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The Physiological Mechanism of Extracellular Calcium-Sensing Receptor Action in the Regulation of Vascular Tone and Blood Pressure

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ABSTRACT

Background: Calcium is the fifth most abundant element in the adult human body. The free ionized calcium (Ca^{2+}) is responsible for a variety of physiological processes and tightly maintained mainly by action of calciotropic hormones and other nutrients. Calcium-sensing receptor (CaSR/CaR) is a cell-surface receptor that responds to, or "senses," extracellular Ca^{2+} concentrations in parathyroid, kidney and other tissues. The aim of the review is to get into the fine details of physiologic mechanisms responsible for extracellular calcium-sensing receptor actions in the regulation of vascular tone and blood pressure.

Method: Studies were accessed through an electronic web-based search strategy from PubMed, Cochrane Library, Google Scholar, Embase, PsycINFO, and CINAHL by using a combination of search terms.

Results/Discussion: The central role of the CaR is the regulation of calcium homeostasis, but it is also expressed in non-calciotropic tissues. It is well known that calcium is an important second messenger and regulator of vascular contractility. An increase in intracellular calcium concentration ($[Ca^{2+}]i$) in endothelium or in VSMCs exerts opposing influences on blood vessel diameter. Ca^{2+} is also an extracellular first messenger and binding of Ca^{2+} to CaR mediate biphasic effects with an initial endothelium-independent vasoconstrictions followed by endothelium-dependent relaxations. The vascular endothelium CaR activation mostly results in an activation of the G proteins ($G_q/11$). In parallel, CaR also activates PI4K and carries out the first step in inositol lipids biosynthesis. Endothelial calcium ''waves'' and "puffs" is an initial step required for endothelium-dependent vasorelaxations. The myoendothelial gap junctions have also a major role in electrical spread of hyperpolarization from the ECs to the VMSCs. Furthermore, the main source of NO• in the vasculature is the microvascular endothelium and contribute to cGMP activation in VMSCs and influence vascular reactivity.

Conclusion/Perspectives: it is not surprising that CaR is involved in the regulation of such diverse processes as hormone secretion, gene expression, ion channel activity, modulation of inflammation, proliferation, differentiation and apoptosis.

Keywords: Mechanism of Action; Extracellular Calcium-Sensing Receptor; Regulation; Vascular Tone and Blood Pressure

Abbreviations: ECF: Extracellular Fluid; ICF: Intracellular Fluid; CaSR: Calcium-Sensing Receptor; VSMCs: Vascular Smooth Muscle Cells; cGMP: Cyclic Guanosine Monophosphate; SR: Sarcoplasmic Reticulum; EDHF: Endothelium Derived Hyperpolarizing Factor; CaR: Calcium Sensing Receptor

Introduction

Humphry Davy first recognized calcium as an element in 1808 and the name was given after the Latin for lime: calx [1]. Calcium is the fifth most abundant element in the adult human body in which 99% resides in the bones and teeth as the hydroxyapatite [$Ca_{10}(PO_4)6(OH)_2$] crystal. Furthermore, about 0.9% is found intracellularly and the remaining is present in the extracellular [2]. The normal serum calcium level is ~8.8 to 10.4 mg/dl (2.2 to 2.6 mmol/L) [3]. It is present in three forms: about 50% is free ionized, about 10% is combined with various anions (bicarbonate, citrate, phosphate, lactate, and sulphate) and the remaining 40% is bound to serum proteins, mainly serum albumin. The extracellular fluid (ECF) ionized calcium (1.0 – 1.25 mmol/L) concentration is 10,000 times higher than the concentration of the intracellular fluid (ICF) ionized calcium because cell membrane permeability to Ca^{2+} is low and cells also have powerful mechanisms for extrusion, sequestration and buffering of calcium [4]. Nevertheless, total calcium concentration in the cell interior varies during normal function by up to 10-fold (e.g. from 10-4 to 10-3 mmol/L) [5]. The free ionized calcium (Ca^{2+}) is responsible for a variety of physiological processes including neuromuscular transmission, muscle contraction, cardiac automaticity, nerve function, hormone secretion, cell division and movement, intercellular adhesion, co-factor in the blood coagulation and cell motility and certain oxidative processes [6-8]. It is also a major intracellular messenger in many intracellular responses to chemical and electrical stimuli and required by many enzymes for full activity. The plasma ionized calcium concentration is tightly maintained mainly by action of three main calciotropic hormones (parathyroid hormone, calcitriol and calcitonin) and other nutrients, most notably magnesium and phosphorus [9,10]. The way the body maintains and regulates extracellular calcium levels is a complex puzzle that has intrigued researchers for decades. One large piece of this puzzle that is falling into place concerns a cell-surface receptor that responds to, or "senses," extracellular calcium-ion concentrations in parathyroid, kidney and other tissues. A receptor exhibiting molecular sensor of free ionized serum calcium (calcium-sensing receptor (CaSR/CaR)) was cloned from the bovine parathyroid gland, human parathyroid cells and rat kidney cells respectively [11-13]. Although the central role of the CaR is the regulation of calcium homeostasis, it is also expressed in non-calciotropic tissues as well as regulates a multitude of cellular processes unrelated to mineral ion homeostasis. This review summarizes the pathophysiology of atherosclerosis plaque progression with emphasis on plaque progression. It also offers the recently published literature on different biomarkers and examine whether incorporation of these markers might improve clinical decision.

Methods

PubMed, Cochrane Library, Google Scholar, CINAHL, Embase, and PsycINFO database were used for studies reporting the physiological mechanism of extracellular calcium-sensing receptor action in the regulation of vascular tone and blood pressure from study conception to May 2021. Zotero reference management software for Windows was used to download, organize, review and cite the articles. I also manually searched cross-references in order to identify additional relevant articles. A comprehensive search was performed using the following search terms: "calcium-sensing receptor", "extracellular calcium-sensing receptor action", "mechanism of extracellular calcium-sensing receptor action in the regulation of vascular tone", and "mechanism of extracellular calcium-sensing receptor action in the regulation of blood pressure". Boolean operators like "AND" and "OR" were used to combine search terms.

Result/Discussion/ on the Role of Vascular Calcium Sensing Receptori the Regulation of Vascular Tone and Blood Pressure

The vascular endothelium is a cell monolayer and plays a key role in the regulation of vasomotor tone through the release of endothelin, NO, PGI_2, and EDHF. Vascular tone and hence blood pressure are also determined by the contractile state of vascular smooth muscle cells (VSMCs) [14,15]. It is well known that calcium is an important second messenger that acts as an important regulator of vascular contractility. The nature of calcium signals in endothelium and smooth muscle are fundamentally different. The major pathways are voltage-dependent Ca^{2+} channels (VDCC) and nonselective cation channels at the plasmalemmal membrane or the internal store release channels found in the sarcoplasmic reticulum (SR) membrane (ryanodine (RyR) and the inositol trisphosphate receptors (IP_3R)) [16,17]. An increase in intracellular calcium concentration ($[Ca^{2+}]i$) in endothelium or in VSMCs exerts opposing influences on blood vessel diameter for precise regulation of organ and tissue perfusion. Vasoconstrictors act through increasing $[Ca^{2+}]i$ as well as on the apparent calcium sensitivity of the contractile process in VSMCs, whereas relaxing factors have the opposite effect. In contrast to the VSMCs, an increase in endothelial $[Ca^{2+}]i$ results in vascular relaxation through endothelium-derived relaxing factors such NO, PGI2, and EDHF [14]. Ca^{2+} is also an extracellular first messenger through the CaR expressed in ECs, VSMCs and on perivascular nerves of blood vessels. It is speculated that CaR has non-trivial effects on vascular tone and blood pressure in response to systemic as well as local changes in $[Ca^{2+}]o$ [18]. Binding of Ca^{2+} to CaR mediate biphasic effects with an initial endothelium-independent vasoconstrictions followed by endothelium-dependent relaxations. An increase $[Ca^{2+}]o$ from 1 mM to 6 mM potentiates pre-contracted tone in endothelium-removed vessel segments by affecting Gα protein subunits [19,20]. However, an increment evokes the endothelial membrane hyperpolarization and factors in a functionally intact endothelium by activating of potassium channels [21,22]. Under physiological condition, CaR-mediate vasorelaxations is more dominant than vasoconstrictions. In support of this hypothesis, increasing di-

etary calcium levels have been reported to have lowering effects on blood pressure in models of hypertension. A calcimimetic, NPS R-568, has been reported to significantly decrease blood pressure in uremic and spontaneously hypertensive rats but not in normotensive rats [23,24].

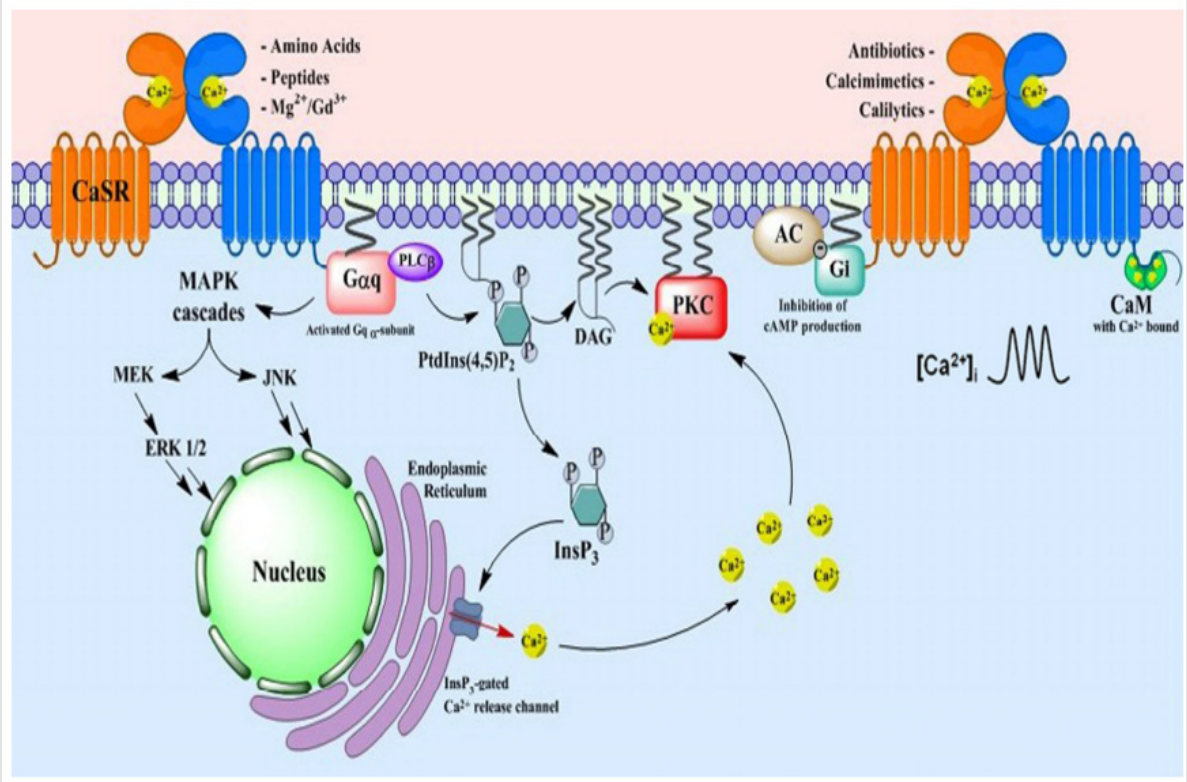

Figure 1: Calcium-sensing receptor-regulated intracellular signaling pathways in the endothelium of blood vessel.

The Major Proposed Mechanisms of Vasodilation

The vascular endothelium CaR activation mostly results in an activation of the G proteins (G_q/11) and causes hydrolysis of membrane phospholipid PIP2 through the stimulation of phospholipase C (PLC) (Figure 1) [25]. The stimulation of PLC then results in the generation of IP_3 and promotes the release of Ca^{2+} into the cytoplasm by activating of endoplasmic or sarcoplasmic reticulum IP_3-gated calcium release channels. Furthermore, PLC activation also causes the generation of diaglycerol and provides the signals for activation of the serine/threonine kinase protein kinase C (PKC) [26]. Due to the absence of VDCC on the endothelial cells (ECs) activation of PKC causes calcium influx through transient receptor potential channels (TRPC1, TRPC3, TRPC4, TRPC6, TRPV4, etc.) from the extracellular milieu and causes feature increase in cytosolic free Ca^{2+} within into ECs. In parallel, independent of heterotrimeric G proteins, CaR also activates PI4K and carries out the first step in inositol lipids biosynthesis by a Rho-dependent mechanism (Figure 1) [26]. Endothelial calcium "waves" and "puffs" (small punctate and local increases of calcium) is an initial step required for endothelium-dependent vasorelaxations. An increase in $[Ca^{2+}]i$ (from ~ 300 – 500 nM), results in the activation of in the vascular endothelium calmodulin (CaM) and induces a conformational change of the complex involving an interlacing of cytoplasmic loops that leads to the opening small and intermediate conductance calcium-activated potassium channels (SK_{Ca} and IK_{Ca}) on endothelium independent of the membrane potential (Figure 2) [27-29]. The intracellular K^+ moves down electrochemical gradient through the opened SK_{Ca} and IK_{Ca} channels to the extracellular space and results in the hyperpolarization of the ECs (Figure 2) [30]. The hyperpolarization of the endothelial cells is transmitted to the smooth muscle cells by direct electrical coupling through myoendothelial junctions and/or by the accumulation of K^+ in the intercellular myoendothelial space. An efflux of K^+ in the lumen of the blood vessel from endothelium would be washed away by the flowing blood and most likely without physiological consequences. However, the membrane potential hyperpolarization induced by SK_{Ca} and IK_{Ca} channels opening would further increase calcium influx in ECs by increasing the electrochemical gradient for calcium [14]. An efflux of K^+ toward the abluminal side can also accumulate in the intercellular space between endothelial and smooth muscle cells. When it reaches sufficient levels

(from ~ 4 mM to 12 mM) there will be an activation of both inwardly rectifying potassium channel (K_{ir}) and Na^+/K^+ ATPase on the membrane of the VSMCs in the immediate vicinity of the ECs releasing K^+ [31,32]. It is important to note that a moderate increase in potassium concentration, in the range of 1 to 15 mM, enhances potassium efflux through K_{ir} at physiologically relevant potentials [33]. At the expense of ATP, Na^+/K^+ ATPase exchanges three intracellular Na+ for two extracellular K^+ [34]. Thus, the net result is loss of positively charged K^+ from VSMCs results in hyperpolarization and subsequent dilation of the artery (Figure 3). It is also possible that other K^+ channels such as K_v7 and K_{ATP} channels expressed in VSMCs may be involved in mediating CaR induced vasorelaxations [35,36]. Gap junctions are the minute tunnels with internal diameter of 1.5 nm and exist not only between ECs and between VMSCs but also between endothelium and vascular smooth muscle (myoendothelial gap junctions). The myoendothelial gap junctions have a major role in electrical spread of hyperpolarization from the ECs to the VMSCs [37,38]. K^+ could be an EDHF or contribute to the mechanism of EDHF-mediated responses. Furthermore, SK_{Ca} and IK_{Ca} channels expressed on the ECs have pivotal roles in mediating endothelium-derived hyperpolarisations and couple to relaxation of VSMCs. The endothelial CaR can also modulate the diameter of blood vessels via another type of endothelium derived hyperpolarizing factor (EDHF) [39]. The endothelial CaR activation via G_q subunits of heterotrimeric G proteins activation, result in activation of phospholipases A2 (PLA_2). CaR-induced activation of ERK can also lead to the phosphorylation and activation of PLA_2 [40]. However, PKC activity is only partially responsible for CaR-mediated activation of PLA_2 (26). Because PLA_2 is constitutively active, the translocation to the membrane places and in contact with the phospholipid substrate, promotes the release of arachidonic acid within the cell. The liberated arachidonic acid has several possible fates: either reincorporated into plasma membrane phospholipids and act as a messenger or metabolized further by cyclooxygenase, epoxygenase, lipoxygenase, or Ω-hydroxylase (Figure 4) [41-43]. The first mechanism proposed for EDHF dilations involves the metabolism of arachidonic acid through the epoxygenase pathway to form epoxyeicosatrienoic acids (EETs). The EETs diffuse from the ECs to the VMSCs and activate large conductance calcium-activated K^+ channel (BK_{Ca}) and results in further K^+ efflux from the smooth muscle cell (VSMCs hyperpolarization) and vasorelaxation (Figure 5) [44,45]. The opening of the BK_{Ca} also promotes the closure of VDCC and thus opposing vasoconstriction [15]. EETs also activate smooth muscle vanilloid transient receptor potential channel (TRPV4) and increases the frequency of calcium sparks and subsequently that of spontaneous transient outward currents. The BK_{Ca} channels are clustered in a plasmalemmal region close to the RyR calcium SR release channels and so are exposed to a high concentration of store-released calcium early after SR calcium channel opening [46,47]. In arterial smooth muscle and intact arteries, Ca^{2+} sparks are observed just under the cell membrane consistent with a predominant subsarcolemmal localization of the RyR Ca^{2+} release channels in the sarcoplasmic reticulum. This EET-dependent activation of a calcium-signaling complex (TRPV4-ryanodine receptors-BK_{Ca}) hyperpolarizes and relaxes the smooth muscle cells [48]. EETs may also regulate the activity of endothelial SK_{Ca} and IK_{Ca}. EETs activate BK_{Ca} through a G protein–signaling cascade, however, the existence of a specific cell membrane receptor (s) for EETs and stimulate production of cAMP and activate protein kinase A and causes hyperpolarization through facilitate opening of both BK_{Ca} and K_{ATP} in VMSCs has been also established (Figure 5) [49,50]. Metabolism of arachidonic acid through the lipoxygenase pathway results in released of 12-(S)-HETE from the endothelium and activates BK_{Ca} on the smooth muscle cells. Similarly, prostacyclin, the major metabolite of arachidonic acid produced by cyclooxygenase in ECs, activates IP_3 receptors on VMSCs [51]. Depending on the artery and/or the species, a hyperpolarization can occur. ATP-sensitive potassium channels (K_{ATP}), BK_{Ca}, inwardly rectifying potassium channels (K_{ir}) and/or voltage activated potassium channels (KV) can be associated with the prostacyclin-induced relaxation [52]. Moreover, myoendothelial gap junctions can also allow passage of small water-soluble molecules (< 1,000 Da) including cyclic guanosine monophosphate, inositol triphosphates, and inorganic ions, therefore, provides VMSCs relaxation [53-55]. Endothelium-derived NO is synthesized by endothelial nitric oxide synthase (eNOS) which converts semi-essential amino acid L-arginine to L-citrulline and NO (Figure 6). The eNOS stimulation is due to the activation of calmodulin, as a consequence of increases in $[Ca^{2+}]$ i in vascular endothelium [56]. Thus, high $[Ca^{2+}]$i-induced eNOS upregulation is indeed CaR mediated. The main source of NO• in the vasculature is the microvascular endothelium and contribute to cGMP activation in VMSCs and influence vascular reactivity. NO regulates vascular tone by different signaling pathways. The first pathway is the classic NO-sGC-cGMP vasodilator mechanisms (Figure 7) [57,58]. The NO• formed diffuses to underlying VMSCs and causes the stimulation of soluble guanylate cyclase (sGC), which induces formation of cyclic guanosine monophosphate (cGMP). Cyclic GMP activates protein kinase G (PKG), which prevents the calcium influx from VDCC and calcium release mediated by IP_3R. PKG also acts on sarco/endoplasmic reticulum calcium ATPase (SERCA) to promote the reuptake of cytosolic calcium into the sarcoplasmic reticulum (SR) and the opening of BK_{Ca} activation in the VMSCs (Figure 7) [59,60]. As a result, the intracellular concentration of calcium decreases and calmodulin is inactivated which no longer able to activate Myosin light chain kinase (MLCK). Calcium depletion also increases the activity of myosin light chain phosphatase (MLCP). The actin-myosin cross-bridge is broken and smooth muscle relaxation ensues. In the second pathway, independent of the classic NO-sGC-cGMP pathway, NO• can undergo reactions in the presence of an electron acceptor with cysteine thiol containing compounds to form biologically active S-nitrosylated molecules [61,62]. Formation of S-nitrosylated has many functions

(Figure 7). S-nitrosylation increases the activity of sarco/endoplasmic reticulum calcium ATPase (SERCA) to enhance the reuptake of cytosolic calcium into the sarcoplasmic reticulum and accelerates calcium depletion and induces relaxation [63]. Similarly, G protein coupled receptors (GPCRs) can be directly S-nitrosylated by NO, which impedes the binding of ligands for the receptor or G-protein coupling. The S-nitrosylated molecules can regulates the expression and functions of GPCRs. NO and S-nitrosothiols also modulate the activity of GPCR kinase 2 (GRK2) which phosphorylates β-adrenoceptors and induce receptor desensitization and internalization to prevent the loss of β-adrenergic signaling in blood vessels to induce vasodilatation [64-66]. S-nitrosoglutathione also inhibits α1-adrenoceptor-mediated vasoconstriction and ligand binding [66]. Likewise, S-nitrosylation of cysteine 289 of the AT1 receptor decreases its binding affinity for angiotensin II. Cytosolic β-arrestin binding to CaR and GRK-phosphorylated GPCRs sterically impedes the interaction of G-proteins with activated GPCRs, resulting in GPCR signaling termination. β-arrestin 2, can be S-nitrosylated on cysteine 410 by endogenous NO and S-nitrosogluthathione, which promotes binding of β-arrestin 2 to clathrin heavy chain/ β-adaptin, thereby accelerating receptor internalization and induces vasorelaxation [67-70].

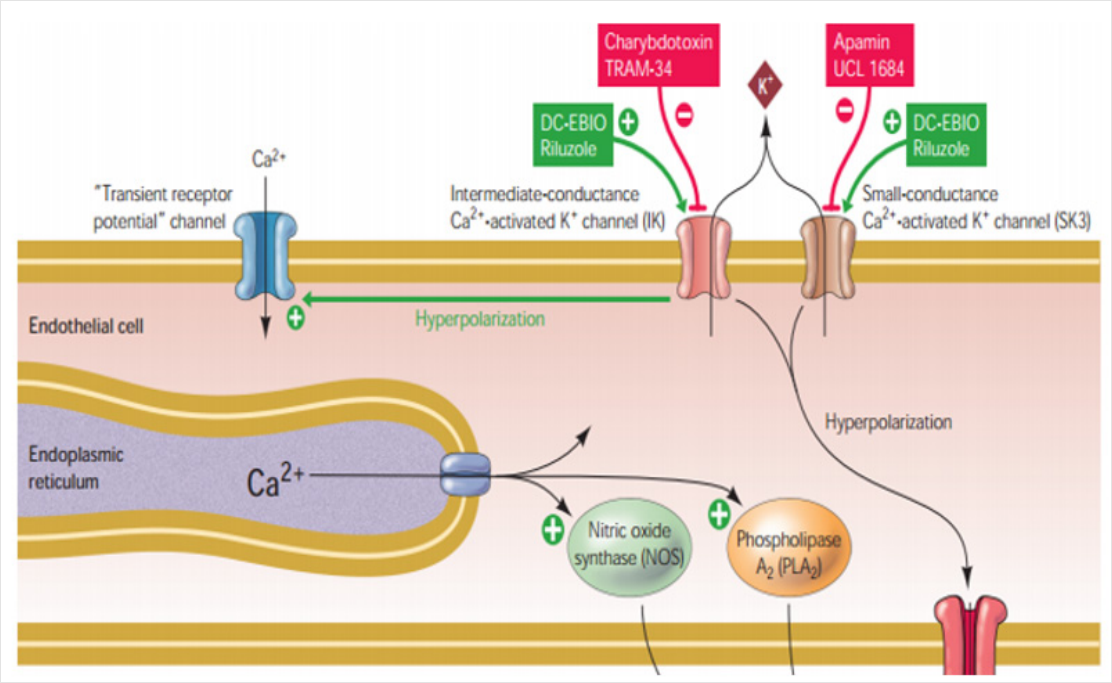

Figure 2: Roles of SK and IK channels in the regulation of vascular function.

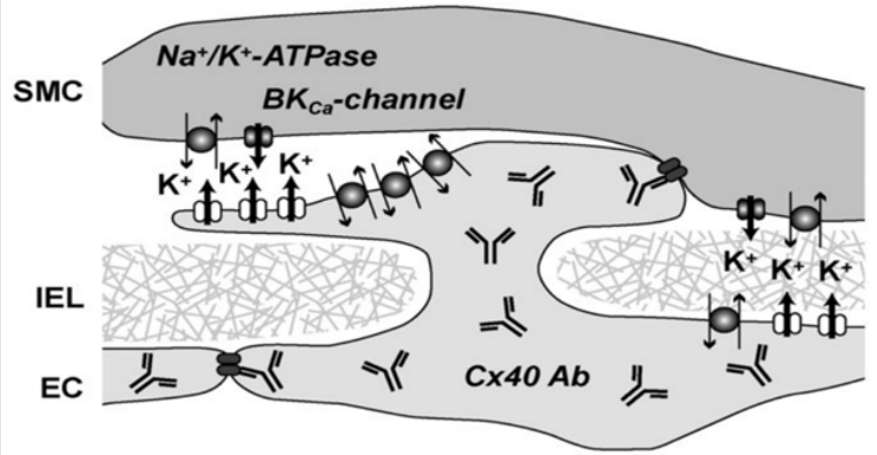

Figure 3: Mechanism of K+ acting as EDHF.

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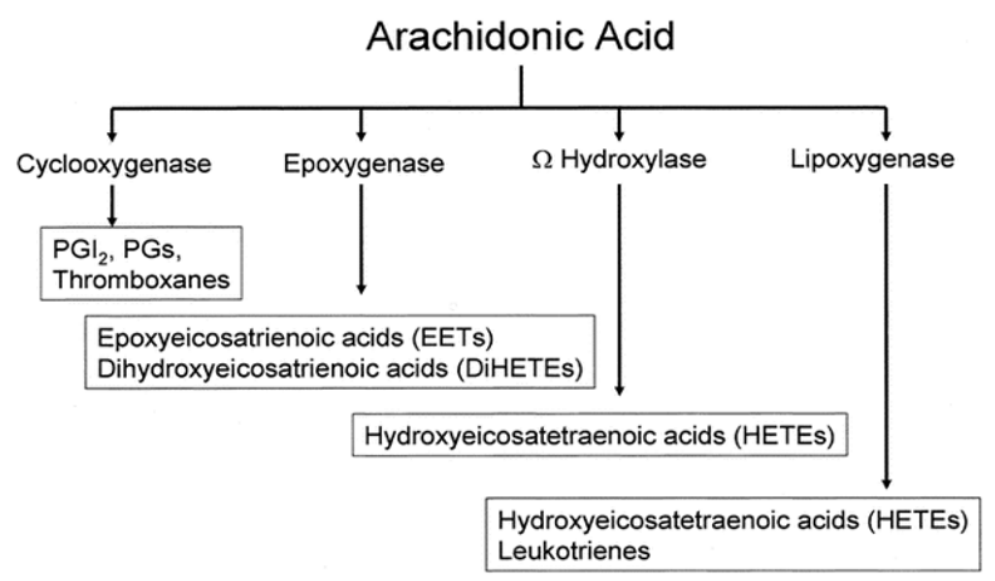

Figure 4: Several possible fates of arachidonic acid.

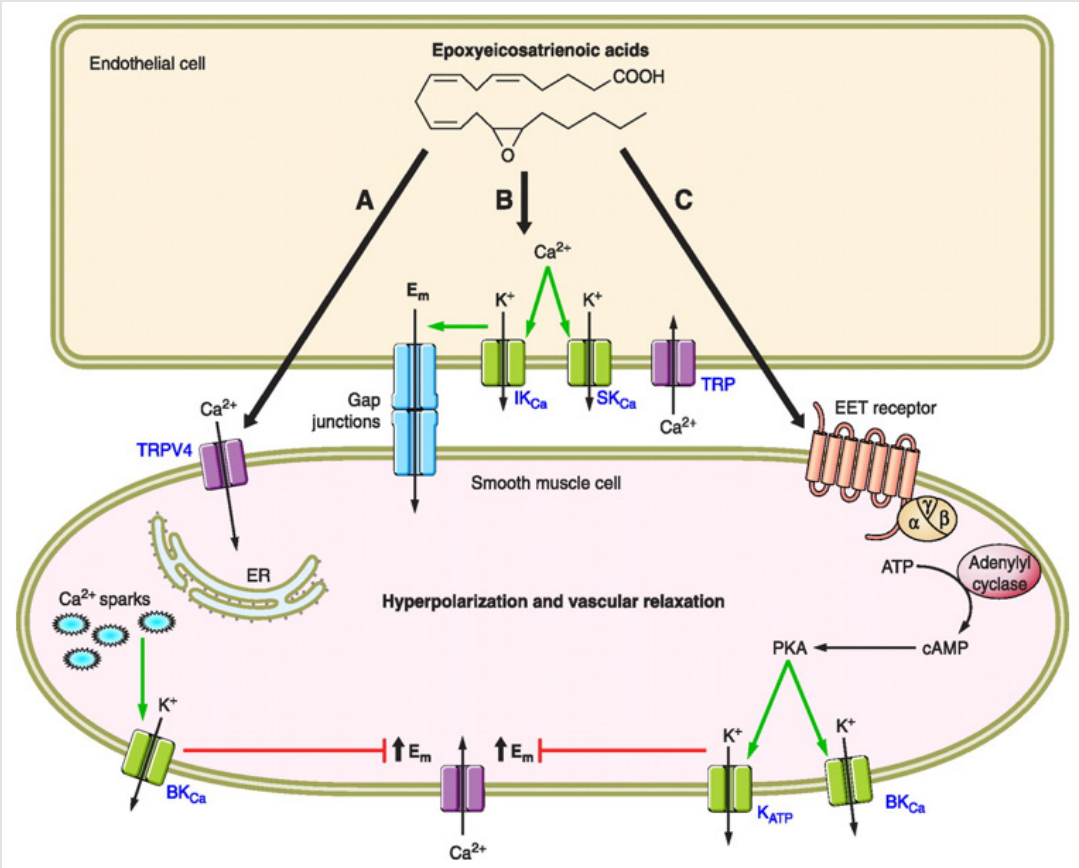

Figure 5: Mechanism of EET acting as EDHF.

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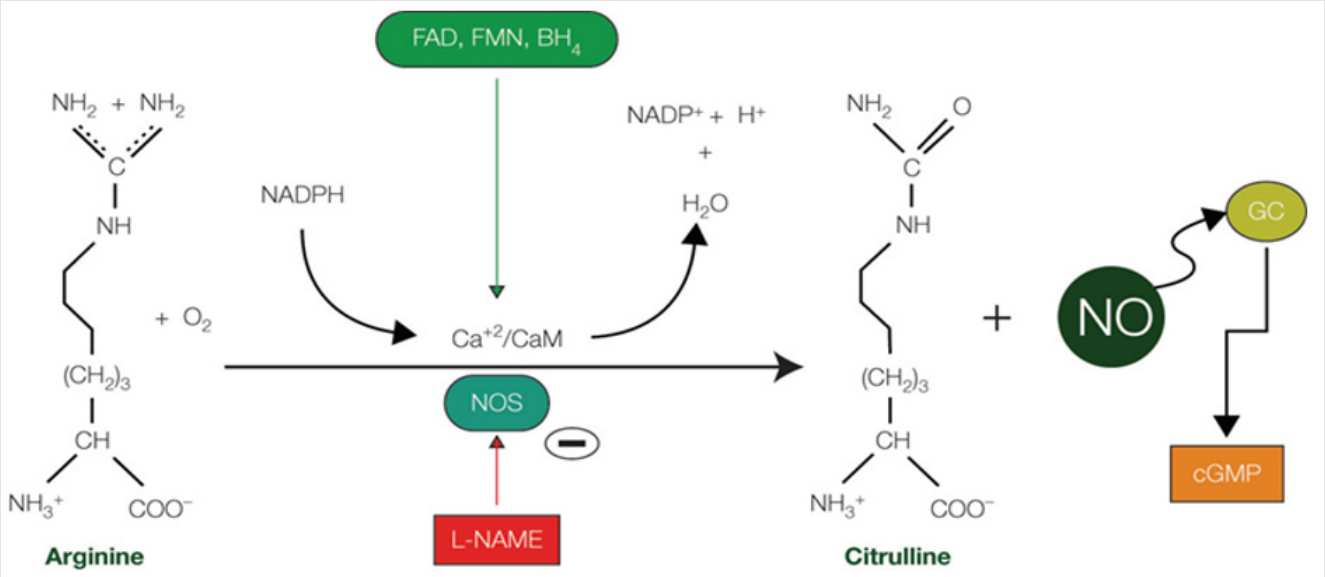

Figure 6: Biosynthetic pathway for nitric oxide. NADPH is an essential cofactor for this reaction and L-NAME acts as an inhibitor of (at least) two steps in the pathway.

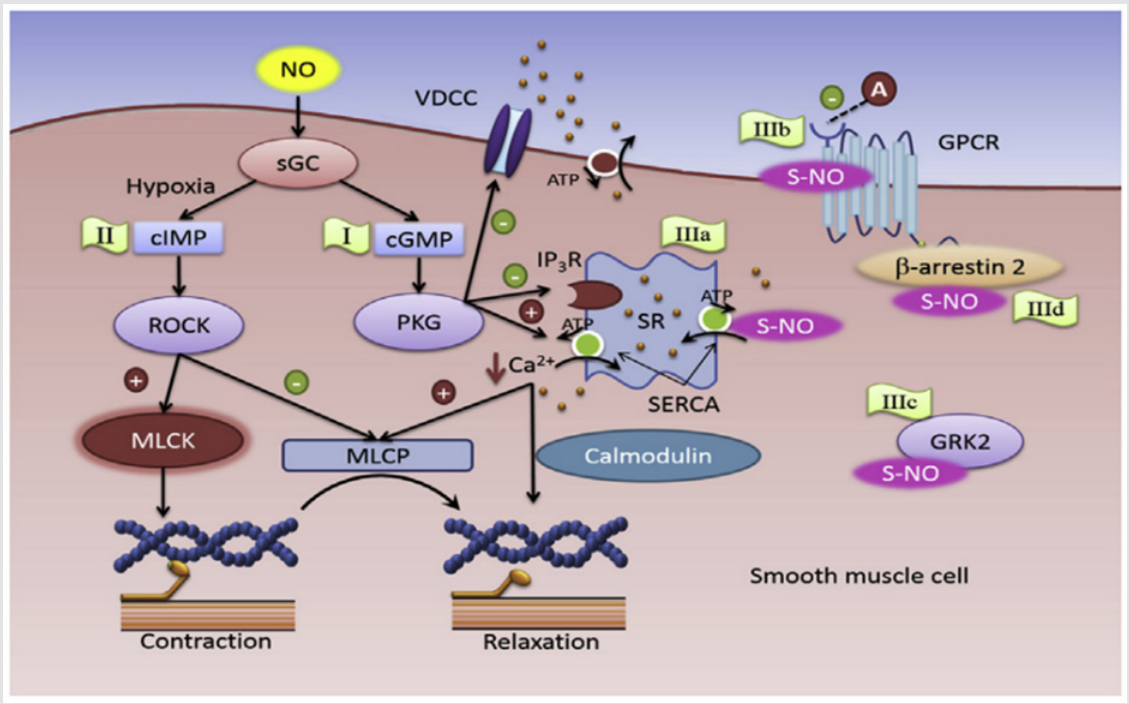

Figure 7: Regulation of vascular tone by nitric oxide (NO).

Conclusion

Calcium is a crucial signal molecule that acts via changes in intracellular Ca^{2+} levels through the actions of calcium channels and pumps. However, it is now well known that calcium may also be an extracellular first messenger through a G-protein-coupled receptor that senses extracellular Ca^{2+} concentration, the calcium sensing receptor (CaR). Binding of extracellular Ca^{2+} or other ligands to the CaR triggers a number of intracellular signaling systems like the activation of Gαq proteins to result in stimulation of phospholipase C, which leads to the generation of second messengers (DAG and IP_3) and intracellular Ca^{2+} release; inhibition of adenylate cyclase activity result in suppression of intracellular cAMP; activation of PKC and MAPK – p38, JNK/SAPK and MEK1/ERK1,2 etc. In addition to the G proteins, the CaR binds the scaffolding protein filamin A, G-protein coupled kinases (GRKs) and β-arrestins, which add the complexity of the downstream signaling mechanism of the receptor. It is now evident that the presence of the CaR in animal blood vessels of many types, in perivascular nerves, endothelial cells and vascular smooth muscle cells, suggests it may regulate the vascular tone. This could provide a mechanism for the almost 100-year-old observation that $[Ca^{2+}]o$ induces vasodilation. In particular, these novel results indicate that stimulation of CaRs induces endothelium-dependent vasorelaxations which are mediated by opening of the Ca^{2+}-sensitive potassium channels, NO production and inhibit renin production. All together, these results indicate that the CaR may have a physiological role in the modulation of blood pressure.

Declarations

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Availability of Data and Material

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Authors' Contributions

LM had participated in the design of the study, data analyses, and manuscript preparation; and the authors could have read and approved the final manuscript.

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