20-HETE modulates myogenic response of skeletal muscle resistance arteries from hypertensive Dahl-SS rats

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Received 27 June 2000; accepted in final form 9 October 2000

Frisbee, Jefferson C., Richard J. Roman, U. Murali Krishna, John R. Falck, and Julian H. Lombard. 20-HETE modulates myogenic response of skeletal muscle resistance arteries from hypertensive Dahl-SS rats. Am J Physiol Heart Circ Physiol 280: H1066–H1074, 2001.—The present study determined the role of 20-hydroxyeicosatetraenoic acid [20-HETE; produced by ω-hydroxylation of arachidonic acid via cytochrome P-450 (CP450) 4A enzymes] in regulating myogenic activation of skeletal muscle resistance arteries from normotensive (NT) and hypertensive (HT) Dahl salt-sensitive (SS) rats. Gracilis arteries (GA) were isolated from each rat and viewed via television microscopy, and changes in vessel diameter with altered transmural pressure were measured with a video micrometer. Under control conditions, GA from both groups exhibited strong, endothelium-independent myogenic activation. Treatment of GA with 17-octadecynoic acid (17-ODYA; inhibitor of CP450 4A enzymes) did not alter myogenic activation in NT rats, but impaired this response in HT animals. Treatment of GA from HT rats with dibromo-dodecynyl-methylsulfimide (DDMS; inhibitor of 20-HETE production) impaired myogenic activation, as did application of 20-hydroxyeicosanoic acid (20-HETE) or cytochrome P-450 4A enzymes (CP450 4A enzymes). Application of iberiotoxin, a Ca2+-activated potassium (KCa) channel inhibitor, restored myogenic activation from HT rats treated with DDMS. These results suggest that myogenic activation of skeletal muscle resistance arteries from NT Dahl-SS rats does not depend on CP450, whereas myogenic activation of these vessels in HT Dahl-SS rats is partly a function of 20-HETE production, inhibiting KCa channels through a receptor-mediated process.

The myogenic response of skeletal muscle resistance arteries to changes in intravascular pressure is an important contributing element underlying the autoregulation of tissue blood flow. The elucidation of the cellular mechanisms contributing to myogenic activation of these vessels is an area of active investigation, and a number of distinct signaling pathways have been identified as playing key contributing roles. Possible mechanisms include the opening of stretch-activated cation channels, causing membrane depolarization and activation of voltage-gated Ca2+ channels, a breakdown of membrane phospholipids in response to elevated stretch that may enhance intracellular Ca2+ release via inositol triphosphate production, and parallel activation of protein kinase C via diacylglycerol that may contribute to an increased Ca2+ sensitivity of the contractile machinery (5, 22).

Studies in recent years have also suggested that cytochrome P-450 (CP450) ω-hydroxylase and the production of 20-hydroxyeicosatetraenoic acid (20-HETE) may play a role in myogenic activation of small arteries and arterioles of the cerebral (12, 17) and renal (14, 16, 21) circulation. Harder et al. (13) reported that inhibition of 20-HETE formation abolishes the autoregulation of blood flow in response to elevated perfusion pressure in the cerebral and renal circulation and prevents constriction of cerebral and renal resistance arteries and arterioles after elevations in transmural pressure. Additional studies addressing the cellular mechanisms underlying myogenic responses of the cerebral and renal vasculature suggest that 20-HETE may exert its effects by the following: 1) inhibiting the opening of large conductance Ca2+-activated K+ (KCa) channels (26), 2) activating L-type Ca2+ channels (8), or 3) activating protein kinase C and inhibiting membrane K+ current (17).

However, to date there has been no attempt to determine the role of CP450 ω-hydroxylase in regulating myogenic activation of skeletal muscle resistance arteries. This represents an important avenue of investigation for two reasons. First, these vessels lie immediately proximal to the microcirculation and play a critical role in regulating the flow of blood through the downstream arteriolar networks. Second, given the inherent nature of tissue-specific differences in the regulation of vascular tone, extrapolation of previous data addressing the role of CP450 ω-hydroxylase and the production of 20-HETE in contributing to myogenic
activation of resistance arteries and arterioles from the renal and cerebral circulation to skeletal muscle resistance arteries is problematic. The purpose of the present study was to determine the contribution of CP450 4A \( \omega \)-hydroxylase, and specifically the production of 20-HETE, to myogenic activation of extraparenchymal resistance arteries from the skeletal muscle circulation of normotensive and hypertensive Dahl salt-sensitive (SS) rats. The use of both normotensive and hypertensive Dahl rats represents an important component of the present study, because previous investigations have suggested that hypertension may be associated with increased CP450 \( \omega \)-hydroxylase expression (23), elevated vascular production of 20-HETE (4), and increased sensitivity of vessels to 20-HETE (9).

**MATERIALS AND METHODS**

**Animals.** The present study used two groups of 10- to 13-wk-old male Dahl SS rats (SS/Jr/Mcw). One group (normotensive) was fed a low-salt diet (0.4\% NaCl) until the day of the experiment, whereas the second group was fed a high-salt diet (4.0\% NaCl) for 4 wk preceding the experiment, causing the development of hypertension. All rats drank tap water ad libitum. The rats were anesthetized with an intraperitoneal injection of pentobarbital sodium (30 mg/kg), and a carotid artery was cannulated for determination of mean arterial pressure. Body weight was 287 ± 11 g in normotensive rats and 307 ± 11 g in hypertensive rats. Mean arterial pressure, measured under anesthesia, was 108 ± 5.8 mmHg in normotensive rats and 174 ± 5.9 mmHg in the hypertensive animals \((P < 0.001)\).

**Preparation of isolated vessels.** The small muscular branch of the femoral artery supplying the gracilis muscle was removed from the anesthetized rat, with care taken to minimize vessel stretching and to handle the artery by its surrounding connective tissue only. The vessels were then placed in warmed physiological salt solution (PSS) equilibrated with a 21\% O\(_2\)-5\% CO\(_2\)-74\% N\(_2\) mixture. The PSS used in these experiments was composed of (in mM) 119 NaCl, 4.7 KCl, 1.17 MgSO\(_4\), 1.6 CaCl\(_2\), 1.18 NaH\(_2\)PO\(_4\), 24 NaHCO\(_3\), 0.026 EDTA, and 5.5 glucose.

After isolation, arteries were placed in a heated (37\°C) chamber that allowed the vessel to be perfused and superfused with the PSS described above from separate individual reservoirs. Gracilis arteries were cannulated at both ends with glass micropipettes (about 100 \( \mu \)m tip diameter) and secured to the inflow and outflow pipettes with the use of a 10-0 nylon suture. Any side branches were ligated with a single strand teased from a 6-0 silk suture. The inflow pipette was connected to a reservoir perfusion system that allowed the intraluminal pressure and luminal gas concentrations to be controlled. Vessel diameter was measured by using television microscopy and an onscreen video micrometer.

Arteries were extended to their in situ length and equilibrated at 80\% of the animal’s mean arterial pressure to approximate the perfusion pressure encountered in vivo (18). Any vessel that did not demonstrate both a functional endothelium and active tone at rest (assessed by vasodilation in response to 1 \( \mu \)M acetylcholine in the vessel chamber) was not used in the study. Active tone at the equilibration pressure was calculated as \((\Delta D/D_{\text{max}}) \times 100\), where \( \Delta D \) is the diameter increase from rest in response to Ca\(^{2+}\)-free PSS and \( D_{\text{max}} \) is the maximum diameter measured at the equilibration pressure in Ca\(^{2+}\)-free PSS. Active tone of gracilis arteries from normotensive rats (37.5 ± 2.4\%) was significantly lower than that for vessels from hypertensive rats (47.3 ± 2.9\%; \( P < 0.05\)).

**Methods for removal of vascular endothelium.** The endothelium of isolated arteries was removed via air bolus perfusion, as described previously (19), with minor modification. Briefly, five 1-ml air boli were injected into the perfusion line (each separated by 1 ml of perfusate) and were allowed to perfuse the vessel lumen. Subsequently, PSS perfusion through the lumen was restored, and the artery was allowed to reequilibrate for 30 min before proceeding with the experiment. In all experiments, the integrity of the endothelium after air bolus perfusion was assessed by determining the ability of the vessel to dilate in response to 1 \( \mu \)M acetylcholine. The endothelium denudation procedures were deemed successful when any dilation of the vessel in response to acetylcholine challenge was eliminated. In no experiment was it necessary to repeat the air bolus perfusion more than twice.

**Inhibition of CP450 4A \( \omega \)-hydroxylase.** To assess the contribution of CP450 4A \( \omega \)-hydroxylase in contributing to myogenic activation of vessels with transmural pressure elevation, these enzymes were inhibited with 17-octadecynoic acid (17-ODYA; Sigma), as described previously (1, 3). 17-ODYA is a suicide substrate inhibitor of CP450 4A enzymes and irreversibly inhibits the production of 20-HETE via \( \omega \)-hydroxylation of arachidonic acid and the production of epoxyeicosatrienoic acid by arachidonic acid epoxidation (25). Briefly, while normal PSS superfusion was interrupted, 17-ODYA was added to the vessel chamber to a final concentration of 10 \( \mu \)M and was incubated with the isolated vessel for 30 min, after which superfusion with normal PSS was restored.

**Inhibition of CP450 \( \omega \)-hydroxylase.** To evaluate the role of arachidonic acid \( \omega \)-hydroxylation and the production of 20-HETE in contributing to myogenic activation of gracilis arteries from these rats, this enzyme was blocked with the selective competitive inhibitor dibromo-dodecynyl-methylsulfonamide (DDMS; Ref. 25), as described previously (3). Briefly, while normal PSS superfusion was interrupted, DDMS was added to the vessel chamber to a final concentration of 10 \( \mu \)M and was allowed to incubate with the vessel for 30 min. After the initial treatment with DDMS, the vessel was continuously superfused with normal PSS containing 1 \( \mu \)M DDMS for the remainder of the experiment.

**Blockade of 20-HETE receptor.** A recent study (2) has suggested that the actions of 20-HETE to regulate potassium channels are receptor mediated. That study (2) also indicted that the synthetic compound 20-hydroxyeicosa-6(Z),15(Z)-dienoic acid [6(Z),15(Z)-20-HEDE] is a highly selective antagonist of this receptor, completely abolishing vascular reactivity in response to challenge with 20-HETE. To more fully evaluate the role of 20-HETE in regulating myogenic activation of skeletal muscle arteries, the myogenic responses were tested after addition of 6(Z),15(Z)-20-HEDE to the tissue bath to achieve a final concentration of 1 \( \mu \)M, as described previously (2).

**Inhibition of \( K_{\text{Ca}} \) channels.** Previous studies have determined that 20-HETE inhibits the opening of large conductance \( K_{\text{Ca}} \) channels, preventing membrane hyperpolarization in the face of elevated intracellular calcium (26). To determine the extent to which \( K_{\text{Ca}} \) channels modulate the actions of CP450 \( \omega \)-hydroxylase and 20-HETE in regulating arterial myogenic responses, the selective \( K_{\text{Ca}} \) channel blocker ibetanide (IBTX) was added to the vessel chamber to a final concentration of 100 nM, as previously described (24).

**Experimental protocols.** Preliminary control experiments demonstrated that myogenic activation of isolated skeletal
muscle resistance arteries did not decay over time courses that were similar to those that were required for the performance of the experimental perturbations and techniques described above. The initial series of experiments in the present study was performed to determine the contribution of the vascular endothelium to myogenic activation of the isolated arteries. Once vessel responses to elevated intraluminal pressure were determined under control conditions, the endothelium was removed as described above, and determination of the myogenic responses was repeated.

For the determination of myogenic responses, the perfusate outflow line was clamped and the height of the perfusion reservoir was changed to vary intraluminal pressure in 20-mmHg intervals between 20 and 160 mmHg. Vessel diameter was determined after ~10 min at each intraluminal pressure, and pressure levels were randomized for each myogenic curve. After the procedures were completed, the perfusate and superfusate were replaced with Ca^{2+}-free PSS and the passive diameter of the fully relaxed vessel was determined over the identical pressure range used for the myogenic responses.

The subsequent set of experiments determined the contribution of CP450 4A products of arachidonic acid to myogenic activation of the isolated gracilis arteries. Once myogenic responses were determined under control conditions, vessels were treated with 17-ODYA, as described above. After incubation with the CP450 4A enzyme inhibitor, the determination of myogenic responses was repeated.

The third series of experiments was designed to determine the contribution 20-HETE production via CP450 4A enzyme system. Throughout the present study, tension development in the vascular wall with alterations in intraluminal pressure was calculated as described previously (16)

\[ T(dyn/cm) = -1,383 (dyn/cm^2 \cdot mmHg) \cdot P \cdot (R_A - R_p) \times 10^{-4} (cm/\mu m) \]

where \( T \) represents the difference in wall tension during passive conditions (Ca^{2+}-free PSS) versus active conditions (normal PSS) at a given intraluminal pressure. In this equation, \( P \) represents transmural pressure (mmHg), and \( R_A \) and \( R_p \) represent active and passive vessel radii (\( \mu m \)) at a given \( P \) in normal PSS and in Ca^{2+}-free PSS, respectively. As such, \( T \), which we have plotted as “active tension,” represents the absolute value of the difference in vessel wall tension between passive conditions and active conditions under a given set of experimental conditions and at a given intraluminal pressure.

For the present study, the myogenic response was defined as the ability of the isolated vessel to maintain its diameter over the imposed intraluminal pressure range. From each experiment, data describing both the change in vessel diameter and the increase in active tension with increasing intraluminal pressure were fit with the following linear regression equation (least-squares analysis; \( r^2 > 0.90 \)); \( y = \alpha + \beta x \); where \( y \) represents arterial diameter or active tension at a specific intraluminal pressure, \( \alpha \) is an intercept term, and \( x \) is the intraluminal pressure. \( \beta \) represents the slope of the pressure versus diameter or the pressure versus active tension curve (i.e., the rate of change in either arterial diameter or active tension for an incremental change in intraluminal pressure). Differences between \( \beta \) coefficients for the curves as well as differences in resting vessel diameter were determined by using ANOVA with Tukey’s test post hoc or Student’s t-test where appropriate. Throughout all analyses, a probability level of \( P < 0.05 \) was considered to be statistically significant.

RESULTS

Resting vessel diameter. Table 1 summarizes data describing the resting diameter of isolated gracilis arteries from normotensive and hypertensive Dahl-SS rats under the experimental conditions in the present study. Neither removal of the vascular endothelium nor treatment of the isolated artery with 17-ODYA significantly altered arterial diameter in either normotensive or hypertensive animals. In addition, treatment of isolated arteries from hypertensive Dahl rats, either with DDMS or with the 20-HETE receptor antagonist, had no significant effect on vessel diameter. Application of IBTX to either control vessels or to vessels treated with DDMS tended to decrease arterial diameter, although this effect was not significant (\( P > 0.20 \) for both). In all cases, vessel diameter was significantly less than that determined during superfusion with Ca^{2+}-free PSS, indicating the maintenance of significant basal tone after the inhibition of the CP450 4A enzyme system.

<table>
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<tr>
<th>Table 1. Data describing resting diameter of isolated gracilis arteries from NT and HT Dahl-SS rats under experimental conditions.</th>
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<tbody>
<tr>
<td>Rats</td>
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<tr>
<td>Control, n = 10 NT and 25 HT</td>
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<tr>
<td>Endothelium removed, n = 5 for each</td>
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<tr>
<td>+ 10 μM 17-ODYA, n = 5 for each</td>
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<td>+ 100 nM IBTX, n = 5 HT</td>
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<td>+ 10 μM DDMS, n = 5 HT</td>
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<td>+ 10 μM DDMS; 100 nM IBTX, n = 5 HT</td>
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<td>Maximum diameter, μm, n = 10 NT and 25 HT</td>
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Values are means ± SE; n, no. of rats in each group. NT, normotensive; HT, hypertensive; SS, salt sensitive; 17-ODYA, 17-octadecynoic acid; IBTX, iberiotoxin; DDMS, dodecylmethylsulfoxide; 20-HEDE, 20-hydroxyeicosanoid-6(Z),15(Z)-dieneoic acid. All measurements were taken at the intraluminal equilibration pressures for the respective vessels. One vessel was used from each rat. *P < 0.05 vs. control conditions. †P < 0.05 vs. NT rats.
Effects of endothelium removal. The effects of removing the vascular endothelium on myogenic responses and the development of active tension in response to elevated transmural pressure in isolated vessels of normotensive and hypertensive rats are shown in Figs. 1 and 2, respectively. Endothelium removal had no effect on myogenic activation or active tension development in either the normotensive rats (P = 0.990 for myogenic responses; P = 0.964 for active tension development) or in hypertensive animals (P = 0.993 for myogenic responses; P = 0.418 for active tension development).

Effects of inhibition of CP450 4A enzymes. The effect of 17-ODYA on pressure-induced constriction of gracilis vessels and development of active tension in normotensive and hypertensive rats are shown in Figs. 3 and 4, respectively. In normotensive rats (Fig. 3), treatment of gracilis arteries with 17-ODYA did not alter myogenic activation (P = 0.849) or active tension development (P = 0.828) compared with responses determined under control conditions. In contrast, treatment of isolated vessels from hypertensive rats with 17-ODYA (Fig. 4) impaired myogenic activation of gracilis arteries (P = 0.003) and the development of active tension (P = 0.009) after elevations in transmural pressure compared with responses determined under control conditions. Removal of the vascular endothelium did not affect the patterns of myogenic activation or active tension development in normotensive and hypertensive rats after inhibition of CP450 4A enzymes (data not shown). The slope of the curves relating active tone versus transmural pressure in 17-ODYA-treated vessels from both normotensive and hypertensive rats was significantly less than that of the pressure-diameter relationship for the vessel in Ca²⁺-free physiological salt solution (PSS). Data are means ± SE; n, 1 vessel per rat from 5 rats. *P < 0.05 vs. control conditions. †P < 0.05 vs. endothelium removal.

Figure 5 summarizes data describing the effects of the specific KCa channel blocker IBTX on myogenic activation and active tension development of control and DDMS-treated gracilis arteries from hypertensive Dahl-SS with increased intraluminal pressure. Application of IBTX alone did not significantly alter either myogenic activation (P = 0.934) or active tension development (P = 0.452) of isolated vessels from control values. As stated above, treatment of vessels with DDMS alone impaired myogenic activation (P = 0.015) and active tension development (P = 0.050) in response to elevated intraluminal pressure. However, combined treatment of vessels from hypertensive rats with IBTX and DDMS restored myogenic activation and active tension development such that slope coefficients describing these responses were not different from those in arteries under control conditions (myogenic activation: P = 0.736, active tension development: P = 0.270). Furthermore, combined treatment with IBTX and DDMS significantly increased both myogenic activation and active tension development compared with values in vessels receiving DDMS treatment alone (myogenic activation, P = 0.020; active tension development, P = 0.018). In all cases, the slope of the pressure-diameter relationship in the presence of
Ca\textsuperscript{2+}-free PSS was significantly greater than the myogenic curve (P < 0.001).

Figure 6 summarizes the effects of 6(Z),15(Z)-20-HEDE, a selective antagonist for 20-HETE receptors, on myogenic activation (Fig. 6, A and B) and active tension development (Fig. 6, C and D) in response to increased intraluminal pressure in isolated arteries of hypertensive rats. Treatment of vessels with the an-

Fig. 2. Changes in vessel diameter (A) and active tension development (C) of isolated GA from HT Dahl-SS rats with elevated intraluminal pressure and slope coefficients describing these relationships (B and D, respectively) for vessels under control conditions, after vascular endothelium removal, and in the presence of Ca\textsuperscript{2+}-free PSS. Data are means ± SE; n, 1 vessel per rat from 5 rats. *P < 0.05 vs. control conditions. †P < 0.05 vs. endothelium removal.

Fig. 3. Changes in vessel diameter (A) and active tension development (C) of isolated GA from NT Dahl-SS rats with elevated intraluminal pressure and slope coefficients describing these relationships (B and D, respectively) for arteries under control conditions, after treatment of the vessel with 17-octadecynoic acid (17-ODYA), and in the presence of Ca\textsuperscript{2+}-free PSS. Data are means ± SE; n, 1 vessel per rat from 5 rats. *P < 0.05 vs. control conditions. †P < 0.05 vs. treatment of the vessel with 17-ODYA.
agonist significantly reduced myogenic activation from control levels ($P = 0.012$) in a manner that was similar to that observed after inhibition of CP450 o-hydroxylase with 17-ODYA or DDMS, although the reduction in the development of active tension with elevated transmural pressure after treatment of the vessels with 6(Z),15(Z)-20-HEDE failed to reach significance ($P = 0.152$).

Fig. 4. Changes in vessel diameter (A) and active tension development (C) of isolated GA from HT Dahl-SS rats with elevated intraluminal pressure and slope coefficients describing these relationships (B and D, respectively) for arteries under control conditions, after treatment of the vessel with 17-ODYA, and in the presence of Ca$^{2+}$-free PSS. Data are means ± SE; $n$, 1 vessel per rat from 5 rats. *$P < 0.05$ vs. control conditions. †$P < 0.05$ vs. treatment of the vessel with 17-ODYA.

Fig. 5. Changes in vessel diameter (A) and active tension development (C) of isolated GA from HT Dahl-SS rats with elevated intraluminal pressure and slope coefficients describing these relationships (B and D, respectively) for arteries under control conditions ($n = 10$), after treatment of the vessel with iberiotoxin (IBTX, $n = 5$), after treatment of the vessel with dodecyl-methylsulfoximide (DDMS, $n = 5$), in vessels receiving both DDMS and IBTX treatment ($n = 10$), and in the presence of Ca$^{2+}$-free PSS ($n = 10$). Data are means ± SE. *$P < 0.05$ vs. control conditions. †$P < 0.05$ vs. treatment of the vessel with IBTX. ‡$P < 0.05$ vs. treatment of the vessel with DDMS. §§$P < 0.05$ vs. treatment of the vessel with DDMS and IBTX.
DISCUSSION

It has recently been suggested that ω-hydroxylation of arachidonic acid via CP450 4A enzymes, and the resulting production of 20-HETE, plays a central role in regulating the pressure-induced constriction of arteries and arterioles in the cerebral and renal circulation that can play an important role in the autoregulation of renal and cerebral blood flow (11, 13). To date, however, there has been little attempt to determine a comparable role for CP450 ω-hydroxylase and the production of 20-HETE in regulating myogenic responses of the skeletal muscle vasculature under either normal physiological conditions or with the development of pathological alterations impacting the vasculature (e.g., SS hypertension). The present study begins to address these questions by evaluating the contribution of CP450 ω-hydroxylase and the production of 20-HETE to the regulation of myogenic response in isolated skeletal muscle resistance arteries from normotensive and hypertensive Dahl-SS rats.

The results of the present study clearly indicate that endothelium removal has no effect on pressure-induced constriction of isolated skeletal muscle arteries or the increase in tone with elevations in transmural pressure of either normotensive and hypertensive Dahl-SS rats. Whereas these results contrast with previous investigations (10, 15), which suggested a role for the vascular endothelium in regulating myogenic responses in other vascular beds, they are in agreement with the majority of the existing literature (5–7, 19, 22), indicating that myogenic activation of skeletal muscle vessels is independent of the endothelium. As such, the results of the present study indicate that production of endothelium-derived products does not play a significant role in mediating the myogenic activation of skeletal muscle resistance arteries of either normotensive or hypertensive Dahl-SS rats in response to increased intraluminal pressure.

In the present study, the inhibition of CP450 4A enzymes had no effect on myogenic activation and active tension development of isolated arteries from normotensive Dahl-SS rats on a low-salt diet. This suggests that production of 20-HETE via the ω-hydroxylation of arachidonic acid does not contribute to pressure-induced constriction or myogenic tone in this strain of rats under normotensive conditions. The lack of an effect of inhibiting CP450 4A enzymes on the myogenic responses of skeletal muscle resistance arteries from normotensive rats is in contrast to results from recent studies indicating a significant contribution of 20-HETE production in mediating pressure-induced activation of renal and cerebral arteries and arterioles of Sprague-Dawley and spontaneously hypertensive rats fed a normal salt diet (13). When integrated, these results suggest that the role of 20-HETE production in contributing to myogenic activation may differ substantially in resistance vessels from different tissues and from different animal strains.

However, the results of the present study indicate that the production of 20-HETE via CP450 pathways is an important mediator of the pressure-induced constriction of skeletal muscle resistance arteries from hypertensive Dahl-SS rats. Specifically, treatment of isolated arteries from hypertensive Dahl-SS with ei-
Consistent with earlier hypotheses of 20-HETE action which results in an increased production of 20-HETE. The results of this study suggest that myogenic reactivity of isolated skeletal muscle resistance arteries is not inhibited with DDMS. When application of IBTX to arteries that have also been treated with DDMS restores myogenic reactivity and active tension development to levels that are not different from those determined in arteries in which 20-HETE formed in response to elevated intraluminal pressure. Our results indicate the production of 20-HETE via CP450 \(\omega\)-hydroxylase working through a receptor-mediated process to inhibit the open-state probability of \(K_{Ca}\) channels. Although the production of 20-HETE in response to elevated intraluminal pressure is not necessary for development of myogenic activation, this process does appear to be critical for the ability of the isolated artery of hypertensive rats to decrease its diameter with elevated intraluminal pressure.

In conclusion, our results suggest that myogenic activation of isolated skeletal muscle resistance arteries from normotensive Dahl-SS rats is independent of both endothelium-derived vasoconstrictor substances and the production of vasoactive metabolites via CP450 4A enzymes. In contrast, the myogenic response in arteries from hypertensive Dahl-SS rats, while still independent of the vascular endothelium, is partially dependent on 20-HETE production via CP450 \(\omega\)-hydroxylase working through a receptor-mediated process to inhibit the open-state probability of \(K_{Ca}\) channels. Therefore, the production of 20-HETE in response to elevated intraluminal pressure would impair full myogenic depolarization of the vascular smooth muscle membrane and the resulting influx of calcium into the cell through voltage-activated (L-type) calcium channels.

This work was supported by National Institutes of Health Grants HL-65289, HL-29587, HL-37374, and GM-31278 and Postdoctoral Fellowship F32 HL-09994.

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