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Endothelial Paracrine Action

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Some endothelial-derived compounds are able to cross the membrane and regulate the function of other nearby cells. The coronary arteries release endothelial factors and as such mediate paracrine action both on myocardiocytes and smooth muscle cells. Among the endothelial vasoactive substances released from the coronary arteries are Endothelial Derived Relaxing Factor (EDRF), Endothelial Derived Hyperpolarizing Factors (EDHFs), prostaglandins and endothelines 1,2,3 (ET-1, ET-2, ET-3). EDRF, which was identified as Nitric Oxide (NO) in 1986 by Moncada and his colleagues [1], has vasodilation effects and in the presence of molecular oxygen (O_2) is formed from L-arginine by the enzyme NO-Synthase (NOS). Basal concentrations of NO released by endothelial cells can be increased by both chemical and physical factors. Among those agents that can up-regulate the synthesis of NO are acetylcholine (Ach), bradykinin (BK), substance P, ATP and ADP; whereas, physical factors such as shear stress and increases in pulsatory pressure are known to augment basal levels of NO.

Nitric Oxide has several mechanisms of action. The vasodilatory effect of NO is mediated by activation of smooth muscle guanylate cyclase and subsequent hyperpolarization and relaxation of the plasma membrane. Similarly, up-regulation of guandylate cyclase within platelets has an anti-aggregation effect. NO-induced myocardial protection, in part, involves translocation of a portion of protein kinase C (PKC) isoforms (PKC-e, PKC-d) and the activation of mytochondrial ATP dependent potassium channels [2]. The NO related anti-polymorphonucleocytes adhesion is responsible for the so called vasoprotection.

The real nature of EDHFs is still controversial. Different investigators point to different candidates, which include NO, prostaglandin I_2, superoxide anion, hydrogen peroxide, phospholipase A_2 (PLA_2) products, non-prostanoid arachidonic acid (AA) derivatives produced by lypo-oxygenase (LOX) action and epoxyeicosatrienoic acids (EETs) through the cytochrome P-450 (CYP-450 mono-oxygenase pathway [3].

The EDHF's action can vary as a function location, type, and size of the vessel, as well as the animal species. Such variation of function suggests that there is not a unique molecule that mediates the observed array of disparate responses, but rather several compounds with similar functions are more than likely responsible for the observed diversity of response. The EDHF pathway is triggered by activation of a M2 membrane receptor, which then results in an increased inward flux of calcium ion. The increased cytoplasmic calcium pool mediates the outward potassium current through the potassium calcium dependent channels. Hence, the smooth muscle cell is hyperpolarized as a result of a decrease in the membrane action potential. The hyperpolization process can be triggered by activation of endothelial membrane receptors. It has been demonstrated in endothelial cells that BK and Ach lead to augmented calcium influx and, as a consequence, the increased calcium flux results in up-regulation of PLA_2 activity. Phospholipid products of AA are further metabolized by CYP-450. Among those products of AA metabolism are the EETs, which can activate smooth muscle cells potassium channels [4]. Yet another inter-relationship wherein endothelial cells can have paracrine effects on smooth muscle cells results from activation of endothelial cytoplasmic enzymes such as NOS, NAD(P)H oxido-reductases, and Cytochrome-dependent oxidoreductases. These enzymes reduce molecular oxygen to superoxide anion and superoxide dismutase (SOD) can convert superoxide anion to hydrogen peroxide (H_2O_2). Among the many reactions of H_2O_2 it can act on smooth muscle cells 1) activating potassium membrane channels through EET-like pathway, and 2) activating PKC with consequent PLA2 increased activity that can elevate the concentration of AA. Up-regulated activity of LOX follows the increased level of AA, which can then lead to opening of membrane potassium channels by yet undefined mechanism. In addition to the above two well described mechanisms of EDHFs, there still may be a third mechanism of interaction which can result from changes in the concentration of potassium ion within the matrix. It has been proved that inhibition of calcium influx in the endothelial cell through a nickel-sensitive cation channel decreases the matrix concentration of K^+ and causes down-regulation of Na^+/K^+ exchange activity in the smooth muscle that is responsible for vasoconstriction. At the same time, as a result in calcium channels activation in endothelial cells, the up-regulation of Na^+/K^+ exchange can then lead to hyperpolarization and vasodilation.

The three different EDHFs pathways act on vessels of different diameter and the effects of each of the independent mode of action can result in synergy. The concomitant action results from the high density of tight junctions that longitudinally and transversally couple both smooth muscle cells and endothelial cells. EDHFs as such could well be responsible for the maintenance of myocardial blood flow in

the case of decreased available NO as a vasodilator agent in pathophysiological states. Nevertheless in pathologic states such as diabetes and hypertension, the lack of EDHFs pathways can result in critical problems because the compensatory effect is absent and the relaxing response resulting from an inward flux of Ca^{2+} through a nickel-sensitive channel is disabled.
Although the chemical identity of endothelium derived hyperpolarizinf factor is controversial and may vary with the vascular bed, EETs acids, derived from AA by the action of CYP-450, are the main candidate to be EDHF.
There are other compounds with vasoactive effects such as the endothelins. Endothelins are polypeptides made up of twenty one aminoacids. ET1 is the most common, ET-2 and ET-3 are present in lower concentrations. Their action is bimodal, in fact ETs activate the ET-b receptors causing transient vasodilation followed by vasocostriction as a result of triggering of the ET-a receptors. ETs are overexpressed in the presence of infarct, stunning, and hypertension.
Endothelial vascular cells release substances able to induce both vasodilation such as NO, EDHFs, PGI_2 and vasoconstriction (most of all endothelines).

References

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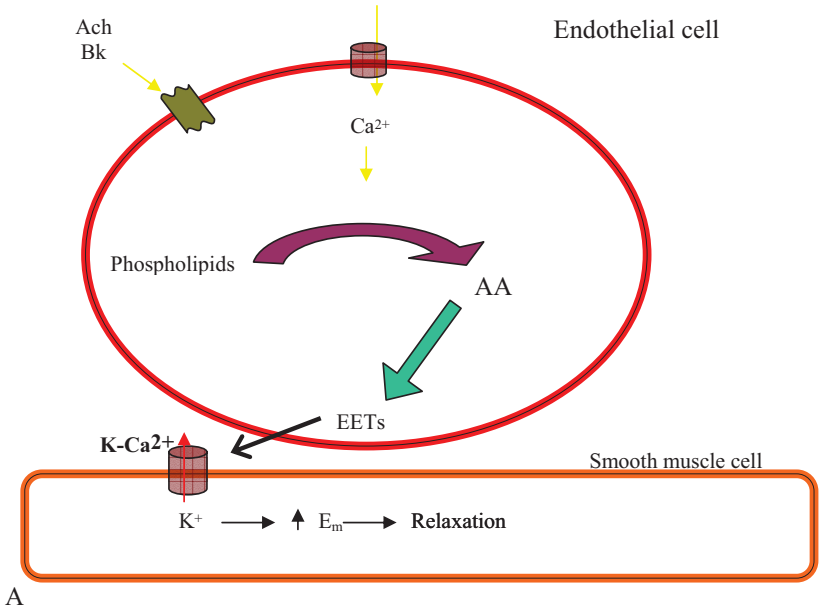

Fig. 1. Proposed mechanism of relaxation induced by EETs.

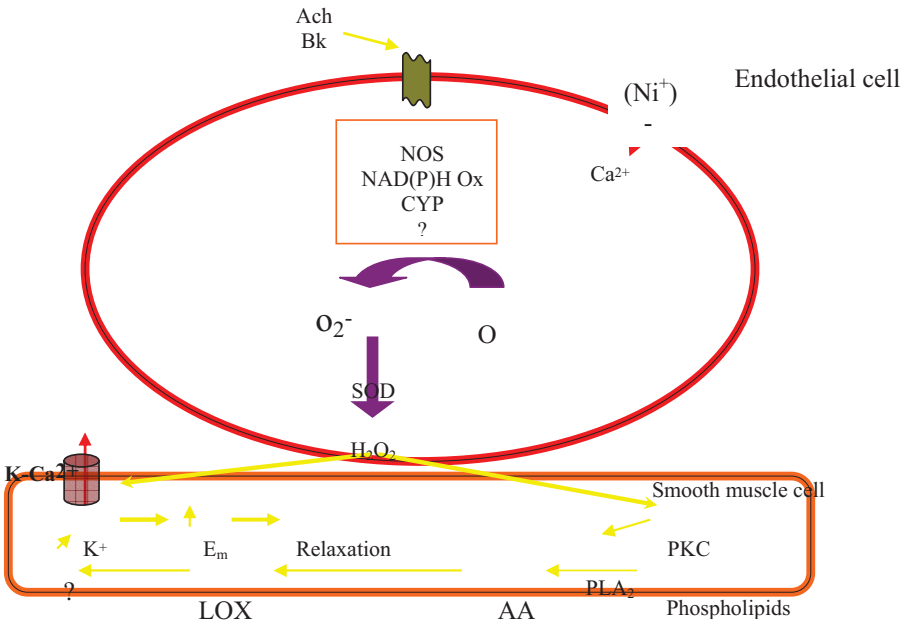

Fig. 2. Proposed mechanism of relaxation induced by H2O2