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Review

Endothelium-dependent hyperpolarization of vascular smooth muscle cells

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KEY WORDS arachidonic acid; cytochrome P-450; vascular endothelium; gap junctions; hyperpolarization; nitric oxide; potassium channels; epoprostenol; vascular smooth muscle; electrophysiology

ABSTRACT

In response to various neurohumoral substances endothelial cells release nitric oxide (NO) and prostacyclin, and produce hyperpolarization of the underlying vascular smooth muscle cells, possibly by releasing another factor termed endothelium-derived hyperpolarizing factor (EDHF). NO and prostacyclin stimulate smooth muscle soluble guanylate and adenylate cyclase respectively and can activate, depending on the vascular tissue studied, ATP-sensitive potassium (K_{ATP}) and large conductance calcium-activated potassium channels (BK_{Ca}). Furthermore, NO directly activates BK_{Ca}. In contrast to NO and prostacyclin, EDHF-mediated responses are sensitive to the combination of charybdotoxin plus apamin but do not involve K_{ATP} or BK_{Ca}. As hyperpolarization of the endothelial cells is required to observe endothelium-dependent hyperpolarization, an electric coupling through myoendothelial gap junctions may explain the phenomenon. An alternative explanation is that the hyperpolarization of the endothelial cells causes an efflux of potassium that in turn activates the inwardly rectifying potassium conductance and the Na^+/K^+ pump of the smooth muscle cells. Therefore, in some vascular tissue K^+ could be EDHF. Endothelial cells produce metabolites of the cytochrome P-450-monooxygenase that activate BK_{Ca}, and induce hyperpolarization of coronary arterial smooth muscle cells. Whether or not EDHF could be an epoxyeicosatrienoic acid is still a matter of debate. The elucidation of the mechanism underlying endothelium-dependent hyperpolarizations and the discovery of specific inhibitors of the phenomenon are prerequisite for the understanding of the physiologic role of this alternative endothelial pathway involved in the control of vascular tone in health and disease.

1 INTRODUCTION

Endothelial cells synthesize and release vasoactive mediators not only in response to various neurohumoral (eg acetylcholine, adenosine triphosphate, bradykinin, thrombin) and chemical substances (toxins, alkaloids) but also in response to physical stimuli such as shear stress exerted by the flowing blood and mechanical stress induced by isometric contraction[1-5]. In blood vessels from numerous species, including humans, endothelium-dependent relaxations are accompanied by hyperpolarization of vascular smooth muscle cells[6-13]. When specific inhibitors of NO-synthases became available[14], it became obvious that endothelium-dependent relaxations and/or hyperpolarizations can be more or less resistant to the inhibition of both cyclooxygenases and NO synthases[15-24]. For instance, as shown in Fig 1, in canine coronary artery, bradykinin induces an endothelium-dependent relaxation which is affected minimally by the presence of inhibitors of nitric oxide synthases and cyclooxygenases.

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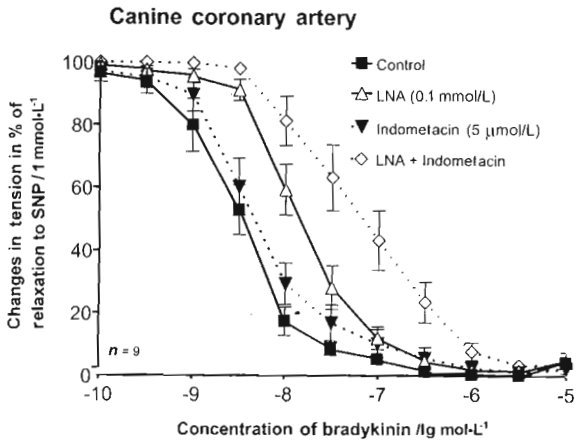

Fig 1. Endothelium-dependent relaxation resistant to inhibitors of cyclooxygenases and nitric oxide synthases. Concentration-relaxation curves to cumulative addition of bradykinin in canine coronary artery.

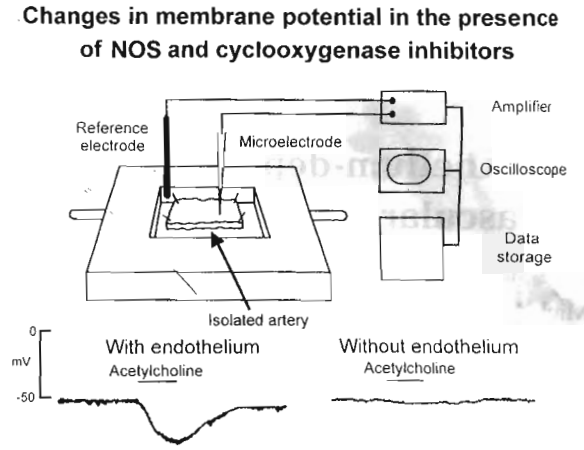

Fig 2. Endothelium-dependent hyperpolariztion in human coronary artery. Recording of endothelium-dependent hyperpolarization.

Furthermore, endothelium-dependent responses, which are resistant to inhibitors of NO synthases and cyclooxygenases, are observed without an increase in intracellular levels of cyclic nucleotides (cyclic GMP and cyclic AMP) in the smooth muscle cells[10,17,25-28]. Thus another unidentified substance (s) termed endothelium-derived hyperpolarizing factor (EDHF), must contribute to endothelium-dependent relaxations[2,29-34]. Endothelium-dependent hyperpolarizations and/or relaxations resistant to inhibitors of nitric oxide synthase and cyclooxygenase are also present in various human blood vessels including coronary arteries[12,35] (Fig 2).

2 ENDOTHELIUM-DERIVED MEDIATORS AND HYPERPOLARIZATION OF VASCULAR SMOOTH MUSCLE

2.1 Prostacyclin

The relaxations caused by prostacyclin, the principal metabolite of arachidonic acid produced by cyclooxygenase in most blood vessels[36,37], involve the stimulation of specific receptors and activation of adenylate cyclase leading to an elevation of intracellular cyclic-AMP. Prostacyclin or its stable analogues (iloprost or cicaprost) induce hyperpolarization of vascular smooth muscle cells from various species. In most of the blood vessels, these hyperpolarizations involve the opening of ATP-sensitive potassium channels (K_{ATP}) and are blocked by sulfonylureas such as glibenclamide[38-43] (Fig 3,4).

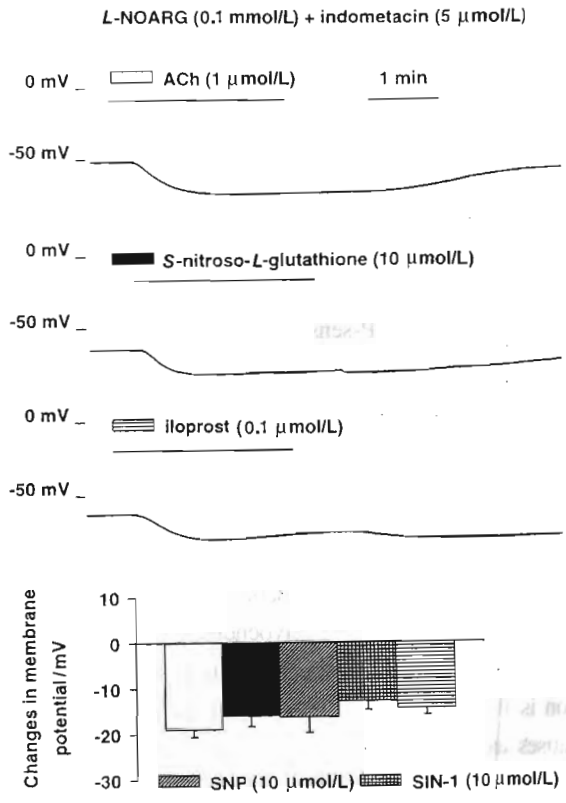

Fig 3. Endothelium-dependent hyperpolariztion and hyperpolarization to nitrovasodelators and iloprost in the guinea-pig carotid artery. The bar graph at the bottom of the figure shows $\bar{x} \pm s_{\bar{x}}$ of the hyperpolarizing responses.

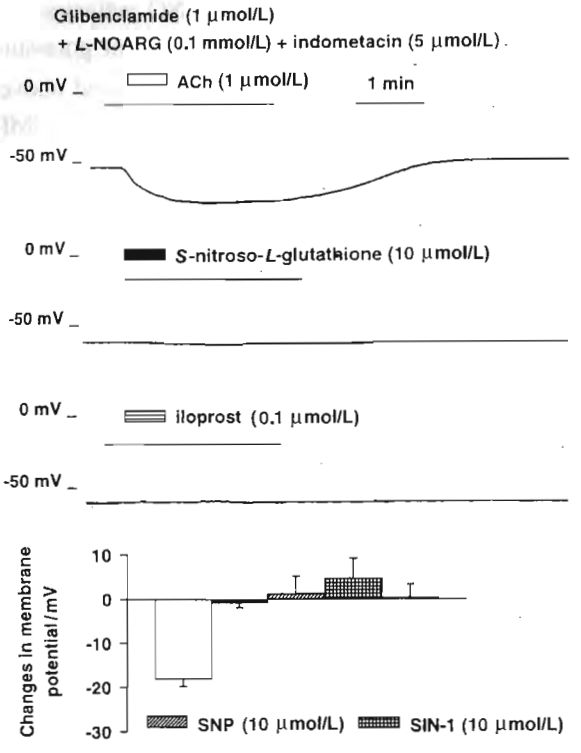

Fig 4. Endothelium-dependent hyperpolariztion and hyperpolarization to nitrovasodelators and iloprost in the guinea-pig carotid artery. Effect of an inhibitor of ATP-sensitive potassium channels. The bar graph at the bottom of the figure shows $\bar{x} \pm s_x$ of the responses.

In the tail artery of the rat, prostacyclin and iloprost activate not only K_{ATP} but also large conductance calcium-activated potassium channels (BK_{Ca}) by a mechanism involving protein kinase A-dependent phosphorylation of the latter[44,45]. In isolated smooth muscle cells of the bovine coronary artery, prostacyclin opens a 4-aminopyridine-sensitive delayed rectifier potassium channel (Kdr) without affecting BK_{Ca}[46]. In contrast, in the isolated coronary artery of the rat, prostacyclin and iloprost do not provoke hyperpolarization[40].

The contribution of the hyperpolarization in the relaxation to prostacyclin can be very significant in some tissues (rabbit coronary artery[39]; rat tail artery[45]) while in others, such as the guinea-pig coronary artery, blockade of hyperpolarization does not affect the relaxation produced by iloprost[41]. Finally, in many blood vessels inhibitors of cyclooxygenases have no or little effects ruling out a role for endogenous prostaglandins in the phenomenon (Fig 1).

2.2 Nitric oxide (NO)

NO is produced by the *L*-arginine-NO synthase pathway[47-51]. Its principal physiological action is associated with the activation of cytosolic soluble guanylate cyclase and the consequent formation of cyclic-GMP[52], but endothelial NO has many other targets on smooth muscle cells including potassium channels[53].

Sodium nitroprusside or nitroglycerin cause hyperpolarization of vascular smooth muscle in the rabbit pulmonary and portal vein[54,55]. The hyperpolarization produced by NO and/or NO donors in the coronary, carotid arteries, and mesenteric lymphatic vessels of the guinea-pig[40,43,56], in the mesenteric artery of the rat[57] as well as in the mesenteric and femoral artery of the rabbit[58,59] are sensitive to glibenclamide, suggesting implication of K_{ATP} channels (Fig 3,4).

In the mesenteric artery of the rat, NO no longer produces hyperpolarization when the cells are contracted and depolarized[57]. Conversely, in carotid and femoral arteries of the rabbit, uterine arteries of the guinea-pig or mesenteric arteries of the dog, NO and nitrovasodilators do not produce hyperpolarization in resting tissue, but repolarize smooth muscle cells previously depolarized by an agonist[59-61]. In some tissues such as the mesenteric artery of the rabbit, to observe hyperpolarization in response to nitrovasodilators, endogeneous production of NO has to be suppressed either by endothelium removal or with a nitric oxide synthase inhibitor[58]. Finally, in some blood vessels such as the canine and porcine coronary arteries, the hepatic artery and the portal vein of the rat as well as in the basilar artery of the rabbit, NO or/and nitrovasodilators do not influence the resting membrane potential[57,62-68].

Electrophysiological experiments involving different configurations of the patch-clamp technique have characterized the potassium channels activated by NO. Activation of K_{ATP} by NO has been demonstrated in isolated smooth muscle cells of the carotid artery of the guinea-pig[69] (Fig 5) and of the porcine coronary artery[70]. These patch-clamp experiments confirm previous microelectrode experiments showing that, in the smooth muscle cells of the guinea-pig carotid artery, NO activates K_{ATP} channels[69] (Fig 5).

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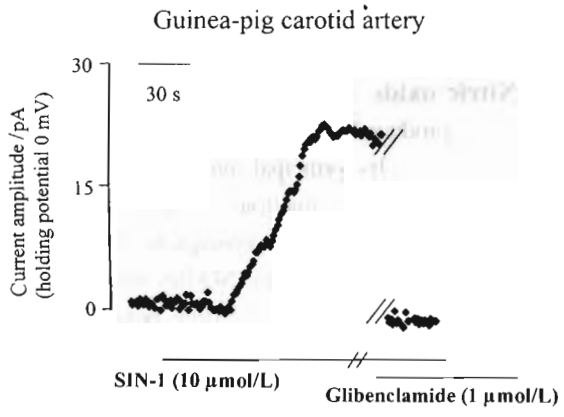

Fig 5. Effects of SIN-1 on K_{ATP} current amplitude in freshly isolated vascular smooth muscle cells of the guinea-pig carotid artery.

However, NO activates BK_{Ca} in isolated smooth muscle cells of cerebral, carotid arteries, and in the aorta of the rabbit[69,71,72] (Fig 6), pulmonary, coronary, mesenteric and cerebral arteries of the rat[73-77], canine coronary artery[78], and human pulmonary and coronary arteries[79,80].

In the bovine coronary artery, NO activates both BK_{Ca} and delayed rectifier voltage-dependent potassium channels[47]. In most of the tissues mentioned above, the activation of BK_{Ca} is dependent upon cyclic-GMP-dependent protein kinase[78]. However, NO produces a cyclic-GMP-independent activation of BK_{Ca} (direct effect) in smooth muscle cells from the rabbit aorta[72] and the mesenteric artery of the rat[76].

When these various observations are taken in conjunction, the effects of NO on vascular smooth muscle potassium channels appear complex. This complexity has several possible explanations: (a) a heterogeneous population of potassium channels may be expressed by vascular smooth muscle cells[81]; (b) repolarization and hyperpolarization of the smooth muscle cells may involve different mechanisms (indeed, in resting canine coronary arteries, nitroglycerin, NO or sodium nitroprusside do not produce hyperpolarization[62,64,67], while in contracted arteries nitroglycerin induces a relaxation sensitive to iberiotoxin[82] and in isolated smooth muscle cells of the same artery NO stimulates

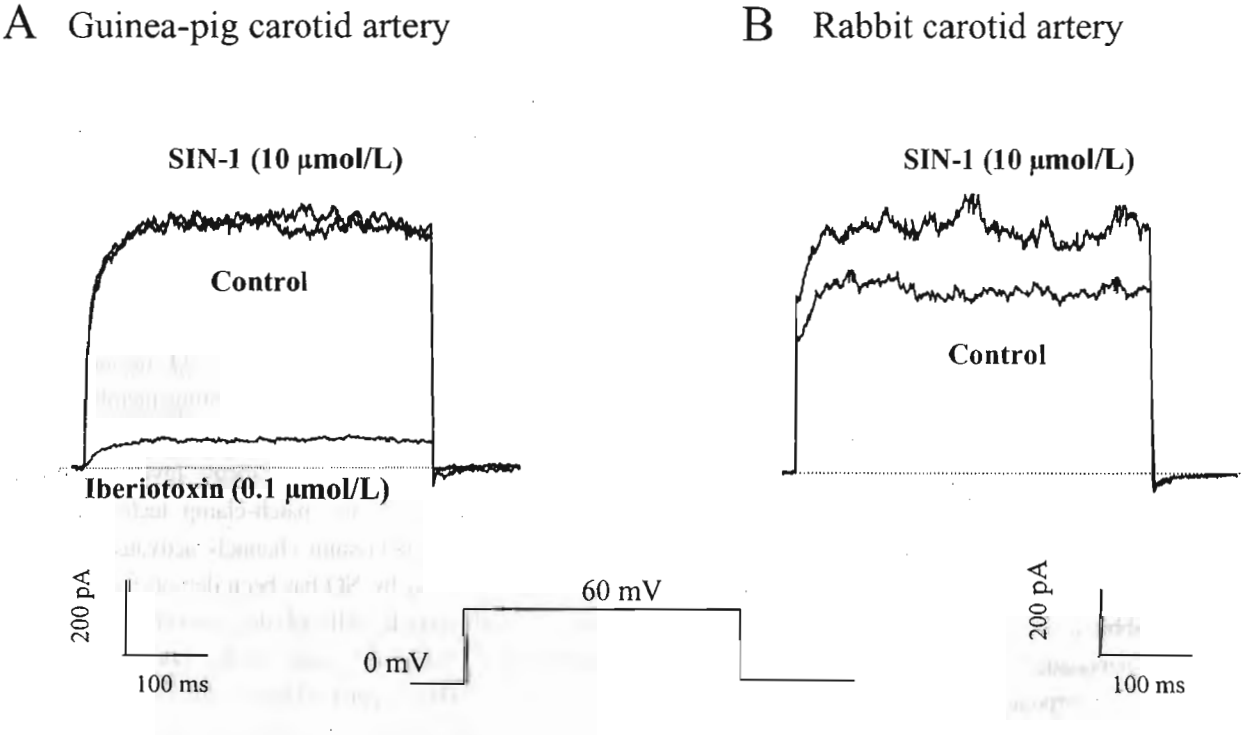

Fig 6. Effects of SIN-1 on whole cell K_{Ca} potassium currents in freshly dissociated vascular smooth muscle cells of guinea-pig (A) and rabbit (B) carotid arteries.

BK_{Ca}[78]); (c) hyperpolarization of the smooth muscle cells may not be the predominant mechanism of relaxation; and (d) different populations of potassium channels could be activated by different forms of NO (endogenous endothelial nitric oxide, exogeneous authentic NO or NO released by nitrovasodilators[83]).

2.3 EDHF

2.3.1 Possible mechanisms

Endothelium-dependent hyperpolarization resistant to inhibitors of NO synthases and cyclooxygenases may involve electrical coupling through myoendothelial junctions[84,85]. Indeed, substances which produce endothelium-dependent hyperpolarization of vascular smooth muscle cells also hyperpolarize endothelial cells, with the same time course[86]. Gap junctions couple smooth muscle and endothelial cells, and conduction of depolarization and hyperpolarization from smooth muscle cells to endothelial cells has been demonstrated[87,88]. In the porcine coronary artery, electrical propagation from endothelial to smooth muscle cells does not seem to occur[86,88] while in guinea-pig mesenteric arterioles hyperpolarization from endothelial to smooth muscle cells has been demonstrated[89,90]. However, conflicting results have been obtained with the non-specific gap junction uncoupler heptanol. It inhibited EDHF-responses in porcine coronary artery[91] but it did not affect these responses in rat hepatic artery[92] or in human coronary artery (unpublished observations). More specific blockers of gap junctions, 18β-glycyrrhetinic acid and Gap27 (a peptide which possesses a conserved sequence homology with a portion of connexin) inhibit EDHF-like responses in rabbit and guinea-pig arteries[89,90,93,94]. At present, this mechanism needs to be explored further to better understand its potential contribution to endothelium-dependent hyperpolarizations.

Endothelium-dependent hyperpolarizations resistant to inhibitors of NO synthases and cyclooxygenases can also be attributed to the release of a diffusable substance. Indeed, its existence has been demonstrated, using conventional intracellular micro-electrode or patch-clamp techniques, under bioassay conditions whereby the source of EDHF was either native vascular segments or cultured endothelial cells[8,28,59,95-99].

The opening of a potassium conductance as the mechanism of EDHF-mediated responses is suggested by the following findings: (a) the amplitude of the hyperpolarization is inversely related to the extracellular concentration of K^+ ions, and it disappears in K^+ concentrations higher than 25×10^{-3} mol/L[101-104]; (b) non-selective inhibitors of calcium-dependent potassium channels, such as tetraethylammonium or tetrabutylammonium prevent the hyperpolarization[96,102-105]; and (c) endothelium-dependent hyperpolarizations are associated with an increase in rubidium efflux[10,11] and a decrease in membrane resistance which suggest that the hyperpolarization is due to the opening and not to the closing of a conductance[6,101-106].

In various tissues, apamin (specific inhibitor of small conductance calcium-activated potassium channels), alone or in combination with charybdotoxin (non-specific inhibitor of calcium-activated potassium channels) inhibit the responses attributed to EDHF[42,43,57,92,104,107,108] (Fig 3,7).

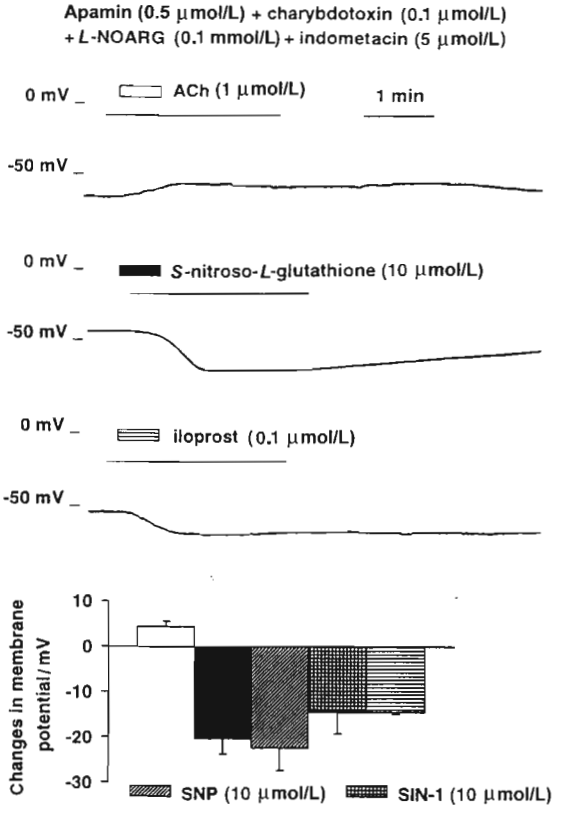

Fig 7. Endothelium-dependent hyperpolariztion and hyperpolarization to nitrovasodilators and iloprost in the guinea-pig carotid artery. Effect of the combination of two toxins apamin plus charybdotoxin. The bar graph at the bottom of the figure shows $\bar{x} \pm s_{\bar{x}}$ of the responses.

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However, the combination of iberiotoxin (specific inhibitor of BK_{Ca}) plus apamin did not mimic the effects of charybdotoxin and apamin[92,107,109-111] indicating that BK_{Ca} channels are not involved in the endothelium-dependent hyperpolarizations. In contrast, the effect of apamin could be mimicked by scillatoxin, a structurally different SK_{Ca} inhibitor, suggesting that SK_{Ca} plays a role in endothelium-dependent hyperpolarizations. The site of action of the various potassium channel inhibitors could be the smooth muscle cells (eg inhibition of the action of EDHF) or the endothelial cells (eg inhibition of synthesis and/or release of EDHF). Indeed, calcium-activated potassium channels are also expressed in endothelial cells[112]. In the endothelial cells of the guinea-pig coronary artery, the combination of apamin plus charybdotoxin does not affect the acetylcholine-induced increase in intracellular free calcium concentration[111]. However, in the hepatic artery of the rat and in the aortic valve of the rabbit, the combination of charybdotoxin plus apamin inhibits the hyperpolarization of the endothelial cells produced by acetylcholine[113,114]. Furthermore, in the mesenteric artery of the rat, charybdotoxin and apamin block EDHF-mediated responses if selectively applied to the endothelium[115]. Finally, the existence of a potassium conductance specifically sensitive to the combination of charybdotoxin plus apamin could not be detected in isolated vascular smooth muscle cells[108,110] (Fig 8).

Thus, charybdotoxin and apamin can act on the endothelial cells and this endothelial effect might be responsible for the inhibition of the responses to EDHF.

2.3.2 Putative candidates as EDHF

Endothelial cells can release various vasoactive substances such as adenine nucleotides (AMP, ADP, ATP) and adenosine[116,117], metabolites of arachidonic acid (through the cytochrome P-450 or the lipoxygenase pathways including epoxyeicosatrienoic acids[28,118,119], trihydrooxyeicosatrienoic acids[120] and 12-hydroxyeicosatetraenoic acid[121,122]), anandamide (presumed to be the endogenous ligand for the cannabinoid CB_1 receptor[123-125]), carbon monoxide[126], hydroxyl radicals[127,128], hydrogen peroxide[129], and potassium ions[130].

2.3.2.1 Potassium ions In certain vascular beds such as the coronary and cerebral arteries of the rat, increasing the extracellular concentration of potassium ions (up to 15 mmol/L) relaxes the blood vessels and hyperpolarizes the smooth muscle cells[131-133]. These hyperpolarizations, induced by potassium, are inhibited by concentrations of barium lower than 0.1 mmol/L, an inhibitor of inward rectifying potassium conductance (K-ir) at these concentrations[134]. The open state

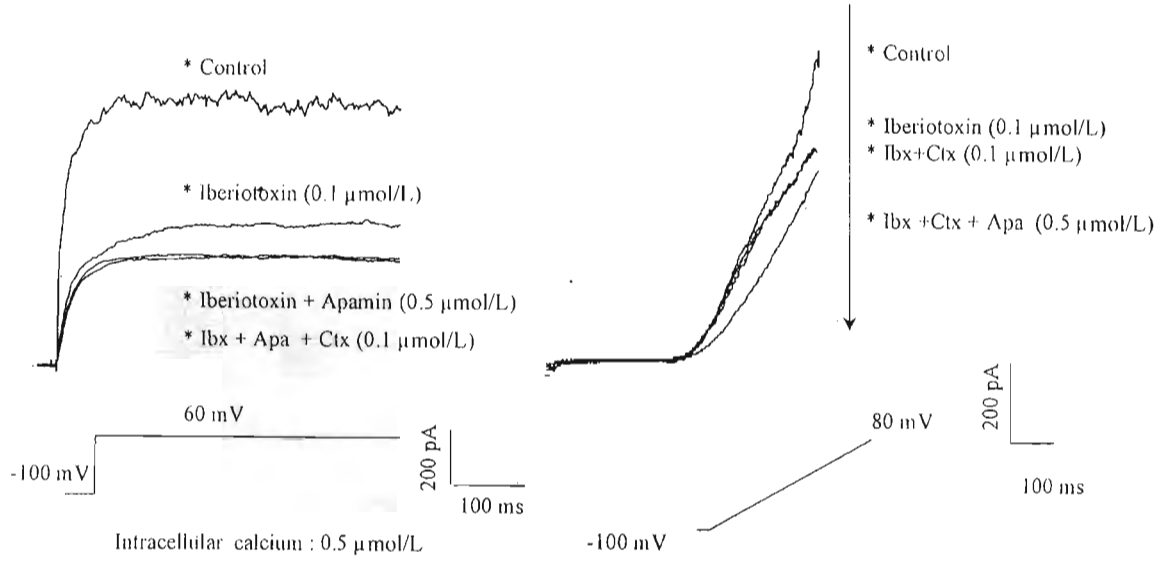

Fig 8. Absence of a potassium channel specifically sensitive to the combination of charybdotoxin plus apamin in freshly isolated smooth muscle cells of the guinea-pig carotid artery.

probability of K-ir is increased by a modest rise in extracellular potassium concentration[135]. The level of expression of K-ir channel in vascular smooth muscle cells is inversely related to the size of the blood vessels. Thus, the expression of K-ir is more preponderant in smaller blood vessels. This explains the different effect of potassium in small and large blood vessels[131]. A rise in extracellular potassium can also cause hyperpolarization and relaxation of the vascular smooth muscle cells by activating the Na^+/K^+ pump without involvement of K-ir[136].

Agonists which produce endothelium-dependent relaxations generate potassium efflux from vascular endothelial cells[130]. Edwards *et al*[113] have suggested that, in the rat hepatic artery, potassium ions are EDHF. The stimulation by acetylcholine of endothelial receptors opens charybdotoxin and apamin-sensitive potassium conductance on the endothelial cell membrane leading to a potassium efflux and its accumulation in the intercellular space. The rise in potassium activates K-ir and the Na^+/K^+ pump in smooth muscle cells provoking hyperpolarization and relaxation sensitive to the combination of barium and ouabain[113].

However, this cannot be generalized to all vascular beds. In guinea-pig carotid and porcine coronary arteries, the endothelium-dependent hyperpolarizations are not affected by the combination of barium plus ouabain and K^+ does not produce hyperpolarizations, possibly because of the poor expression of K-ir[104] (Fig 9, 10). These results suggest that potassium is not EDHF at least in these two blood vessels.

2.3.2.2 Epoxyeicosatrienoic acids In some tissues EDHF may be a short-lived metabolite of arachidonic acid produced through the cytochrome P-450 monooxygenase pathway[29,137]. In the perfused heart and kidney of the rat and in human isolated renal as well as in porcine, bovine, and human coronary arteries, inhibitors of this pathway inhibit endothelium-dependent vasodilator responses attributed to EDHF[138~145]. Muscarinic agonists induce not only endothelium-dependent relaxation and hyperpolarization of bovine coronary arterial smooth muscle but also the release of epoxyeicosatrienoic acids from bovine coronary arterial endothelial cells[118,146]. Epoxyeicosatrienoic acids relax most blood vessels[118,144,147~150], hyperpolarize coronary arterial smooth muscle cells[118,148] and increase the open-state probability of large conductance calcium-activated potassium channels sensitive to tetraethylammonium, charybdotoxin or iberiotoxin[28,46,118,147,151,152]. In isolated smooth muscle cells

Effects of ouabain plus barium in the guinea-pig isolated carotid artery

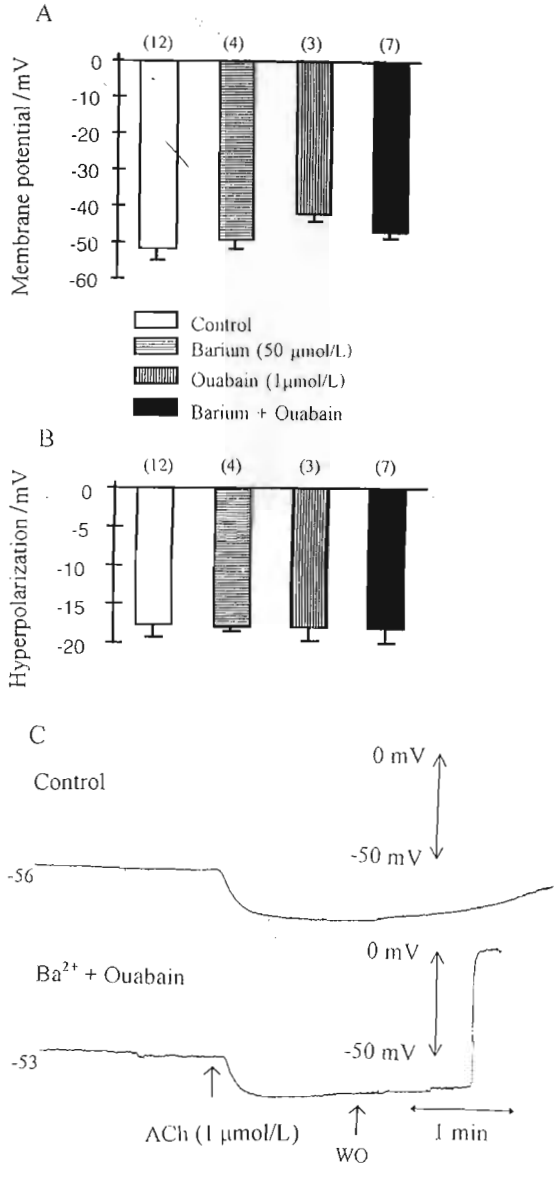

Fig 9. Potassium ion is not EDHF in the guinea-pig carotid artery. Data are shown as $\bar{x} \pm s_x$, numbers in brackets indicate the number of experiments. A) Resting membrane potential. B) Hyperpolarization elicited by acetylcholine. C) Original traces showing the endothelium-dependent hyperpolarizations elicited by acetylcholine (1 μmol/L) in control condition (upper trace) and in the presence of the combination of barium (50 μmol/L) plus ouabain (1 μmol/L, lower trace).

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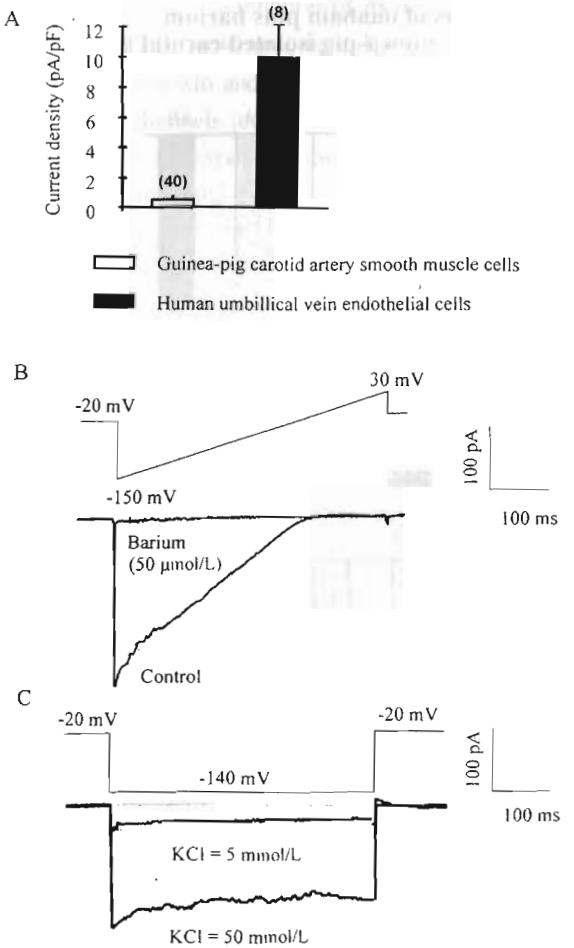

Fig 10. Inwardly rectifying potassium currents in isolated vascular smooth muscle cells of the guinea-pig carotid artery and in isolated endothelial cells of the human umbilical vein. Data are shown as $\bar{x} \pm s_x$, numbers in brackets indicate the number of experiments. A) Comparison of the inwardly rectifying, barium sensitive, potassium current density at − 150 mV (holding potential − 20 mV) in isolated vascular smooth muscle cells of the guinea-pig carotid artery and in endothelial cells of the human umbilical vein. The density of current recorded in the smooth muscle cells of the guinea-pig carotid artery is significantly lower than the density recorded in the endothelial cells of the human umbilical vein. B) Effect of barium (50 μmol/L) in a freshly isolated vascular smooth muscle cell of the guinea-pig carotid artery expressing an inwardly rectifying potassium current (ramp depolarisation from − 150 mV to + 30 mV, holding potential: − 20 mV). C) Effect of reducing the potassium concentration from 50 mmol/L to 5 mmol/L in the amplitude on the inwardly rectifying potassium current in a freshly isolated vascular smooth muscle cell of the guinea-pig carotid artery (holding potential − 20 mV, hyperpolarizing pulse to − 140 mV)[104].

of the bovine coronary artery, 11, 12 epoxyeicosatrienoic acid activates BK_{Ca}, in a cyclic-AMP and cyclic-GMP-independent manner, through a guanine nucleotide binding protein, Gsα, suggesting the possible existence of specific receptors to epoxyeicosatrienoic acids on the membrane of these cells[153]. Bradykinin stimulates the release of a transferable factor from isolated bovine and porcine coronary areries as well as from cultures of human umbilical vein endothelial cells that produced activation of BK_{Ca} and hyperpolarization of vascular smooth muscle cells[28,98,152]. Taken in conjunction, these observations support the hypothesis that epoxyei-cosatrienoic acids act as EDHF in certain blood vessels.

However, cytochrome P-450 inhibitors, studied at high concentrations, are notoriously unspecific and can inhibit hyperpolarizations induced by potassium channel openers such as levcromakalim[30,154-156]. In other studies involving blood vessels from humans (coronary and omental arteries), rats, guinea-pigs, dogs, and pigs, chemically unrelated inhibitors of cytochrome P-450 do not inhibit the EDHF responses or produce a non-specific inhibition[35,103,107,144,157-159]. In guinea-pig carotid arteries, epoxyeicosatrienoic acids do not produce relaxation or hyperpolarization (Fig 11).

The discrepancies between the various studies presented can be explained in different ways. Without considering the non-specific effects of cytochrome P-450 inhibitors already mentioned, activation of cytochrome P-450 in human endothelial cells appears to be a more general requirement for increasing the intracellular calcium concentration and thus the release of endothelium-derived factors such as NO and EDHF[161] The agonist inducing endothelium-dependent hyperpolarization could be crucial (eg in human arteries: bradykinin vs arachidonic acid[34,145]). Finally, epoxyeicosatrienoic acids produce effects which are not only tissue and/or species specific (bovine coronary and guinea-pig carotid artery for example[107,118]), but can also be markedly different following the size of the vessel studied as in (eg canine coronary artery[150]). Therefore, the fundamental endothelial function of cytochrome P-450, the choice of the agonist and the tissue studied may confuse the issue when interpreting results of studies investigating the effects of inhibitors of cytochrome P-450 on EDHF-mediated responses.

2.3.2.3 Anandamide Anandamide, another

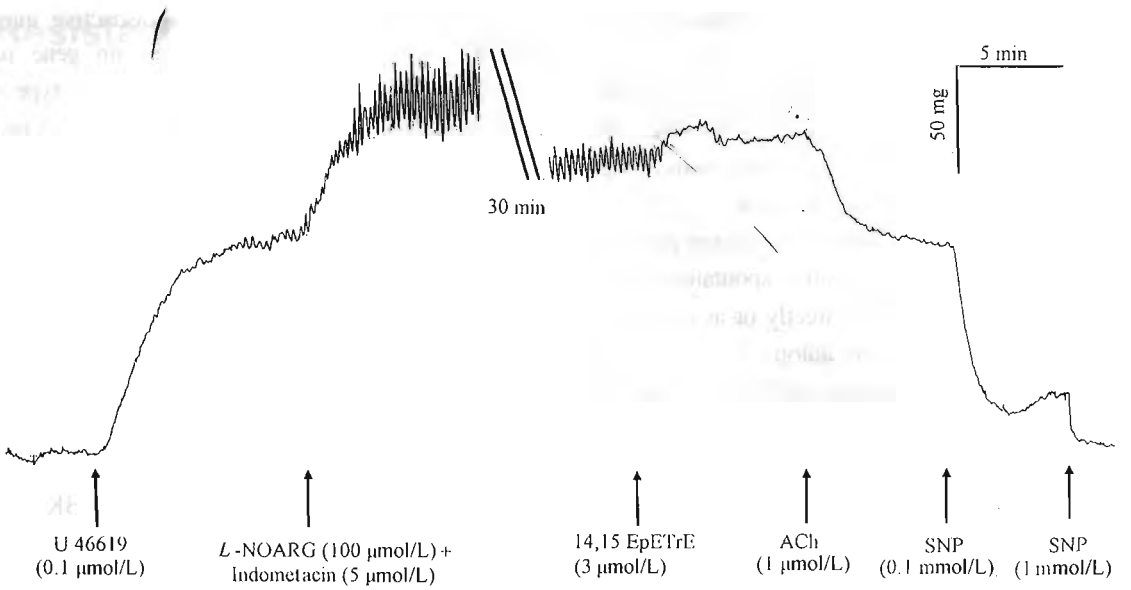

Fig 11. Tension in the isolated guinea-pig internal carotid artery with endothelium.

derivative of arachidonic acid, is supposed to be an endogenous ligand for the cannabinoid CB_1 receptor[123,124]. In the isolated and perfused mesenteric and coronary arterial bed of the rat, anandamide induces a dilatation which mimics responses to EDHF and which is blocked by the combination of charybdotoxin and apamin[125,162-164]. In isolated blood vessels from various species (pig, guinea-pig, rat), anandamide does not produce hyperpolarization or, if it does so, the underlying mechanism differs from EDHF-mediated responses. Indeed some of these responses to anandamide are endothelium-dependent[165,166]. In the kidney of the rat the dilatation caused by anandamide is due to the release of NO[167] and in the rat mesenteric and hepatic as well as in the guinea-pig basilar arteries the vasodilatation is mediated by CGRP released from perivascular sensory nerves after activation of prejunctional VR1 vanilloid receptor[168]. Finally CB_1 receptor antagonists do not inhibit endothelium-dependent hyperpolarization. These observations do not support the suggestion that an endogenous cannabinoid is the major mediator of endothelium-dependent hyperpolarizations[165,166,169-171] (Fig 12).

2.3.2.4 Carbon monoxide The predominant biological source of carbon monoxide is the degradation of heme by heme oxygenase, an enzyme which could be inducible (HO-1) or constitutive (HO-2)[172].

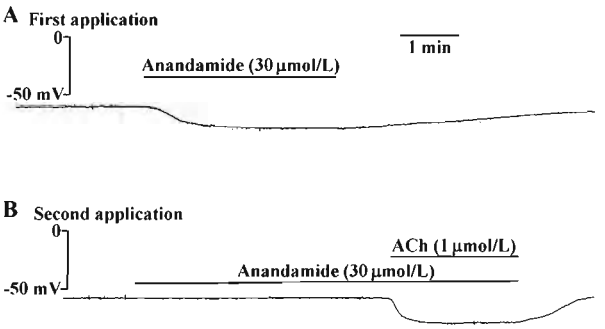

Fig 12. Anandamide is not EDHF in the rat mesenteric artery. Original recording of the smooth muscle membrane potential, in the rat isolated mesenteric artery with endothelium in the presence of *L*-NOARG (0.1 mmol/L) and indometacin (5 μmol/L). Continuous recording from the same smooth muscle cell.

Some arterial endothelial cells express HO-2[172] and the expression of HO-1 in endothelial cells has been demonstrated in the ductus arteriosus of the lamb[124] and in the rat thoracic aorta subjected to hypoxia[173]. Carbon monoxide relaxes and hyperpolarizes vascular and non-vascular smooth muscles by activating soluble guanylate cyclase[172,174,175] and in the rat tail artery by directly opening BK_{Ca} potassium channels[176].

Zinc protoporphyrin Ⅸ, a poorly specific inhibitor of heme oxygenase, does not inhibit endothelium-

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dependent hyperpolarizations in the rat hepatic artery or in the guinea-pig carotid artery[92,177]. Furthermore carbon monoxide is scavenged actively by oxyhemoglobin which in a variety of blood vessels does not affect endothelium-dependent hyperpolarizations, suggesting that EDHF is not carbon monoxide.

2.3.2.5 Hydrogen peroxide Hydrogen peroxide can be produced by endothelial cells, spontaneously or in response to bradykinin either directly or as a byproduct of the release of superoxide anion[178,179]. In the isolated rabbit aorta and in canine and porcine coronary arteries, hydogen peroxide, but not superoxide anion or hydroxyl radical, produces relaxation and/or hyperpolarization[129,180,181]. In isolated smooth muscle cells from the rat aorta and the porcine coronary artery, the relaxation and/or hyperpolarization produced by hydrogen peroxide has been attributed to the opening of calcium-activated potassium channels[182,183].

However in porcine coronary arteries, the hyperpolarization produced by hydrogen peroxide and the endothelium-dependent hyperpolarization to either substance P or bradykinin do not have the same time-course. While the former was sensitive to catalase, the latter was not, indicating that, in this blood vessel, EDHF and hydrogen peroxide are two distinct molecules[129].

2.3.2.6 Adenosine Adenine nucleotides (AMP, ADP, ATP) and adenosine are released by endothelial cells[116,117]. Endothelial cells release mainly ATP, but the nucleotide is rapidly transformed into ADP, AMP and adenosine by ectonucleotidases. Adenosine induces relaxation and hyperpolarization of vascular and non-vascular smooth muscle including the human coronary artery[184-186]. In most of the studies the hyperpolarization of the vascular smooth muscle cells involves K_{ATP} channels either through a cyclic-AMP- protein kinase A-dependent pathway[187,188] or, in blood vessels such as the canine coronary, rat pulmonary and porcine retinal arteries, through a cyclic-AMP-independent pathway[189-191]. However, in canine epicardial artery the relaxation produced by adenosine may not involve K_{ATP} but BK_{Ca} channels activation[192,193]. In most blood vessels, EDHF responses do not involve the activation of K_{ATP} or BK_{Ca}; indicating that adenosine-related compounds cannot be considered as putative EDHF.

2.3.2.7 Peptides Endothelial cells may release numerous neuropeptides including, vasoactive intestinal peptide (VIP), substance P, calcitonin gene related peptide (CGRP), arginine-vasopressin or C-type natriuretic peptide (CNP). Some of these peptides produce direct relaxation of the vascular smooth muscle[194].

In rabbit cerebral arteries VIP stimulates adenylate cyclase and produces hyperpolarization by opening K_{ATP} channels[195]. In smooth muscle cells of the porcine coronary artery, VIP activates BK_{Ca} and K-v channels[196]. CGRP opens K_{ATP} channels in the rabbit mesenteric artery and in the human mammary artery[197,198]. In the porcine coronary artery, CGRP activates the adenylate cyclase-cyclic-AMP-protein kinase A pathway which induces K_{ATP} and BK_{Ca} activation[199,200]. CNP produces relaxation and hyperpolarization of porcine coronary arteries and canine femoral veins via the accumulation of cyclic-GMP and the opening of BK_{Ca}[201,202].

3 CONCLUSION

Endothelial cells are able to synthesize and release numerous vasoactive substances. The regulation of the opening and closure of potassium channels by the release of endothelium-derived factors or directly through myoendothelial gap junctions is a key element in the control of the underlying vascular tone. The identification of the chemical structure of EDHF (s), of its (their) endothelial biosynthetic pathway (s) and of its (their) target (s) on the smooth muscle cells may provide a better understanding of the endothelial control of the local regulation of peripheral resistance and thus of the distribution of blood flow in health and disease (Fig 13).

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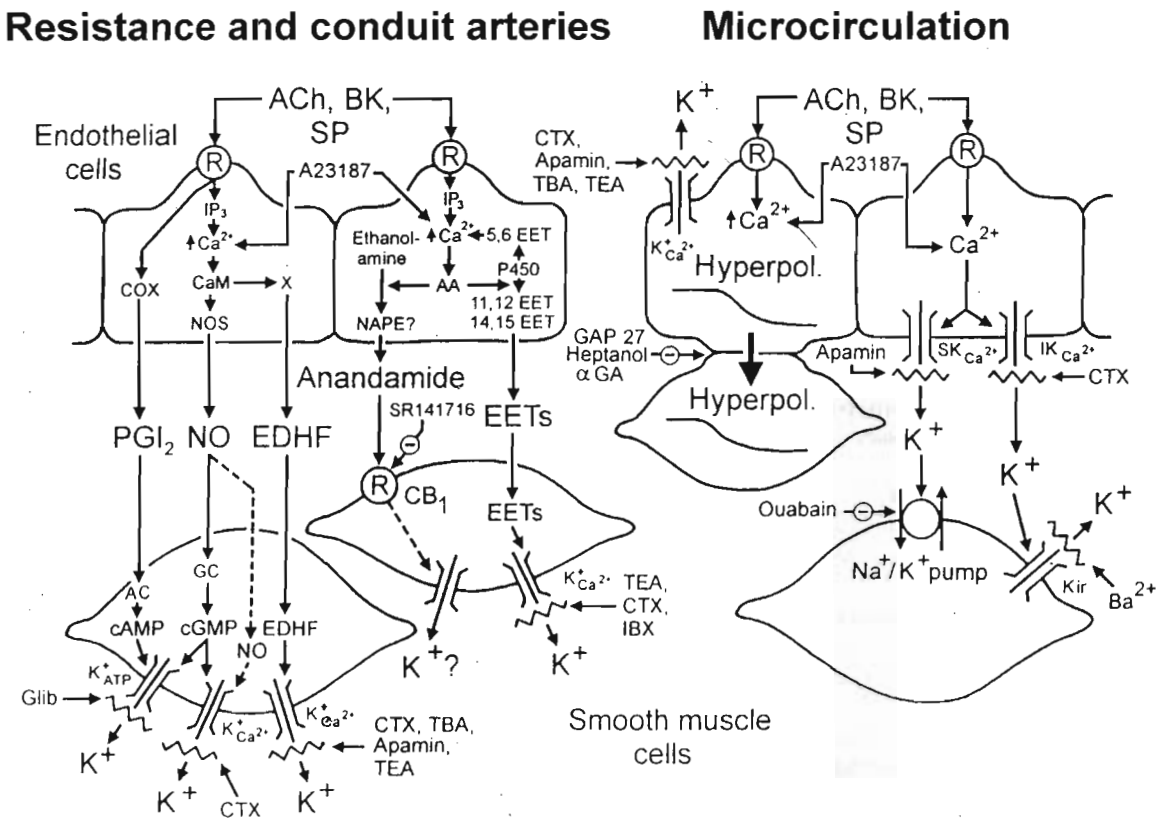

Fig 13. Endothelium-dependent hyperpolarizations. Acetylcholine (ACh), bradykinin (BK), and substance P (SP), through the activation of their respective receptor subtypes (M_3 = muscarinic, B_2 = bradykinin, and NK_1 = neurokinin receptors), and agents that increase intracellular calcium, such as the calcium ionophore A23187, provoke endothelium-dependent hyperpolarization. R: receptor; NOS: nitric oxide synthase; COX: cyclooxygenase; X: putative EDHF synthase; P-450: cytochrome P-450 monooxygenase; CaM: calmodulin; NO: nitric oxide; PGI2: prostacyclin; EDHF endothelium-derived hyperpolarizing factor; 5,6 EET: 5,6-epoxy-eicosatrienoic acid; 11,12 EET: 11,12-epoxy-eicosatrienoic acid; 14,15 EET: 14,15-epoxy-eicosatrienoic acid; NAPE: *N*-acylphosphatidylethanolamine; GC: guanylate cyclase, cGMP: cyclic guanosine monophosphate; cAMP: cyclic adenosine monophosphate; ATP: adenosine trisphosphate; IP3: inositol trisphosphate; Hyperpol: hyperpolarization. SR 141716 is an antagonist of the cannabinoid CB_1 receptor subtype (CB_1). Glibenclamide (Glib) is a selective inhibitor of ATP sensitive potassium channels (K^+_{ATP}). Tetraethyl ammonium (TEA) and tetrabutyl ammonium (TBA) are non specific inhibitors of potassium channels when used at high concentrations (>5 mmol/L) while at lower concentrations (1–3 mmol/L) these drugs are selective for calcium-activated potassium channels ($K^+_{Ca^{2+}}$). Iberiotoxin (IBX) is a specific inhibitor of large conductance $K^+_{Ca^{2+}}$. Charybdotoxin (CTX) is a non selective inhibitor of large conductance $K^+_{Ca^{2+}}$, intermediate conductance $K^+_{Ca^{2+}}$ ($IK_{Ca^{2+}}$) and some voltage-dependent potassium channels. Apamin is a specific inhibitor of small conductance $K^+_{Ca^{2+}}$ ($SK_{Ca^{2+}}$). Barium (Ba^{2+}) in the micromolar range, is a specific inhibitor of inward rectifyer potassium channel (K_{ir}). Gap27, an eleven amino acid peptide possessing conserved sequence homology to a portion of the second extracellular loop of connexin, 18β-glycyrrhetinic acid (αGA) and heptanol are gap junction uncouplers[203].

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血管平滑肌细胞的内皮依赖性超极化

关键词 花生四烯酸类; 细胞色素 P-450; 血管内皮; 间隙连接; 超极化; 一氧化氮; 钾通道; 依前列醇; 血管平滑肌; 电生理学

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