Epoxyeicosatrienoic Acids and Dihydroxyeicosatrienoic Acids Are Potent Vasodilators in the Canine Coronary Microcirculation

Christine L. Oltman, Neal L. Weintraub, Mike VanRollins, Kevin C. Dellsperger

Abstract—Cytochrome P450 epoxygenases convert arachidonic acid into 4 epoxyeicosatrienoic acid (EET) regioisomers, which were recently identified as endothelium-derived hyperpolarizing factors in coronary blood vessels. Both EETs and their dihydroxyeicosatrienoic acid (DHET) metabolites have been shown to relax conduit coronary arteries at micromolar concentrations, whereas the plasma concentrations of EETs are in the nanomolar range. However, the effects of EETs and DHETs on coronary resistance arterioles have not been examined. We administered EETs and DHETs to isolated canine coronary arterioles (diameter, 90.0 ± 3.4 μm; distending pressure, 20 mm Hg) preconstricted by 30% to 60% of the resting diameter with endothelin. All 4 EET regioisomers produced potent, concentration-dependent vasodilation (EC50 values ranging from −12.7 to −10.1 log [M]) and were approximately 1000 times more potent than reported in conduit coronary arteries. The vasodilation produced by 14,15-EET was not attenuated by removal of the endothelium and indicated a direct action of 14,15-EET on microvascular smooth muscle. Likewise, 14,15-DHET, 11,12-DHET, 8,9-DHET, and the d-lactone of 5,6-EET produced extremely potent vasodilation (EC50 values ranging from −15.8 to −13.1 log [M]). The vasodilation produced by these eicosanoids was highly potent in comparison to that produced by other vasodilators, including arachidonic acid (EC50 = −7.5 log [M]). The epoxide hydrolase inhibitor, 4-phenylchalone oxide, which blocked the conversion of [3H]14,15-EET to [3H]14,15-DHET by canine coronary arteries, did not alter arteriolar dilation to 11,12-DHET; thus, the potent vasodilation induced by EETs does not require formation of DHETs. In contrast, charybdotoxin (a KCa channel inhibitor) and KCl (a depolarizing agent) blocked vasodilation by 11,12-DHET and 11,12-DHET. We conclude that EETs and DHETs potently dilate canine coronary arterioles via activation of KCa channels. The preferential ability of these compounds to dilate resistance blood vessels suggests that they may be important regulators of coronary circulation. (Circ Res. 1998;83:932-939.)

Key Words: epoxyeicosatrienoic acids ■ dihydroxyeicosatrienoic acids ■ arachidonic acid ■ endothelium-derived hyperpolarizing factor ■ coronary microcirculation
Other investigators have demonstrated that the contribution of EDHF to endothelium-dependent responses is greater in small arteries than in large arteries. Thus, taken together, these studies suggest that the vasodilatory role of EETs and DHETs may be more important in coronary microcirculation than in conduit coronary blood vessels.

In the present study, we examined responses to EETs and DHETs in isolated canine coronary arterioles (diameter, <125 μm) preconstricted with endothelin. In contradistinction to coronary conduit arteries, resistance coronary arterioles were found to dilate to extremely low (picomolar) concentrations of EETs and DHETs, suggesting that these cytochrome P450 metabolites may contribute importantly to vasoregulation of the coronary circulation. We also examined potential mechanisms involved in the potent EET-induced coronary microvascular dilation.

Materials and Methods

All animal protocols were approved by the University of Iowa Animal Care and Use Committee and conform with the Guide for the Care and Use of Laboratory Animals published by the NIH (NIH publication No. 85-23, revised 1985).

Synthesis of EETs and DHETs

Vasoactivity was tested using radiolabeled EETs and DHETs to permit confirmation of the final concentrations by liquid scintillation techniques. The radiolabeled eicosanoids were synthesized, using methods originally developed for unlabeled compounds.

The radiolabeled EET regioisomers were synthesized from methylated arachidonate (American Radiolabeled Chemicals, St Louis, Mo). In brief, [1-14C]AA was mixed with AA to a specific activity of 12.3 Ci/mmol and methylated using ethereal diazomethane. The methylated arachidonate was mixed with 0.2 equivalents of m-chloroperoxybenzoic acid, and the resulting EET methyl esters were extracted, resolved by silicic acid high-performance liquid chromatography (HPLC), and collected. The isolates were saponified, again resolved by silicic acid HPLC, collected, and stored in methanol at −80°C until use.

The radiolabeled DHET regioisomers were synthesized from the corresponding [1-14C]EET methyl esters. The epoxide ring first was hydrolyzed at 40°C for 16 hours in the presence of acetic acid, and the remaining methyl ester was removed by saponification. Each DHET regioisomer was subjected to silicic acid HPLC, collected, and stored in methanol at −80°C until use.

Based on absorption at 192 nm during reversed-phase HPLC and radioassays of collected fractions, the combined normal-phase HPLC procedures produced regioisomers with >98% chemical and radiopurity. The identity of each regioisomer was established by coelution with unlabeled standards during HPLC and gas chromatography and by mass spectrometry.

Procurement of Tissue

Seventy-two adult mongrel dogs of either sex (8 to 25 kg) were euthanized with sodium pentathol (50 mg/kg). The hearts were harvested quickly and placed immediately in cold (4°C) oxygenated (20% O2; 5% CO2; 75% N2) Krebs bicarbonate buffer solution (see details below). Ventricular arterioles (60 to 150 μm; mean diameter, 90±3.4 μm) were dissected, trimmed of fat and connective tissue, and transferred to organ chambers.

Isolated Microvessel Preparation

A pressurized arteriole preparation was used to study the isolated coronary microvessels. Each end of the arteriole was cannulated with a glass micropipette. The cannulated pipettes were attached to a hydrostatic pressure reservoir under conditions of no flow. The organ chamber was placed on the stage of an inverted microscope, to which a video camera, monitor, and calibrated caliper were attached. The organ chamber was connected to a rotary pump, which continuously circulated oxygenated Krebs buffer warmed to 37°C. Internal diameters were measured by manually adjusting the video micrometer.

Each arteriole was allowed to equilibrate for 30 minutes at a distending pressure of 20 mm Hg. KCl (50 mmol/L) was added to the bath to test constrictor capacity. When stable levels of constriction were reached, the chambers were rinsed and the arterioles allowed to return to baseline diameter. Endothelin-1 (0.4 to 8.0 nmol/L) was used to constrict the arterioles to 30% to 60% of their resting diameters. Cumulative concentration-response relationships were evaluated for AA (10−10 to 10−3 mol/L), acetylcholine ([Ach] 10−10 to 10−4 mol/L), Ca2+ ionophore (A23187; 10−10 to 10−7 mol/L), and sodium nitroprusside ([SNP] 10−10 to 10−4 mol/L) by adding the drugs directly to the organ chambers. In separate experiments, concentration-response curves were performed using the 4 EET regioisomers and 8,9-DHET, 11,12-DHET, and 14,15-DHET regioisomers, as well as the 5,6-EET-methyl ester, and the 8-lactone of 5,6-EET (10−18 to 10−6 mol/L). After completing the concentration-response studies, a single dose of SNP (100 μmol/L) was applied; in the KCl depolarization and charybdoxin experiments, papaverine (100 μmol/L) was also administered. Arterioles were considered to be unacceptable for experimentation if they (1) demonstrated obvious leaks, (2) failed to constrict >50% to 50 mmol/L KCl and >30% to endothelin, or (3) failed to dilate >80% to 100 μmol/L SNP or papaverine.

In some studies, we examined whether the vasodilatory responses produced by 14,15-EET required an intact endothelium. Before microvessel cannulation, the endothelium was denuded by passing a thin wire several times through the vascular lumen. The endothelium was considered to be functionally denuded when bradykinin (1 μmol/L) produced <10% dilation. Damage to underlying smooth muscle was considered minimal if SNP (100 μmol/L) produced >80% dilation.

In other experiments, we examined whether epoxide hydroxylase inhibitors altered the dilation response induced by EET. Responses to 11,12-EET were determined in the presence of vehicle (dimethyl sulfoxide [DMSO]) or 20 μmol/L 4-phenylchalone oxide (4-PCO), an inhibitor of epoxide hydroxylases.

To examine the role of K+ channels in EET- and DHET-induced vasodilation, arteriolar responses to 11,12-EET and 11,12-DHET were performed in vessels depolarized with isotonic KCl solutions (prepared by substituting equimolar amounts of KCl for NaCl) or in endothelin-preconstricted vessels treated with 50 mmol/L charybdotoxin.

Isolated Vascular Rings

Coronary arteries were studied using a common isometric ring technique. Vascular rings (OD, 1.0 to 1.5 mm) were mounted on 2 stirrups made by passing stainless steel wires through the vessel lumen. One stirrup was attached to a force transducer and the other to a micrometer microdrive for stretching the vessel by known increments. Each vessel apparatus was placed in a 10-ml water-jacketed organ bath containing Krebs buffer equilibrated at 37°C and aerated with 20% O2, 5% CO2, and 75% N2. Isometric contractions and relaxations were measured using a computer. Rings were individually stretched to the maximum of the length-developed tension relationship by repeated test exposures to 75 mmol/L KCl at increasing vessel diameters.

The vessels were allowed to stabilize for 30 minutes before performing concentration response curves. PGF2α was used to constrict the vessels to 30% to 50% of their resting tension. After steady-state tension was achieved, concentration-response relationships were evaluated for several of the vasodilators used in the microvessel studies, including AA (10−10 to 10−3 mol/L), Ach (10−10 to 10−4 mol/L), A23187 (10−12 to 10−6 mol/L), SNP (10−10 to 10−4 mol/L), and 11,12-DHET (10−9 to 10−7 mol/L), by adding the drugs directly to the organ baths. A single dose of SNP (100 μmol/L) was added at the end of the concentration-response curve to determine maximal relaxation. Acceptable ring experiments developed >1 g of tension to PGF2α and dilated 75% to 150% in response to SNP.

Canine epicardial coronary arteries were cleaned and cut into rings 2 to 4 mm in length. The rings were placed into 24-well plates containing 1.0 mL of Krebs buffer solution with 0.1 μmol/L BSA and constantly rotated for 2 hours in a 5% CO$_2$ incubator (37°C). The rings were rinsed with fresh Krebs solution containing 4-PCO (20 μmol/L), or vehicle was added. After 1 hour, the Krebs solution was replaced with fresh solution containing 14,15-EET (5.0 μmol/L) and $[^3]$H14,15-EET (0.3 μCi) along with 4-PCO or vehicle. (Note—$[^3]$H14,15-EET: the $^3$H is present at carbons 5, 6, 8, 9, 11, 12, 14, and 15. The “14,15-” refers to the location of the epoxide group.) After 1 hour, 50-μL aliquots of the incubated solution were collected to determine total radioactivity by scintillation counting. Lipids were extracted from the incubation solution using 4-vol water-saturated ethyl acetate. Phases were separated by centrifugation at 600g for 10 minutes, and the ethyl acetate phase was collected and evaporated under N$_2$. The lipid extracts were resuspended in acetonitrile and stored at −20°C until analysis by HPLC.

Lipids were separated by reverse-phase HPLC using a Gilson 302 pump plus 2050 UV detector, and a 2.1×30-mm C$_{18}$ column containing 3-μm spherical particles of EQC (Alltech). The elution profile, developed with a Gilson 715 gradient controller, consisted of water adjusted to pH 3.4 with phosphoric acid and an acetonitrile gradient increasing from 25% to 100% over 60 minutes at a flow rate of 0.4 mL/min. Radioactivity was measured by combining the column effluent with Budget-Solve™ solution and passing the mixture through a Radiomatic Flo-One Beta isotope detector, as described previously. The amount of 14,15-DHET formed (normalized to ring wet weight) was calculated from the specific activity of the radio-labeled 14,15-EET used in the incubation. In some experiments, the radiolabeled 14,15-EET was incubated under the same conditions but in the absence of coronary artery rings. No $[^3]$H14,15-DHET was detected under these conditions (data not shown).

Solutions and Test Compounds

All solutions were prepared on the day of the experiment. Krebs solution contained (in mmol/L): NaCl, 131.5; KCl, 5; CaCl$_2$, 2.5; MgCl$_2$, 1.2; NaHCO$_3$, 23.5; KH$_2$PO$_4$, 1.2; and glucose, 11, pH 7.4. All solutions were prepared on the day of the experiment. Krebs solutions and test compounds

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<th>Regiosomer</th>
<th>EC$_{10}$</th>
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<td>14, 15</td>
<td>−16.0±0.6</td>
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<td>−14.3±1.2*</td>
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Endothelium-intact canine coronary artery preconstricted with endothelin were exposed to increasing concentrations of one of the EET or DHET regiosomers, and changes in diameter were measured. The δ-lactone of 5,6-DHET was tested (rather than 5,6-DHET) because it is the major 5,6-EET product due to an enhanced chemical stability of the lactone arising from formation of a 5-membered ring. EC$_{10}$ and EC$_{50}$ responses for each of the 4 EET and DHET regiosomers were calculated and compared using the unpaired Student t test. Values are expressed as geometrical mean±SEM (log [M]). Superscript Nos. in parentheses refer to the No. of observations. * P<0.05 vs the corresponding EET regiosomer.

Figure 1. Concentration-dependent vasodilation produced by 11,12-EET and 11,12 DHET. Canine coronary arterioles were constricted with endothelin to 53.4±4.1% (11,12-EET group) and 51.1±10.7% (11,12-DHET group) of their resting diameters, and 11,12-EET or 11,12-DHET was administered in concentration-dependent fashion. Values represent mean±SEM; n=5 for both groups. *P<0.05.
Responses to 11,12-DHET, the diol metabolite of 11,12-EET, were determined and compared with those produced by the parent EET. Surprisingly, 11,12-DHET was more potent than its parent compound at every concentration tested (Table 1). Maximal vasodilation was observed at 100 pmol/L. Surprisingly, the 11,12-DHET EC50 was 281000-fold more potent than the parent 11,12-epoxide (11,12-EET). Comparisons of the EC10 and EC50 values were 51.5±7.4%, 45.2±5.6%, and 53.6±7.1% of resting diameter in the 5,6-EET, δ-lactone, and methyl ester groups, respectively. Values represent mean±SEM; n=4 for 5,6-EET; n=3 for the other 2 groups. P=NS vs 5,6-EET. For 5,6-EET vs δ-lactone, P=0.70 and P=0.22 at 0.1 and 10.0 nmol/L, respectively. #P<0.05 for 5,6-δ-lactone vs 5,6-EET-ME.

Responses to 11,12-DHET, the diol metabolite of 11,12-EET, were determined and compared with those produced by the parent EET. Surprisingly, 11,12-DHET was more potent than its parent compound at every concentration tested (Figure 1). Moreover, with substantial vasodilation occurring at a concentration of ≈10^{-18} mol/L, 11,12-DHET was the most potent agent tested in this study. The calculated EC10 and EC50 values were −17.8±0.6 and −15.8±0.7 (log [M]), respectively (Table 1). Thus, comparisons of the EC50 and EC50 values indicated that the 11,12-diol was 13,000- to 1,000,000-fold more potent than the parent 11,12-epoxide (Table 1). Maximal vasodilation was observed at 100 pmol/L 11,12-DHET; at this concentration, the diameter of the arteriole was essentially that of the preconstricted state.

Next, we examined responses to 5,6-EET and the δ-lactone of 5,6-EET. Similar to the results obtained with 11,12-EET, significant vasodilation occurred at subpicomolar concentrations of 5,6-EET, and the calculated EC10 and EC50 values were −13.3±1.0 and −10.8±0.8 (log [M]), respectively (Figure 2, Table 1). Maximal vasodilation was 91±9% and occurred with a concentration of 1 μmol/L. Surprisingly, the δ-lactone was found to be at least as potent as the parent 5,6-EET (41±12% vasodilation at 0.01 pmol/L; EC50 (log [M])=−13.3±0.8). Vasodilation (100%) to the δ-lactone occurred at 100 pmol/L. We did not investigate responses to 5,6-DHET, because this compound is known to rapidly rearrange to the δ-lactone in aqueous solutions. However, to assess whether the neutral lactone’s sustained potency was largely due to an enhanced lipophilicity at pH 7.4, we examined the potency of the neutral 5,6-EET methyl ester (5,6-EET-ME). The latter compound produced vasodilation that is somewhat less potent than that produced by the δ-lactone; P<0.05 (Figure 2, Table 1). Thus, the high potency of the 5,6-DHET lactone was not simply due to removal of the anionic charge, and the DHET product remained as potent as the parent EET.

Responses to the remaining 2 EET regioisomers, 8,9-EET and 14,15-EET, and their diol metabolites, were also determined. All 4 compounds were found to be potent vasodilators of canine coronary arteries (Figure 3, Table 1). Similar to 11,12-DHET, 8,9-DHET possessed an EC50 that was lower than its EET precursor (Table 1); that is, the 8,9-diol was slightly more potent than its 8,9-epoxide precursor in initiating vasodilation. However, at the higher concentrations the DHET and EET curves tended to overlap (Figure 3A), and the 8,9-DHET EC50 {−13.1±0.7 (log [M])} was essentially the same as that of 8,9-EET {−11.0±0.4 (log [M])}. Although the concentration-response curve of 14,15-DHET tended to be to the left of the parent 14,15-EET (Figure 3B), the 2 compounds were equipotent (P=0.09).

To address whether EET-induced vasorelaxation is dependent on the presence of endothelium, we examined responses to 14,15-EET in endothelium-denuded coronary arteries. Denuded microvessels did not respond to bradykinin (1 μmol/L); however, SNP (100 μmol/L) produced 94±3% relaxation. Despite the absence of functional endothelium, 14,15-EET produced potent vasodilation that did not differ significantly from the responses observed in endothelium-
pretreated with 4-PCO as compared with vehicle (Figure 4B): EC$_{50}$ (log [M]) = −12.5±0.9, maximal vasodilation=88±8% at 1 μmol/L; and EC$_{50}$ (log [M]) = −11.68±0.9; maximal vasodilation=77±3% at 1 μmol/L, respectively (n=5 for both groups). These data suggest that the 11,12-EET-induced vasodilation is not dependent on conversion of the regioisomer to 11,12-DHET.

Further studies were performed to investigate the role of K$^+$ channels in EET- and DHET-induced coronary microvascular dilation. Canine coronary arterioles were constricted with endothelin or isotonic KCl solution (35±2 mmol/L) to 30% to 60% of their resting diameter. 11,12-EET or 11,12-DHET was administered in a concentration-dependent manner. KCl depolarization abolished the dilation to 11,12-EET (Figure 5A) and 11,12-DHET (Figure 5B).

We also examined the effects of charybdotoxin, an inhibitor of K$_{Ca}$ channels, on EET- and DHET-induced vasodilation. Responses to 11,12-EET (Figure 5C) and 11,12-DHET (Figure 5D) were attenuated in the presence of 50 mmol/L charybdotoxin by 59% and 56%, respectively. Together, these data suggest that EET- and DHET-induced microvascular relaxation involves activation of vascular smooth muscle K$_{Ca}$ channels.

Responses to AA (the precursor of EETs and DHETs), calcium ionophore (A23187), Ach, and SNP were also determined. AA produced concentration-dependent vasodilation, with 20% and 90% dilation at concentrations of 1 mmol/L and 10 μmol/L, respectively. The calculated EC$_{50}$ value for AA was −7.5±0.4 (log [M]) (Table 2), which was 1000- to 10 000-fold less than found for the EETs and their DHET products. All of the other vasodilators also produced concentration-dependent vasodilation of endothelin-preconstricted microvessels. However, 11,12-DHET was far more potent than all of these compounds tested. It is interesting that the potency of A23187 approached those of other EETs and their metabolites (Table 2). A23187 was more potent than Ach, AA, and SNP.

Responses to AA, A23187, Ach, SNP, and 11,12-DHET also were determined in PGF$_{2_\alpha}$-constricted conduit coronary arterial rings. AA and SNP produced complete relaxation of the conduit arterial rings, whereas Ach and A23187 produced 89±4% and 78±7% relaxation, respectively, at the highest concentrations studied (100 and 1 μmol/L, respectively). EC$_{50}$ values of these agents are shown in Table 2. Up to 0.1 μmol/L 11,12-DHET produced minimal relaxation (24±13%) of PGF$_{2_\alpha}$-constricted conduit arterial rings; at higher concentrations, 11,12-DHET actually constricted the vessels. As was observed in microvessels, A23187 was more potent than SNP, Ach, and AA in conduit vessels.

**Discussion**

There are several major findings in the present study. First, all 4 EET regioisomers produced extremely potent, concentration-dependent dilation of isolated canine coronary arterioles. The vasodilation produced by 14,15-EET was not attenuated by removal of the endothelium, suggesting a direct action of the compound on microvascular smooth muscle cells. Second, the major EET metabolites, DHETs, each produced vasodilation that was at least as potent as that
produced by the parent EETs. However, suppression of DHET formation by inhibition of epoxide hydrolases did not attenuate 11,12-EET–induced vasodilation, suggesting that the potent 11,12-EET–induced vasodilation is not dependent on conversion to 11,12-DHET. Third, vasodilation produced by 11,12-EET and 11,12-DHET was blocked by depolarization with KCl or charybdotoxin, suggesting that the responses were mediated by activation of KCa channels. Finally, the potency of EETs and DHETs to dilate coronary arterioles was found to be far greater than the potency reported for conduit coronary arteries. Together, these findings suggest that EETs and their diol metabolites may importantly regulate the coronary microcirculation.

Roslosky et al reported that in canine conduit coronary arteries contracted with U46619, the 4 EET regioisomers ranged between 1 and 100 pmol/L (Table 1), whereas Campbell et al and Weintraub et al showed similar results using bovine and porcine conduit coronary arteries. In contrast, we found that the markedly enhanced EET and DHET potency in arterioles is not due to nonspecific enhancement in smooth muscle sensitivity or differences in experimental methodology. It was possible that the markedly enhanced EET potency could have been due to a nonspecific augmentation in the vasodilatory capacity of coronary arterioles as compared with conduit coronary artery responses. Such augmented vasodilatory capacity could be an inherent attribute of the arterioles, or it could stem from differences in the methodology used to examine responses in microvessels as compared with conduit arterial rings.

Responses to coronary arteriolar vasodilators were determined as described in Table 1. Conduit arteries were constricted with PGE2, before exposure to vasodilators. 11,12-DHET produced only minimal (24%±13%) relaxation of PGE2–constricted conduit arterial rings. The E50 values are expressed as geometrical mean±SEM (log M). Superscript numbers refer to the No. of observations. *P<0.05 vs 11,12-DHET.
to EDHF are more prominent in smaller blood vessels in rabbit and rat.14,22–28 Recently, Nagao et al.21 reported that smaller blood vessels exhibited enhanced potency to aprikalamin, an agonist that produces vasorelaxation through activation of ATP-sensitive K+ channels, suggesting that small arteries are more sensitive to the actions of hyperpolarizing vasodilators than are large arteries. Therefore, a plausible explanation for the moderately enhanced potencies of AA, Ach, and A23187 in coronary arteries is that these agonists stimulate the formation of EDHF, which, in turn, produces more potent dilation of arterioles than conduit arteries.

We also report for the first time that 14,15-DHET, 11,12-DHET, 8,9-DHET, and the δ-lactone of 5,6-EET are potent dilators of resistance blood vessels. In previous studies, it was reported that DHETs did not produce vasorelaxation of rabbit aorta, rat mesenteric microvessels, or the isolated perfused rat tail artery.14–16 Based on these observations, it was proposed that after a 3-minute incubation of porcine coronary arteries, 11,12-DHET yields a more potent vasodilator compound in smaller blood vessels than in conduit arteries. We also report for the first time that 14,15-DHET, 11,12-DHET, 8,9-DHET, and the δ-lactone of 5,6-EET are potent dilators of resistance blood vessels. In previous studies, it was reported that DHETs did not produce vasorelaxation of rabbit aorta, rat mesenteric microvessels, or the isolated perfused rat tail artery.14–16 Based on these observations, it was proposed that after a 3-minute incubation of porcine coronary arteries, 11,12-DHET yields a more potent vasodilator compound in smaller blood vessels than in conduit arteries.

Cultured vascular smooth muscle and endothelial cells rapidly convert EETs into DHETs.12,13,17,18 We recently reported that after a 3-minute incubation of porcine coronary artery smooth muscle cells with 1 μmol/L [3H]14,15-EET, 8% of the radioactivity recovered in the medium already had been converted to [3H]14,15-DHET.52 These findings, together with the current observation that 11,12-DHET is far more potent than its parent compound, 11,12-EET, in coronary microvessels, raised the possibility that the 11,12-EET–induced vasodilation might be mediated by its diol metabolite. However, the epoxide hydrolase inhibitor 4-PCO, which effectively blocked DHET formation in canine coronary microvessels, did not inhibit vasodilation to 11,12-EET in coronary microvessels. Thus, although conversion of 11,12-EET to 11,12-DHET yields a more potent vasodilator compound in canine coronary microvessels, the mechanism of the 11,12-EET–induced vasodilation is not dependent on the formation of 11,12-DHET.

In summary, the 4 EET regioisomers, and their diol metabolites, produced extremely potent vasodilation of canine coronary arterioles. The vasodilation, which was 10 000-fold more potent than has been reported in conduit coronary arteries, was mediated by activation of vascular smooth muscle KCa channels. The preferential ability of these compounds to dilate resistance arterioles suggests that they may contribute to the physiological and/or pathophysiological regulation of coronary microcirculation.

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References


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