Arachidonic Acid Metabolites as Endothelium-Derived Hyperpolarizing Factors

William B. Campbell, John R. Falck

Abstract—The endothelium regulates vascular tone through the release of a number of soluble mediators, including NO, prostaglandin I₂, and endothelium-derived hyperpolarizing factor. Epoxyeicosatrienoic acids are cytochrome P450 epoxygenase metabolites of arachidonic acid. They are synthesized by the vascular endothelium and open calcium-activated potassium channels, hyperpolarize the membrane, and relax vascular smooth muscle. Endothelium-dependent relaxations to acetylcholine, bradykinin, and shear stress that are not inhibited by cyclooxygenase and NO synthase inhibitors are mediated by the endothelium-derived hyperpolarizing factor. In arteries from experimental animals and humans, the non-NO, non–prostaglandin-mediated relaxations and endothelium-dependent hyperpolarizations are blocked by cytochrome P450 inhibitors, calcium-activated potassium channel blockers, and epoxyeicosatrienoic acid antagonists. Acetylcholine and bradykinin stimulate epoxyeicosatrienoic acid release from endothelial cells and arteries. These findings indicate that epoxyeicosatrienoic acids act as endothelium-derived hyperpolarizing factors and regulate arterial tone. (Hypertension. 2007;49[part 2]:590-596.)

Key Words: Cytochrome P450 system ■ endothelium ■ arachidonic acid ■ vascular relaxation ■ endothelium-derived hyperpolarizing factor

Endothelial Metabolism of Arachidonic Acid
Arachidonic acid is metabolized by cyclooxygenase (COX), lipooxygenase (LO), or CYP. With the suggestion that endothelium-derived relaxing factor was an LO metabolite, we undertook the identification of the arachidonic acid metabolites produced by endothelial cells. Our studies were conducted on endothelial cells from human pulmonary arteries and veins, human umbilical veins, and bovine coronary arteries.7-10 Endothelial cells metabolized arachidonic acid by the 3 pathways (Figure 1).11,12 The major metabolites of the COX pathway were PGI₂ with lesser amounts of PGE₂ and 12-hydroxyheptadecatrienoic acid (HHT). 12- and 15-Hydroxyeicosatetraenoic acids (HETEs) were the major LO metabolites. Endothelial cells synthesized the 4 regioisomeric EETs, 14,15-, 11,12-, 8,9-, and 5,6-EETs, with 14,15- and 11,12-EETs being the major metabolites.12 These cells also contain soluble epoxide hydrolase (SEH), which hydrolyzes the epoxide converting the EETs to vic-dihydroxyicosatrienoic acids (DHETs).13,14 Thus, EETs and their metabolites, the DHETs, are the only CYP metabolites made by the endothelium. In contrast, vascular smooth muscle cells have approximately one fifth of the activity of endothelial cells in metabolizing arachidonic acid.15 In addition, the major metabolites produced by smooth muscle cells from the bovine coronary artery are PGI₂, 20-HETE, and 15-HETE. No EET production was detected in smooth muscle cells.
methacin reduced the relaxations to arachidonic acid by metabolites of arachidonic acid. Inhibition of COX with indo-

increased the release of PGs, HETEs, DHETs, and EETs.9,10 Thus, 

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anandamide is metabolized in endothelial cells by FAAH 

8,9-EET. Methacholine stimulated the release of all 3 EETs. 

major regioisomer produced with lesser amounts of 11,12- and 

glycerol. 16 The free arachidonic acid is then metabolized as 

(FAAH) or monoglyceride lipase to arachidonic acid and 

membrane phosphatidylinositol (Figure 1). The 2-AG is an 

endocannabinoid and activates cannabinoid receptors. In endo-

thelial cells, 2-AG is metabolized by fatty acid amidohydrolase 

(FAAH) or monoglyceride lipase to EETs and glycerol. 16 The free arachidonic acid is then metabolized as described above. Thus, 2-AG serves as a source of free arachidonic acid when endothelial cells are stimulated by agonists such as acetylcholine. We also detected the synthesis of glycerol-EETs in endothelial cells suggesting that 2-AG may be metabolized by CYP epoxygenase.16 The glycerol-EET may be active on its own or metabolized by FAAH or monoglyceride lipase to EETs and glycerol. Anandamide is another endocannabinoid. We did not detect its synthesis by endothelial cells.17 Exogenous anandamide is metabolized in endothelial cells by FAAH to free arachidonic acid and ethanolamine. The arachidonic acid is metabolized to eicosanoids, including EETs.

Stimulation of endothelial cells with histamine or carbachol increased the release of PGs, HETEs, DHETs, and EETs.3,10 Thus, the synthesis of these metabolites is regulated by agonists. In bovine coronary endothelial cells, the release of EETs was measured by liquid chromatography/mass spectrometry.18 14,15-EET was the major regioisomer produced with lesser amounts of 11,12- and 8,9-EET. Methacholine stimulated the release of all 3 EETs.

**EETs as Mediators of Arachidonic Acid–Induced Relaxation**

In bovine coronary arteries, arachidonic acid caused concentration-related relaxations in arteries with an intact endothelium but was without effect in arteries with the endothelium removed.19 Thus, the relaxations were mediated by endothelial metabolites of arachidonic acid. Inhibition of COX with indomethacin reduced the relaxations to arachidonic acid by \(\approx 50\%\).19 The combined COX and LO inhibitor BW755c also inhibited the relaxations by 50%, and when indomethacin and BW755c were tested together, there was no further inhibition. These findings indicate that a portion of the relaxations to arachidonic acid was mediated by PGs and that LO metabolites did not contribute to the response. The CYP inhibitor SKF525a inhibited the relaxations to arachidonic acid by \(\approx 50\%\), and when SKF525a and indomethacin were combined, the relaxations were blocked. Similar results were observed in human coronary arteries.20 These studies indicate that COX and CYP metabolites mediated the response to arachidonic acid. Like endothelial cells, coronary arteries metabolized arachidonic acid to PGs and EETs.19 PGI2 and the EETs relaxed the coronary artery. The 4 EET regioisomers were equally active in causing relaxation.19,21 The relaxations to the EETs were similar in arteries with and without an intact endothelium.22,23 These findings suggest that PGI2 and the EETs represent the endothelial mediators of arachidonic acid–induced relaxation.

In bovine coronary arteries, relaxations to the EETs and arachidonic acid were inhibited by increasing the extracellular K concentration to 20 mmol/L and by inhibitors of calcium-activated K (\(K_{Ca}\)) channels including iberiotoxin, tetraethylammonium chloride, and charybdotoxin.15,21 Similar results were observed in human coronary arteries.20,24 These results suggest that arachidonic acid and EETs activate \(K_{Ca}\) channels. When membrane potential of coronary arterial vascular smooth muscle was measured, 11,12-EET caused membrane hyperpolarization.21,23 This hyperpolarization was also blocked by iberiotoxin. Similarly, in human coronary and internal mammary arteries, 11,12-EET relaxed and hyperpolarized the smooth muscle, and these effects were blocked by iberiotoxin.24,25 These findings indicate that the EETs relax arteries from humans and experimental animals by activating \(K_{Ca}\) channels and causing hyperpolarization of the smooth muscle cell membrane. The hyperpolarization inhibits activation of voltage-activated calcium channels reducing calcium entry and causing relaxation.

EETs activate \(K_{Ca}\) channels in smooth muscle cells. Using a patch clamp in the whole cell mode, 11,12-EET activated an outward current that was blocked by iberiotoxin in smooth muscle cells from bovine coronary and human internal mammary arteries.22,23 In the cell-attached mode, 14,15- and 11,12- 

EET activate a \(K\) channel in coronary smooth muscle cells.21,26–28 Characterization of this \(K\) channel revealed voltage and calcium dependence, unitary conductance of 256 pS, and inhibition by tetraethylammonium and iberiotoxin. Activation of the channel by EETs did not alter the calcium or voltage sensitivity. These data were consistent with EETs activating the large conductance or maxi \(K_{Ca}\) (BKCa) channel. These results indicate that EETs have the properties of an EDHF.

**EETs and EDHFs**

EDHF was originally described as an endothelial factor released by agonists, such as acetylcholine or bradykinin, that hyperpolarized the membrane of the underlying vascular smooth muscle.4–6,29 The acetylcholine-induced hyperpolarization was mediated by the opening of K channels because it was inhibited by increased extracellular K concentration and K channel blockers. EDHF activity was also defined as endothelium-dependent relaxations resistant to inhibition by COX and NO synthase (NOS) inhibitors but blocked by increased extracellular K concentration or K channel inhibitors.29,30 PGI2, NO, and EDHF
serve the same function, that is, to dilate the blood vessels in response to agonists, such as acetylcholine and bradykinin, and physical forces, such as flow and shear stress. They antagonize the activity of vasoconstrictors and maintain organ blood flow. The activity of NO differs from EDHF along the vasculature. Endothelium-dependent dilation to NO was greatest in large arteries, whereas EDHF had its greatest effect in small arteries and arterioles.31,32 In addition, the synthesis of EDHF was enhanced after NOS inhibition and inhibited by NO.22,33,34 Thus, there are complex anatomic, biochemical, and functional interrelationships between NO and EDHF that are not defined completely.

EETs and EDHF have identical properties. Both are produced by the endothelium and open KCa channels, hyperpolarize, and relax smooth muscle. Like EDHF, EETs are more potent in relaxing small coronary arteries than large epicardial arteries.35,36

Endogenous EETs mediate the EDHF response to acetylcholine and bradykinin. In bovine coronary arteries treated with COX and NOS inhibitors, methacholine-induced relaxations were blocked by CYP inhibitors SKF535A and miconazole21 and EET antagonists.37,38 Similarly, methacholine hyperpolarized the smooth muscle of endothelium-intact coronary arteries, and the hyperpolarizations were blocked by CYP inhibitors.

Methacholine stimulated the release of EETs from perfused coronary arteries and coronary endothelial cells.18,21 Identical results were obtained with human internal mammary arteries.25 Similar studies were performed with bradykinin in bovine and porcine coronary arteries and human internal mammary arteries.22,25,37–41 Relaxations and hyperpolarization by bradykinin were inhibited but not blocked by CYP inhibitors and EET antagonists. In addition, antisense oligonucleotides against CYP2C inhibited the relaxations and hyperpolarizations to bradykinin, whereas sense and scrambled oligonucleotides were without effect.34 This inhibition by the antisense oligonucleotides was accompanied by a reduction of the expression of CYP2C. These studies indicate that the hyperpolarizations and relaxations to methacholine and bradykinin are mediated by CYP metabolites of arachidonic acid, the EETs.

In arteries from experimental animals and humans, shear stress and flow increases cause endothelium-dependent relaxations that are reduced by inhibitors of NOS and COX.42–44 The non-NO, non-PG–dependent relaxations to increases in flow are blocked by CYP inhibitors and are associated with the release of EETs. In unpublished studies, we have confirmed endothelium-dependent dilation to increases in flow in bovine coronary arteries treated with COX and NOS inhibitors.45 These dilations are blocked by miconazole and an EET antagonist.

EETs are not synthesized by smooth muscle cells.15 These cells have muscarinic receptors, and muscarinic agonist increases intracellular calcium.46 However, metacholine does not increase EET synthesis or alter BKCa channel activity.6 Transduction of smooth muscle cells with a CYP BM-3 (F87V) containing adenovirus confers epoxygenase activity to the cells.15 In adenovirus-transduced cells, 14,15-EET and 14,15-DHET are synthesized from arachidonic acid. Also, methacholine stimulates 14,15-EET synthesis and BKCa channel activity. The increase in BKCa activity is blocked by CYP inhibition indicating that channel activation is mediated by 14,15-EET. Thus, conferring epoxygenase activity to smooth muscle is sufficient for methacholine to stimulate BKCa channels in the absence of the endothelium.

Development of Selective EET Agonists and Antagonists

CYPs produce EETs in endothelial cells and 20-HETE in smooth muscle cells.47 20-HETE is a constrictor that antagonizes the action of the EETs. Inhibitors of CYPs block the synthesis of both EETs and 20-HETE, so specific EET antagonists are needed to study their role as EDHFs. 14,15-EET analogs, with modifications in the epoxy and carboxyl groups, depletions of the double bonds, and variations in the carbon chain length, were synthesized.48 When the analogs were tested for their ability to cause relaxation, specific structural features were identified for full agonist activity: an acidic group at carbon-1, a 20 carbon backbone, a Δ8 double bond, and a 14(S),15(R)-cis epoxide. Thus, the basic full agonist was 14(S),15(R)-(cis)-epoxyeicosa-8Z-enoic acid (14,15-EE-8Z-E) (Figure 2).

Analogs with low agonist activity were tested for their ability to inhibit EET-induced relaxations. 14,15-EE-5Z-E inhibited the relaxations to 14,15-, 11,12-, 8,9-, and 5,6-EET; however, it was most active in inhibiting 14,15-EET (Figure 2).37 The non-PG–mediated relaxations to arachidonic acid were also blocked by 14,15-EE-5Z-E. In contrast, it did not alter the relaxations to the NO donor sodium nitroprusside, the PGI2 analog iloprost, or the K channel openers bimakalim and NS1619. Thus, 14,15-EE-

![Figure 2. Structures of EET agonists (A) and antagonists (B).]
5Z-E was a selective EET antagonist that did not inhibit other endothelial factors or K channels. It also did not affect the constriction to the thromboxane agonist U46619 or 20-HETE and did not alter the metabolism of arachidonic acid to 20-HETE or EETs. These studies indicate that 14,15-EE-5Z-E is a selective antagonist of the 4 regioisomeric EETs that does not affect the vasoactivity of other dilators or constrictors and does not alter the metabolism of arachidonic acid.

Addition of a methylsulfonamide (mSI) group to carboxyl of 14,15-EET reduced its metabolism by β-oxidation and incorporation into membrane phospholipids. 14,15-EE-5Z-E-mSI was also an antagonist (Figure 2). It inhibited relaxations to 14,15- and 5,6-EET but not to 11,12- or 8,9-EET. It also blocked the ability of 14,15-EET to increase BK<sub>Ca</sub> channel activity in smooth muscle cells. 14,15-EE-5Z-E-mSI inhibited the indomethacin-resistant relaxations to arachidonic acid; however, the inhibition was less than what occurred with 14,15-EE-5Z-E. The combination of 14,15-EE-5Z-E-mSI and the CYP inhibitor MSPPOH inhibited arachidonic acid–induced relaxations to the same extent as 14,15-EE-5Z-E alone. Thus, 11,12- and/or 8,9-EET must contribute to the relaxation response to arachidonic acid. 14,15-EE-5Z-E-mSI did not alter the relaxations to sodium nitroprusside, iloprost, bimakalim, or NS1619 and did not affect the metabolism of arachidonic acid. Thus, 14,15-EE-5Z-E-mSI is a selective antagonist of 14,15- and 5,6-EET.

These EET antagonists provided important pharmacological tools to examine the role of EETs as EDHFs. In the presence of COX and NOS inhibitors, bradykinin relaxes and hyperpolarizes the vascular smooth muscle of coronary arteries. Both the relaxations and hyperpolarization are inhibited by 14,15-EE-5Z-E. Relaxations to methacholine are also blocked by the EET antagonist. In human internal mammary arteries treated with NOS and COX inhibitors, bradykinin and acetylcholine caused relaxations that were blocked by 14,15-EE-5Z-E. 14,15-EE-5Z-E-mSI also inhibited the relaxations to bradykinin and methacholine in bovine coronary arteries; however, the inhibition was less than with 14,15-EE-5Z-E, suggesting that a component of the relaxation is mediated by 11,12- and/or 8,9-EET. These studies indicate that EETs mediate the non-NO, non-PG–mediated relaxations to bradykinin and acetylcholine and mediate the smooth muscle cell hyperpolarization by bradykinin.

**EETs Are Endothelium-Derived Transferable Factors**

Because EETs are synthesized in the endothelium and hyperpolarize the vascular smooth muscle, we concluded that EETs, like NO, are paracrine factors transferred from the endothelium to the smooth muscle (Figure 3A). However, endothelial EETs may be autocrine factors and hyperpolarize the endothelium by opening K channels (Figure 3B). K ions released from the endothelium activate inward rectifying K channels or the sodium–potassium ATPase in the smooth muscle to cause hyperpolarization and relaxation. Also, hyperpolarization of the endothelium by EETs may result in smooth muscle cell hyperpolarization via myoendothelial gap junctions. These EETs are autocrine effectors in the endothelium.

Several bioassay methods were developed to address this question. Gebremedhin et al and Harder et al devised a novel bioassay method for EDHF in which the perfusate of a bovine coronary artery superfused an isolated coronary smooth muscle cell. BK<sub>Ca</sub> channel activity or membrane potential was measured in the smooth muscle cells by patch clamp. The coronary artery was treated with COX and NOS inhibitors. Thus, the coronary artery served as the EDHF donor and the BK<sub>Ca</sub> channel on the smooth muscle cell as the EDHF detector. The addition of bradykinin to the donor artery increased BK<sub>Ca</sub> channel activity and hyperpolarized the detector smooth muscle cells. Pretreatment of the donor

![Figure 3. Views of vascular EET activity. A, EETs act as a transferable factor released from the endothelium and act on smooth muscle cells to open BK<sub>Ca</sub> channels, hyperpolarize smooth muscle, and cause relaxations. B, EETs act on endothelial cells to cause hyperpolarization and release K ions. K ions activate smooth muscle Na-K ATPase or inward rectifying K channels to cause hyperpolarization and relaxation.](image-url)
artery with CYP inhibitors blocked the bradykinin stimulation of BK<sub>Ca</sub> channel activity in the detector cell. Bradykinin was without effect when added to donor arteries without an intact endothelium. These studies indicate that bradykinin stimulates the release of a transferable EDHF from the donor artery. The release of this EDHF was blocked by CYP inhibitors implicating EETs in this activity. Addition of EETs to the superfusate of the smooth muscle cells mimicked the effects of bradykinin added to the donor artery. Similar findings with related experimental approaches were reported by other groups. Popp et al used porcine coronary arteries and coronary endothelial cells as the EDHF donor. In both circumstances, bradykinin hyperpolarized the detector smooth muscle cells, and the hyperpolarization was blocked by CYP inhibitors. Induction of CYP with β-naphthoflavone increased the bradykinin-induced EDHF activity. These studies indicate that bradykinin releases a transferable EDHF, and the release of EDHF depends on endothelial CYP activity. However, none of the studies indicate whether the transferable factor is an EET or if the EET acts on the endothelium to release another transferable factor.

The discovery of EET antagonists provided the needed pharmacological tool to determine whether the site of action of the endothelial EETs is on the endothelium or smooth muscle. Gauthier et al perfused 2 bovine coronary arteries in series so that the perfusate from the donor artery with endothelium perfused a detector artery without endothelium. The diameter of the detector artery was measured by videomicroscopy. Both arteries were treated with COX and NOS inhibitors. The addition of bradykinin to the detector artery was without effect, because the endothelium was removed. The addition of bradykinin to the donor artery caused dilation of the detector artery, indicating the release of a transferable dilator factor. Removal of the endothelium from the donor artery blocked this effect of bradykinin. When the donor artery was treated with 14,15-EEZE to block the action of EETs on the endothelium, bradykinin caused dilation of the detector artery. This indicated that EETs did not act on the donor endothelium. The addition of 14,15-EET to the donor artery did not dilate the detector artery, indicating that the EET did not release a transferable dilator factor from the endothelium of the donor. However, when the detector artery was treated with 14,15-EEZE, bradykinin, in addition to the donor artery, failed to dilate the detector artery. These studies indicate that EETs act as transferable EDHFs released by bradykinin and act on the smooth muscle. Furthermore, 14,15-EET and 11,12-EET were detected in the perfusate of the donor artery, and their concentrations were increased by bradykinin. These studies indicate that EETs are synthesized and released by the endothelium and are transferred to the smooth muscle cells where they cause hyperpolarization and relaxation (Figure 3A).

**Mechanism of Action of EETs on Vascular Smooth Muscle**

EETs hyperpolarize and relax vascular smooth muscle by activating BK<sub>Ca</sub> channels. EETs activate BK<sub>Ca</sub> channels in nanomolar concentrations in cell-attached patches in which the cell cytosol is in contact with the channel. However, when this association is disrupted using inside-out patches, the EETs are without effect. The addition of GTP, but not ATP, to the cytoplasmic side of the inside-out patch restores the ability of the EET to activate BK<sub>Ca</sub> channels. This can be blocked by the guanine nucleotide-binding (G) protein inhibitor GDP-β-S. It is also blocked by the addition of an antibody against Gsα but not by anti-G<sub>αi</sub> or anti-Gβγ antibodies. Activation of Gsα by ADP ribosylation with cholera toxin also increases BK<sub>Ca</sub> channel activity in cell-attached patches. In inside-out patches, BK<sub>Ca</sub> channel activity is increased by Gsα-GTP; however, Gsα-GDP and Gβγ do not alter channel activity. Other evidence implicates Gs in EET action. In 11,12-EET increases tissue plasminogen activator activity and protein expression in endothelial cells. This is associated with a 3.5-fold increase in GTP binding to Gsα but not G<sub>ai</sub>. These studies indicate that a G protein with the characteristics of Gsα mediates the EET activation of BK<sub>Ca</sub> channels, and this occurs by a membrane-delimited mechanism. In addition, in intact smooth muscle cells, EETs promote endogenous ADP ribosylation of Gsα to increase BK<sub>Ca</sub> channel activation. It is thought that EETs activate the BK<sub>Ca</sub> channel by a Gsα-mediated, membrane-delimited mechanism, which is sustained by ADP ribosylation of Gsα.

In most instances, heterotrimeric G proteins are coupled to membrane receptors and transduce the cellular response to ligand binding to the receptor. Several lines of evidence suggest that EETs act by a membrane receptor or binding site. First, the agonist activity of 14,15-EET requires specific structural features, including a specific stereochernistry of the epoxide. Variation in the EET structure results in antagonists. Second, EET action is coupled to a G protein, and EETs promote GTP binding to membranes. Third, in smooth muscle cells, 14,15-EET inhibited aromatase activity. tethering a 14,15-EET analog to a silica bead excluded the EET from entering the cell. Like 14,15-EET, the silica bead tethered 14,15-EET–inhibited aromatase activity. This indicates that 14,15-EET acts at the cell surface of smooth muscle cells. Fourth, using ligand binding, <sup>3</sup>H-14,15-EET showed high affinity, saturable, specific binding in monocytes and U937 cells. Other eicosanoids and fatty acids did not compete for binding. There may be separate receptors or binding sites for the EET regioisomers. Thus, there is suggestive evidence that EETs act on a G protein–coupled, cell surface receptor(s) or binding site(s). However, the EET binding site/receptor(s) remains to be characterized in vascular cells. Further studies are needed to clarify the mechanism of action of the EETs.

**Role of EDHF and EETs In Vivo**

There is also in vivo evidence for EDHF regulation of vascular tone. Small coronary arterioles dilate to bradykinin and acetylcholine in open-chest dogs treated with COX and NOS inhibitors. These non-NO, non-PG relaxations are inhibited by iberiotoxin, high extracellular K concentration, and CYP inhibitors. Similarly, in aspirin-treated normal human subjects, bradykinin increases forearm blood flow. Inhibition of NOS reduced, but did not block, the relaxations to bradykinin. The remaining non-NO, non-PG dilations to bradykinin were inhibited by the K channel blocker tetraethylammonium and the CYP inhibitors miconazole and sulfaphenazole. In hypertensive patients, the dilation to bradykinin...
was markedly reduced and unaffected by NOS inhibition, indicating that the NO component of dilation is lost in hypertension.68 The remaining dilations to bradykinin were inhibited by sulfaphenazole. These studies indicate that EDHF contributes to bradykinin dilation in human forearm and dog coronary arteries in vivo and that EDHF is a CYP metabolite. In hypertension, the NO component of dilation is lost, but the EDHF and EET component is preserved.

**Other Actions of the EETs**

In addition to regulating vascular tone, other vascular actions are described for the EETs. They inhibit platelet aggregation, promote angiogenesis, promote neutrophil aggregation, and inhibit endothelial adhesion molecule expression.69–73

**Perspectives**

In diseases such as hypertension, diabetes, and heart failure, dilator function of the endothelium is lost or reduced, and this has been termed endothelial dysfunction.74 In hypertension, there is loss of the NO component to dilation; however, the EDHF or EET component remains as the guardian against excessive vasoconstriction. Future therapeutic agents that enhance the activity of the endogenous EETs or mimic the EET-induced dilation may result in new treatments for hypertension and may restore the dilator function of the endothelium.

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**Disclosures**

None.

**References**


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