activated Cl^- channels have not been characterized in the same detail as the voltage-dependent anion channels or the cation channels. This is partly because there are no selective blockers for these channels, and partly because the molecular identity of the channels is still controversial (Jentsch *et al*., 2002; Nilius & Droogmans, 2003). In a search for a Cl^- channel that could be important in vasomotion, we have exploited the observation that the synchronization of oscillating smooth muscle $[Ca^{2+}]_i$ activity as well as the inward current and depolarization induced by release of Ca^{2+} from intracellular Ca^{2+} stores is cGMP-dependent in rat mesenteric small arteries (Peng *et al*., 2001). The channel responsible for these electrophysiological effects is likely a Ca^{2+}-activated, cGMP-dependent Cl^- channel, with unique biophysical and pharmacological characteristics, which we have recently described (Matchkov *et al*., 2004a). This

channel is voltage- and time-independent, has a distinct anion permeability sequence with bromide being more permeable than iodide, is relatively insensitive to classical Cl^- channel blockers such as niflumic acid, IAA-94 and DIDS, but is quite sensitive to Zn^{2+}. Single-channel recordings have shown that the channel has three conductance levels (15, 35 and 55 pS) (Piper & Large, 2004b) and is calmodulin-dependent (Piper & Large, 2004a). The channel is present in rat mesenteric arteries together with the Ca^{2+}-activated, but cGMP-independent Cl^- channel (Matchkov *et al*., 2004a) seen in many vascular preparations (Large & Wang, 1996). It is a distinct possibility that this novel Cl^- channel provides the Ca^{2+}-induced inward current necessary for the synchronization of the vascular SMCs in rat mesenteric small arteries. However, it remains to corroborate these suggestive observations with direct experimental evidence that this channel or another chloride channel is indeed involved in vasomotion. Obviously, other Ca^{2+}-activated channels giving rise to an inward current could also be involved. Particularly in cGMP-independent forms of vasomotion, it is likely that another current is involved. However, little is known and this is an area that needs investigation to understand vasomotion.

Also, potassium channels may play a role as discussed above for the membrane-oscillator-based vasomotion. But also for the vasomotion based on release of Ca^{2+} from the SR, potassium channels may be involved since vasomotion frequency is often affected by potassium channel blockers. Although this demonstrates an influence of potassium channels, it also indicates that potassium channels are not an essential element in the feedback loop constituting the oscillation, since the blockers were incapable of inhibiting vasomotion. Potassium channels may also be involved through a different mechanism. Inhibition of potassium channels with tetraethylammonium (TEA) has consistently been shown to promote vasomotion (Kannan & Daniel, 1978; Watts *et al*., 1994; Wu *et al*., 2000; Haddock & Hill, 2002; Kamouchi *et al*., 2002). One possible explanation for this is a TEA-induced decrease in membrane conductance, which would promote intercellular coupling. Another suggested mechanism (Kannan & Daniel, 1978; Watts *et al*., 1994) is that TEA induces the formation of gap junctions (Kannan & Daniel, 1978; Sheppard & Meda, 1981; Watts *et al*., 1994) and in this way promotes vasomotion (see below).

The importance of gap junctions

A key element for the synchronization of the SMCs is the gap junctions, which undoubtedly mediate the electrical coupling of the SMCs in the vascular wall. The presence of gap junctions in the vascular wall has been documented with a variety of techniques (Beny & Connat, 1992; Watts *et al*., 1994; Little *et al*., 1995; Christ *et al*., 1996; Sandow & Hill, 2000). Most importantly in this context, it has been demonstrated that knockout of connexin 40 is associated with irregular arteriolar vasomotion (de Wit *et al*., 2003); however, a variety of substances that are blockers of gap junctions have been shown to inhibit vasomotion (Tsai *et al*., 1995; Chaytor *et al*., 1997; Sell *et al*., 2002; Matchkov *et al*., 2004b). Although some of these substances have nonjunctional or unspecific effects (Chaytor *et al*., 1997; Santicioli & Maggi, 2000; Tare *et al*., 2002; Matchkov *et al*., 2004b), the consistent inhibitory effects on vasomotion of these substances, which include peptides with specificity for the extrafacial loops of the connexins (Chaytor *et al*., 1997), strongly support the key role of gap junctions for vasomotion. Although so far no conclusive evidence has been presented for the role of regulation of gap junctions in vasomotion, there are interesting suggestions that this could be the case. One possibility is that TEA, as discussed in the preceding section, promotes vasomotion through induction of gap junctions, which would suggest that upregulation of gap junctions could influence the probability of getting vasomotion. Another possibility discussed in the following sections is that cGMP, through an effect on gap junctions, may modify the prevalence of vasomotion.

Role of the endothelium for vasomotion

Even though current views on vasomotion hold that vasomotion originates in the SMCs, the important modulatory role of the endothelium on smooth muscle function makes it relevant to consider the role of the endothelium in vasomotion. The influence of the endothelium seems to vary between preparations. In some arteries, removal of the endothelium or blockade of NO production with arginine analogues prevents vasomotion. This is the case in hamster aorta (Jackson, 1988), hamster cheek pouch (Jackson, 1993), rat mesenteric arteries (Gustafsson, 1993; Huang & Cheung, 1997; Mauban *et al*., 2001; Peng *et al*., 2001; Okazaki *et al*., 2003), rabbit mesenteric (Omote & Mizusawa, 1993; Akata *et al*., 1995) and coronary arteries (Akata *et al*., 1995) and the human cutaneous circulation (Kvandal *et al*., 2003). Vasomotion is promoted when the endothelium is removed (or the NO synthase inhibited) in the rabbit ear artery (Griffith & Edwards, 1993), rat aorta (Marchenko & Sage, 1994), hamster cheek pouch (Bertuglia *et al*., 1995) and rat mesenteric arteries (Sell *et al*., 2002), while in some situations the presence or absence of the endothelium is reported to be without effect on vasomotion rat aorta (Chemtob *et al*., 1992; Freeman *et al*., 1995), rabbit mesenteric arteries (Omote & Mizusawa, 1993) and pig coronary arteries (der Weid & Beny, 1993). Such a variability of results even within the same artery might suggest that one or more factors from the endothelium influence one or more of the key control variables that are important for vasomotion.

In hamster aorta (Jackson *et al*., 1991) and rat mesenteric arteries (Gustafsson & Nilsson, 1993; Peng *et al*., 2001), the role of the endothelium could be to provide a certain level of cGMP, which is necessary for coordination of the oscillators in the SMCs. This is suggested from the observation that in the absence of the endothelium, addition of cGMP will lead to a synchronization of the Ca^{2+} transients in the vascular SMC (Peng *et al*., 2001) and vasomotion (Jackson *et al*., 1991; Gustafsson & Nilsson, 1993; Peng *et al*., 2001). A constant concentration of cGMP is thus able to get the oscillation back. It has been suggested that this may be mediated by the cGMP-dependence of a Ca^{2+}-activated, cGMP-dependent Cl^- channel in the vascular SMC (Peng *et al*., 2001; Matchkov *et al*., 2004a). To explain the situations with an inhibitory effect of the endothelium and cGMP on vasomotion, it has been suggested that cGMP could inhibit vascular SMC communication *via* inhibition of gap junctions (Sell *et al*., 2002). The effect of cGMP on vascular SMC gap junctions seems complex (Hoffmann *et al*., 2003; Kameritsch *et al*.,

2003), but in cardiac myocytes, conduction is decreased by cGMP (Burt & Spray, 1988; Kwak & Jongsma, 1996). On the other hand, it has been shown that conduction of a change in membrane potential in the vascular wall is inhibited after removal of the endothelium (Emerson & Segal, 2000; Segal & Jacobs, 2001; Takano *et al*., 2004). Although this finding has been interpreted to indicate the current runs in the endothelium, it is also possible that this may reflect inhibition of a positive effect of cGMP on SMC gap junctional conductance. If this is correct, it would support a role for gap junctions in mediating the cGMP dependence of vasomotion.

It is well documented that endothelial cells can exhibit oscillations in Ca^{2+} (Jacob *et al*., 1988; Sage *et al*., 1989; Laskey *et al*., 1992; Kasai *et al*., 1997; Paltauf-Doburzynska *et al*., 2000), which take the form of waves (Kasai *et al*., 1997). Oscillations of endothelial membrane potential are also reported (Laskey *et al*., 1992; Segal & Beny, 1992; der Weid & Beny, 1993). Furthermore, the oscillations of $[Ca^{2+}]_i$ can be synchronized between the endothelial cells both in primary culture (Laskey *et al*., 1992) and in the intact artery (Schuster *et al*., 2001), and it is suggested that the Ca^{2+} oscillations drive oscillations in membrane potential (Laskey *et al*., 1992). The observation that the endothelial Ca^{2+} oscillations in the intact vascular wall are not always synchronized, for example, during activation with acetylcholine (Huang *et al*., 2000; Marie & Beny, 2002), suggests that endothelial membrane potential is not always important for endothelial cell $[Ca^{2+}]_i$. Whether under some circumstances oscillations in endothelial membrane potential can drive oscillations in endothelial $[Ca^{2+}]_i$ is not known. In this respect, it would be very interesting to know whether synchronized oscillations in endothelial $[Ca^{2+}]_i$ occurs in situations where the endothelial membrane potential is clamped. If this can occur, it becomes very relevant to understand which mechanism can cause the synchronization of endothelial cell Ca^{2+} oscillations. One possibility might be diffusion of Ca^{2+}, IP_3 (Boitano *et al*., 1992; Demer *et al*., 1993) or another second messenger through gap junctions between the endothelial cells. This, however, needs experimental testing or testing with a quantitative modelling approach. The endothelial cells may therefore have the capacity to pace directly the vascular SMCs and be responsible for vasomotion, but so far nobody has provided evidence that this might be the case.

Theoretical models of vasomotion

In the foregoing sections, we have discussed experiments that have addressed the question of which mechanisms are responsible for vasomotion and the schemes based on these experiments that have suggested an explanation for vasomotion. In this section, we will summarize those attempts that have been made to mathematically model these suggestions based on quantitative considerations.

There is a large body of literature dealing with models of oscillations of $[Ca^{2+}]_i$, primarily in nonexcitable cells. This work is of obvious interest in the context of vasomotion.

Membrane oscillators (Figure 3) underlie oscillation in a number of cell types, and have been extensively modelled in, for example, sinoatrial node cells (Noble & Noble, 1984; Kurata *et al*., 2003; Ono *et al*., 2003) and in pituitary cells (Li *et al*., 1995; Tomic *et al*., 1999). These generally depend on alternating activation of various depolarizing currents (such as calcium or sodium currents) and hyperpolarizing currents (typically potassium currents). In membrane oscillators, the feedback signal is often provided by voltage dependence, or by, for example, calcium feedback on ion channels; phase delay is often provided by time-dependent currents.

With respect to cytosolic oscillators, a useful overview of simple models for the generation of oscillations in $[Ca^{2+}]_i$ is given by Goldbeter (1996). In the simple models presented by Goldbeter, the feedback is the facilitation of Ca^{2+} release by $[Ca^{2+}]_i$, and the phase shift is caused by the emptying–refilling of the SR. The facilitation of Ca^{2+} release, in other words CICR, could be modelled either *via* the ryanodine receptor or *via* the IP_3 receptor. This is a critical component of systems producing Ca^{2+} oscillations. A very simple system, comprising an intracellular store with one of these receptors and a reuptake mechanism refilling the store, can theoretically suffice for oscillation. $[Ca^{2+}]_i$ in such a system is primed by agonist-induced IP_3 elevation setting $[Ca^{2+}]_i$ to a level on top of which the CICR system oscillates. Another important conclusion from this analysis is that a system where Ca^{2+} simply overflows after refilling, with no CICR, is not able to sustain oscillation.

Most of these simple models incorporate the positive feedback into the Ca^{2+} release channel (be it either the ryanodine or the IP_3 receptor). Interestingly, Meyer & Stryer (1988) found that in a model where the positive feedback was by Ca^{2+} on IP_3 generation and not on the IP_3 receptor, only a bistable $[Ca^{2+}]_i$ was obtained: $[Ca^{2+}]_i$ switched from low to high at a critical level of PLC activity. However, if an additional pathway for Ca^{2+} sequestration (*via* mitochondria) was included, spike-like oscillation emerged. Thus, a limit on the positive feedback may be required for oscillation.

Extensions of the models by Goldbeter are reviewed by Schuster *et al*. (2002), covering not only minimal models but also more involved models. As pointed out by these authors, mitochondrial Ca^{2+} sequestration may be important in Ca^{2+} oscillations for several reasons: maintaining the amplitude of Ca^{2+} oscillations constant over a large frequency range, and limiting the Ca^{2+} peaks so as not to induce apoptosis, which might be initiated by high Ca^{2+} levels.

The multitude of models of cytosolic Ca^{2+} oscillators can be regarded as a demonstration of the inherent strong tendency to oscillation of the SR calcium release mechanism. The modelling here is consistent with experimental findings.

Only a few attempts have been made to comprehensively model the mechanisms underlying vasomotion. Griffith and collaborators have modelled the cellular mechanisms underlying the complex vasomotion of the rabbit ear artery (Parthimos *et al*., 1999). The various patterns of oscillation that can be provoked in this artery can be modelled rather precisely by a combination of an intracellular oscillator and a membrane oscillator.

The intracellular oscillator was modelled like those described above: a cytosolic oscillator depending on ryanodine-receptor CICR to release Ca^{2+} from the SR in an oscillating manner. The sequestration into and release of Ca^{2+} from this store produce oscillation but do not affect $[Ca^{2+}]_i$, and thus do not influence the average contraction level. This suggests that here vasomotion may be regarded as oscillation around a mean, not as superimposed contractions or relaxations on a steady contraction.

The membrane oscillator was modelled as direct or indirect Ca^{2+} feedback on a multitude of transport processes in the membrane: Ca^{2+} channels, calcium-activated K^+ channels, Cl^- channels, plasma membrane Ca^{2+}-ATPase, Na^+/Ca^{2+} exchange and the Na^+,K^+-ATPase. Ca^{2+} entry through voltage-gated channels is the central mechanism here, co-ordinating other membrane events. However, in this model, the only ion channel directly sensing Ca^{2+} is the calcium-activated potassium channel. Depolarizing effects of intracellular Ca^{2+} are thus not included.

Either the cytosolic or the membrane oscillator alone can induce oscillation in this model. The membrane oscillator is responsible for fast oscillation (period less than a minute), while the cytosolic oscillator is slower. Interestingly, including the latch state of smooth muscle in the model (force being carried by slowly cycling, dephosphorylated crossbridges) dampened the oscillations even to a point where those due to the fast (membrane) oscillator were no longer visible.

The model of Parthimos *et al*. (1999) correlates well with available experimental data, and explains how oscillations in the individual cell may occur, but does not deal with multiple cells. The other aspect of vasomotion – synchronization – has been accommodated in three recent models (Imtiaz *et al*., 2002; Jacobsen, 2004; Koenigsberger *et al*., 2004).

Imtiaz *et al*. (2002) studied slow waves in gastrointestinal muscle (in the presence of L-type channel blockers) (van Helden *et al*., 2000), and found these to be favoured by agonists, suggesting an important contribution of IP_3. They were also favoured by depolarization, which was taken as an indication of an influence of membrane potential on IP_3 generation. In the model, which is based on a cytosolic oscillator model, Ca^{2+} release is assumed to trigger membrane channels to open and cause depolarization. This is assumed to spread between cells *via* gap junctions and to promote IP_3 formation throughout the tissue. The positive feedback here is the indirect feedback of Ca^{2+} release on IP_3 production, further enhancing release. However, direct evidence for IP_3 oscillation is still lacking.

The model of Jacobsen (2004) is based on the experimental data of Peng *et al*. (2001). This model is similar to that of Imtiaz *et al*. (2002), although cell coupling here is mediated by the effect of depolarization on L-type Ca^{2+} channels, not on IP_3 formation (in contrast to the model of Imtiaz *et al*. (2002), L-type channels were functional in this model). In both this and Imtiaz' models, spread of depolarization between cells is assumed to be *via* gap junctions and to be responsible for the synchronization.

The model by Koenigsberger *et al*. (2004) is based on the model by Parthimos *et al*. (1999) with respect to the cellular oscillator, but was expanded to a multicellular tissue by including cell connections. In contrast to the two models described above, this model does not include calcium-sensitive depolarizing ion channels. Interestingly, in this model electrical coupling alone was not sufficient to induce synchronization of calcium oscillations – a certain calcium permeability through gap junctions was necessary. This model also suggested that electrical communication may be a two-edged sword: a high degree of electrical coupling may accentuate the current–sink effect of neighbouring cells and therefore reduce the chances of membrane potential synchronization. Both this model and that of Jacobsen (2004) are based on data from the same tissue, but have different starting points. It would be interesting to see the influence on the Koenigsberger model of the inclusion of calcium-sensitive depolarizing channels.

Conclusion

Vasomotion has been observed for more than a 100 years, is probably present in every vascular segment and has been a nuisance to many vascular researchers who want to ascribe a well-defined tone to their preparation under a given condition; yet, the physiological and possible pathophysiological function is still not known. Based on this background, it is important to try to understand the cellular mechanisms leading to vasomotion, so as to hopefully provide instruments that can be used to interfere with vasomotion in specific ways.

Our understanding of the cellular mechanisms responsible for the synchronized oscillatory activity of the SMCs has improved substantially in recent years. In most situations, a cytosolic oscillator appears to be important because vasomotion is very sensitive to interference with release or uptake of Ca^{2+} from intracellular stores. Furthermore, to achieve synchronization of the cytosolic oscillators in the individual SMCs, it has been suggested that the cytosolic oscillator interacts with the membrane to establish membrane-potential changes that mediate the synchronization. Other types of oscillations, either based solely on interactions of ion currents in the sarcolemma or based on oscillations of the glycolytic pathway and consequently the Na,K-pump, have also been suggested and could play a role under some conditions, although these pathways are probably less frequent.

With tone as a relatively straightforward read-out and with well-developed techniques to study the details of excitation–contraction coupling in SMCs, we believe that the attempts to unravel the mechanism of vasomotion not only will provide information of value for vascular physiology and pharmacology but also will provide novel information on mechanisms of cell oscillation and cell synchronization in many other areas of cell biology.

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