Identification of Capric Acid as a Potent Vasorelaxant of Human Basilar Arteries

Richard P. White, PhD; Gregory F. Ricca, MD;
Abdullah M. El-Bauomy, PhD; and James T. Robertson, MD

To determine whether naturally occurring fatty acids, especially saturated ones, might act directly as vasodilators, segments of human basilar arteries and umbilical arteries were precontracted submaximally with prostaglandin $F_{2\alpha}$ and then exposed to different saturated fatty acids (C4 through C16) or unsaturated fatty acids (C14:1, C18:1, C18:2, and C18:3) at concentrations from 4 μM to 4 mM. The results showed caprate (C10) to be the most potent vasorelaxant and basilar arteries to be more responsive (EC_{50}=63 μM) than umbilical arteries (EC_{50}=780 μM). Caprate also inhibited contractions elicited by KCl, serotonin, and the thromboxane analogue U46619. The relaxation was independent of the endothelium, and potency was not related to the weak capacity of caprate to inhibit Ca^{2+}-induced contractions of K^+-depolarized basilar arteries. The pattern of potencies for the arteries differed, but among unsaturated fatty acids the monounsaturated (C14:1, C18:1) were more potent than the polyunsaturated (C18:2, C18:3). Comparing the potencies obtained with the concentrations reported for the free fatty acid content of arteries, brain, and plasma indicates that these lipids could influence vasomotion in health and disease. (*Stroke* 1991;22:469–476)

The diverse effects that saturated fatty acids have on enzymes suggest that these acids serve physiological functions beyond that of yielding energy. These acids, for instance, uncouple phosphorylation, inhibit Na,K-ATPase, inhibit adenylate cyclase, and inhibit cytosolic guanylate cyclase but stimulate membranous guanylate cyclase.[1–4]

Moreover, each fatty acid may produce selective effects. Oleic acid more effectively inhibits Ca^{2+} influx into mast cells than other lipids and at physiological concentrations blocks 100% of an experimentally induced release of histamine.[5] Among the saturated fatty acids, myristic acid was the most stimulatory of cyclic guanosine monophosphate (cGMP) production, and more so than several unsaturated ones.[3] The reasons for such stereospecificity are unknown.

It is well known that the essential fatty acid arachidonate and its metabolites are vasoactive.[6] However, isolated studies suggest that other fatty acids influence vasomotion. Thus, approximately 50% of the fatty acids found in arteries are derived from de novo synthesis from acetate,[7] and high concentrations of free (nonesterified) fatty acids are stored in varying amounts in the intimal, medial, and adventitial layers, the concentrations averaging 1.8 mM.[8] Also, these acids are metabolized differently from other tissues in that their metabolism does not require carnitine.[9] Hyperlipidemia elevates the arterial free fatty acid content,[8] and short-chain saturated fatty acids present in blood are found in the cerebrospinal fluid of animals[10] and humans[11] so that arteries not only manufacture nonesterified fatty acids but may be exposed to varying concentrations from other sources. The acids appear to be vasodilators as several short-chain fatty acids (C4 and C8) given intravenously were found to double cerebral blood flow in experimental animals without altering systemic blood pressure,[12] and oleic acid was found to be twice as effective as arachidonate in inhibiting contractions of isolated bovine arteries.[13] Although these latter findings indicate important vascular effects of saturated and unsaturated fatty acids, there has been no systematic study of the pharmacodynamic properties of fatty acids on isolated blood vessels.

Isolated arteries of laboratory animals may respond to vasoactive agents differently from the corresponding human vessels, and arteries from different regions may respond quite differently to the same agent.[14–17] The present study was therefore performed primarily to determine whether fatty acids

From the Departments of Pharmacology (R.P.W., A.M.E.) and Neurosurgery (G.F.R., J.T.R.), University of Tennessee, Memphis, Tenn.

Supported in part by National Institutes of Health Grant NS-21405, Biomedical Research Support Grant RR05423, and an Egyptian Peace Fellowship awarded to A.M.E.

Address for correspondence: Richard P. White, PhD, Department of Pharmacology, College of Medicine, University of Tennessee, Memphis, TN 38163.

Received August 15, 1990; accepted December 21, 1990.

(other than arachidonate) affect human arteries, to identify the most potent fatty acids, and to ascertain whether cerebral arteries differ in sensitivity from another vessel of the same species. The present study was also prompted by the posit of others that saturated fatty acids participate in the normal regulation of cerebral blood flow.[12]

Materials and Methods

The basilar arteries studied were obtained at autopsy from 53 adult victims of accidents and other unnatural causes within 24 hours after death. The mean±SEM age of the victims was 28.4±1.7 years, and the mean±SEM outside diameter of the basilar arteries was 3.3±0.13 mm. The umbilical arteries studied were carefully extirpated from the cords of 70 normal full-term infants within 8 hours after birth. The mean±SEM outside diameter of 19 umbilical arteries was 2.11±0.56 mm. The vessels were placed in cold physiological saline and cleared of blood and superfluous tissue. Some arteries were aerated and stored overnight, refrigerated. A 4-mm segment (ring) of the artery was mounted on two prongs, one fixed to the 10-ml tissue chamber and one movable, from which isometric contractions were recorded. The physiological saline used had the following millimolar composition: NaCl 118.3, KCl 4.7, $MgSO_4$ 1.2, KH_2PO_4 1.2, $CaCl_2$ 2.5, $NaHCO_3$ 25, and glucose, 11.0. The arterial segment was aerated with 95% O_2 and 5% CO_2 and kept at 37°C. The bath pH was 7.35.

Two tissue baths were used so that arterial segments were studied in duplicate. The type of experiment performed on each segment from the same individual differed so that any peculiarity of one artery would not unduly affect the overall findings. The passive tension initially placed on the segment was 2 g. If the segment relaxed more than 1 g in response to the initial stretch (stress-relaxation), additional tension was applied as necessary to establish a basal tone of between 1 and 2 g. One hour later, the responses elicited by 10, 30, 50, and 90 mM KCl were recorded. This was repeated every 20 minutes until the maximal contractile response was obtained. The responses to KCl are independent of receptors, indicate the viability of the tissue, and correlate well with the responsiveness to other contractile agonists.[14]

The basic protocol for this study was to precontract the arterial segment with an agent that in our experience produces prolonged, steady contractions.[14–16] Once the tonic phase became evident (3–5 minutes), a fatty acid was applied cumulatively to the bath at concentrations of 4 μM to 4 mM. The 4 μM concentration was based on the report that 4 mM/kg of certain fatty acids given intravenously to cats selectively increases cerebral blood flow.[12]

Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) and serotonin (5-HT) were used to precontract the arterial segments at concentrations estimated to represent EC_{80-90} from previous experience[14–16] and by trial in each artery. The umbilical arteries were precontracted with 10 μM $PGF_{2\alpha}$ or 1 μM 5-HT, and the basilar arteries were exposed to 6–10 (average 8.7) μM $PGF_{2\alpha}$. The thromboxane analogue U46619 was also used to precontract the basilar arteries. After washout of the drugs, a period of 30–40 minutes elapsed between experiments.

Similar studies were performed on precontracted arterial segments that had been reamed to destroy the endothelium, as previously described.[17] In some experiments, the effect of fatty acids on the contractions elicited by $CaCl_2$ in arterial segments exposed to calcium-free buffer and depolarized with KCl was determined. In addition, the effectiveness of the fatty acid to alter responses to $CaCl_2$ and KCl was compared with that of the calcium channel blocker diltiazem.

The sodium salts of even-numbered saturated fatty acids from C4 to C16 (butyrate, caproate, caprylate, caprate, laurate, myristate, and palmitate) were studied for vasorelaxant properties. The unsaturated fatty acids studied were myristoleate (C14:1), oleate (C18:1), linoleate (C18:2), and linolenate (C18:3). The acids and $PGF_{2\alpha}$, 5-HT, caprylcarnitine, sodium β-hydroxybutyrate, sodium γ-aminobutyrate, and thrombin were purchased from the Sigma Chemical Co., St. Louis, Mo. Diltiazem was obtained gratis from Marion Laboratories, Inc., Kansas City, Mo. The stable thromboxane analogue U46619 (9,11-epithio-11,12-methano-TxA_2) was provided by the Upjohn Co., Kalamazoo, Mich. Concentrated stock solutions of the experimental compounds were made so that only 10–100 μl stock solution was needed to achieve the final bath concentration of each substance. Fresh solutions were used, and only concentrated laurate and palmitate required heating to solubilize. The modest increase in bath pH produced by the fatty acids was unrelated to their potency as vasorelaxants, nor did the addition of $NaHCO_3$ to increase the bath pH comparably have any vasorelaxant effect.

The results are expressed as mean±SEM grams or as percentage change from control. An appropriate Student's t test was applied to determine the level of significance. The EC_{50} values were determined from regression equations derived from computer analysis of the data.

Results

Figure 1 illustrates the basic protocol and shows that the saturated fatty acid caprate (C10) was clearly more potent at 0.4 mM than butyrate (C4), caproate (C6), or caprylate (C8) in relaxing basilar artery segments precontracted with $PGF_{2\alpha}$. However, C8 and C10 produced maximal relaxation, below the basal tone, at 4 mM while C4 and C6 lacked this property (Figure 1). The relaxant effect persisted unabated for at least 20 minutes and was completely reversed by washout of the fatty acids in that the contraction afterward to $PGF_{2\alpha}$ was not diminished. There was no evidence of tachyphylaxis to the vasorelaxant effect (n=9 for C10 and n=7 for C8).

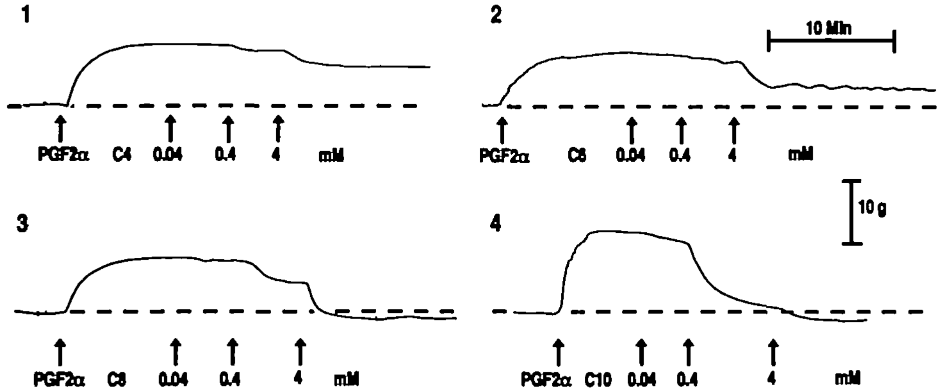

FIGURE 1. *Tracings showing relaxation produced by four saturated fatty acids (1, C4, butyrate; 2, C6, caproate; 3, C8, caprylate; 4, C10, caprate) in precontracted human basilar arteries. Dashed lines indicate basal tonè prior to application of prostaglandin $F_{2\alpha}$. Note greater effectiveness of caprate at 0.4 mM.*

Among the saturated fatty acids, C10 was the most potent relaxant of the basilar artery (Figure 2). This was especially evident at 40 and 400 μM. The EC_{50} for C10 was 63 μM in the basilar artery, seven times more potent than the next most potent saturated fatty acid (Table 1). C10 was also at least 19 times more potent than any of the unsaturated fatty acids, of which C14:1 and C18:1 were the most potent and were equieffective (Table 1).

The basilar artery was more responsive to C10 than the umbilical artery, with ED_{50}s of 63 μM and 780 μM, respectively (Table 1). The notable differences in the potency of C10 are summarized in the concentration–response curves of Figure 3. The unsaturated fatty acids were less potent than C10 in both types of vessels (Table 1). In the basilar artery, however, the monounsaturated fatty acids were more potent than the polyunsaturated, whereas in the umbilical artery the relation between a double bond and potency was not as evident (Table 1). Nevertheless, the most

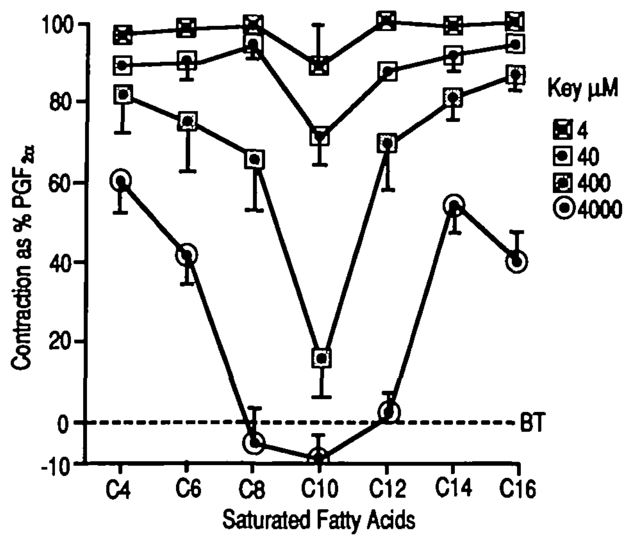

FIGURE 2. *Structure–activity relation of saturated fatty acids as relaxants of human basilar arteries. Note that potency, most evident at 400 μM, peaked with caprate (C10). Each point represents 8–12 responses except for 4 μM (n=3–5). $PGF_{2\alpha}$, prostaglandin $F_{2\alpha}$; BT, basal tone.*

abundant mammalian fatty acid, oleate (C18:1), was more potent in the basilar artery than in the umbilical artery and more potent than some of the saturated fatty acids.

To ascertain whether the saturated fatty acids act synergistically, six basilar artery segments were precontracted with $PGF_{2\alpha}$ and the effects of the EC_{50}s for C8 and C10 (Table 1) were measured separately and in combination. The relaxant response to C8 alone averaged 49±9.2%, that to C10 46±8.3%, and that to the combination 90.7±5.6%. The results indicate an additive effect, being within 10 percentage points of the expected combined effect. Also, at random intervals 0.4 mM C10 was applied to vessel segments that had failed to relax completely in response to other fatty acids, and the first acid never interfered with the response to C10.

U46619 was used to precontract six basilar artery segments from three individuals to determine whether a different contractile agent influenced the response to C10 (data not shown). The vessels were alternately contracted with the EC_{85} for $PGF_{2\alpha}$ and equieffective concentrations of U46619, usually 10 or 100 nM. The agonists were applied twice to each segment, and the contraction elicited by $PGF_{2\alpha}$ averaged 12.5±0.3 g and that elicited by U46619 12.1±1.4 g. The relaxant effects that 4 μM to 4 mM C10 had on the contractions generated by each agent did not differ significantly (Student's *t* test for paired data), the maxima being 105.1% after U46619 and 107.6% after $PGF_{2\alpha}$.

Among the other compounds tested, caprylcarnitine at 1 μM was nearly as effective as C10 in inhibiting the contractions produced by 1 μM 5-HT in the same umbilical artery segments, reducing the contractions by 49.9±12.3% and 67.7±5.8%, respectively (n=7) (data not shown). While the inhibitions were not significantly different (Student's *t* test for paired data), caprylcarnitine was on average less effective and less predictable as reflected in the SEM. In four basilar artery segments precontracted with $PGF_{2\alpha}$, the application of β-hydroxybutyrate at 0.4 mM had no effect and at 4 mM reduced the contraction by only 20.6±1.8%. At comparable concentrations γ-aminobutyrate relaxed the vessel

TABLE 1. EC_{50}s for Vasorelaxant Effect of Fatty Acids on Human Arteries

Fatty acid carbon length	Segments (No.)	Concentration (M)	Potency ratio (C*n*/C10)
Basilar artery			
Saturated			
C4	8	3.3×10^{-2}	523.8
C6	9	2.5×10^{-3}	39.7
C8	10	4.4×10^{-4}	6.9
C10	11	6.3×10^{-5}	1.0
C12	10	4.5×10^{-4}	7.1
C14	14	7.4×10^{-3}	117.5
C16	11	2.7×10^{-3}	42.8
Unsaturated			
C14:1	13	1.2×10^{-3}	19.0
C18:1	16	1.2×10^{-3}	19.0
C18:2	15	4.0×10^{-3}	63.5
C18:3	11	2.4×10^{-2}	380.9
Umbilical artery			
Saturated			
C4	7	2.3	2,948.7
C6	9	4.3×10^{-2}	55.1
C8	13	1.4×10^{-3}	1.8
C10	7	7.8×10^{-4}	1.0
C12	8	8.8×10^{-4}	1.1
C14	10	1.2×10^{-3}	1.5
C16	9	1.8×10^{-3}	2.3
Unsaturated			
C14:1	7	1.2×10^{-1}	153.8
C18:1	11	5.0×10^{-3}	6.4
C18:2	8	6.3×10^{-3}	8.1
C18:3	6	1.5×10^{-1}	192.3

by 6.5±2.1% and 13.6±2.8%, respectively, while C10 diminished the contraction by 86.7±1.3% and 104.3±0.8%, respectively.

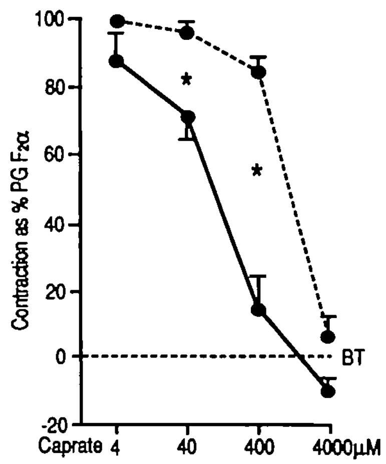

FIGURE 3. *Comparison of relaxant effect of caprate on human basilar (—, n=11) and umbilical (---, n=7) arteries. *p<0.05 different at 40 μM and p<0.001 at 400 μM between arteries by Student's t test. $PGF_{2\alpha}$, prostaglandin $F_{2\alpha}$; BT, basal tone.*

The profile of potency for the saturated fatty acids also differed, resembling a distorted V for the basilar artery (Figure 2, Table 1) while being more L-shaped for the umbilical artery (Table 1). Thus, in basilar arteries potency decreased markedly as carbon length changed from C10, whereas potency changed little in the umbilical arteries as carbon length increased from C10. Also, differences between the responses to C10 and C8 or C12 were significant in the basilar artery ($p<0.05$) but not in the umbilical artery.

Contractions elicited in umbilical artery segments by 40 mM KCl, due to an influx of Ca^{2+} through voltage-operated channels, were inhibited only when C10 or diltiazem was administered 6–8 minutes before KCl (Figure 4). By extrapolation, the calcium antagonist was about 500 times more potent than C10. The contractions produced by 5-HT, which opens receptor-operated calcium channels, were affected differently by diltiazem and C10 in that inhibition occurred whether the agents were administered before or after 5-HT (Figure 4). An estimate of the EC_{50}s indicated that diltiazem was only about 66 times more potent than C10 against 5-HT–induced contractions. In any case, diltiazem and C10 pro-

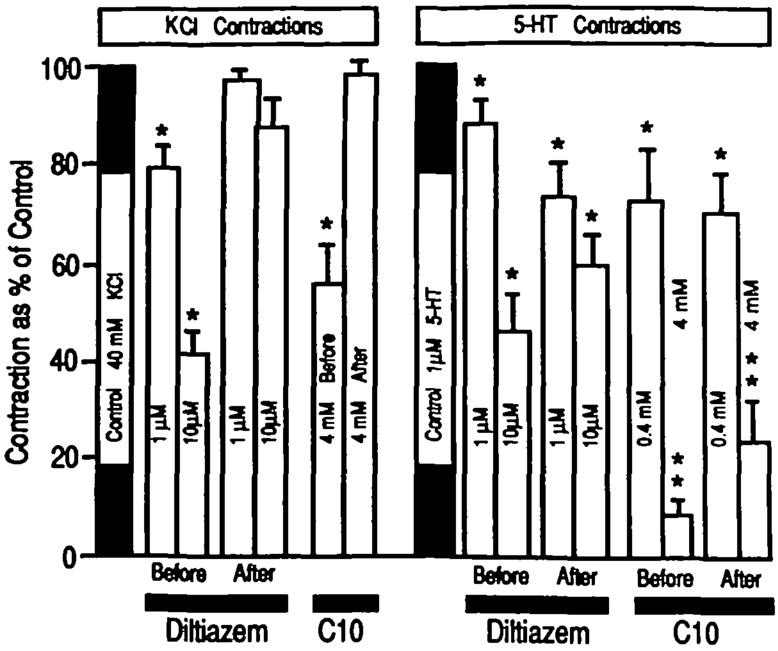

FIGURE 4. *Pharmacodynamic comparison of diltiazem and caprate (C10) when given before or after contractions elicited in human umbilical arteries by KCl or serotonin (5-HT). Note that both diltiazem and C10 were inhibitory when administered before but not after KCl, while both diminished contractions generated by 5-HT regardless of when they were applied (*p<0.05 different from control). Contractions generated by 5-HT were more inhibited by C10 than by diltiazem when concentration of inhibitor increased 10-fold (**p<0.01 different from corresponding bars). Before and after effects based on 9–11 experiments.*

duced qualitatively similar effects on the contractions elicited by KCl and 5-HT.

Figure 5 illustrates the protocol and one result of experiments designed to better define the effect C10 has on transmembrane Ca^{2+} exchange. The artery segments were first exposed to calcium-free buffer for approximately 2 hours, then depolarized with 40 mM KCl; 3–5 minutes later 0.1–10 mM $CaCl_2$ was added to elicit contractions (tracing 1, Figure 5). After five or six washouts with calcium-free buffer and an elapsed time of about 60 minutes, the experiment was repeated but with 0.4–4 mM C10 added to the bath 6–8 minutes prior to K^+ depolarization. The contractions elicited by high concentrations of $CaCl_2$ in the basilar artery were unaffected by 0.4 mM C10 but were inhibited significantly by 4 mM C10 (Figure 6). In contrast, all concentrations of C10 inhibited the Ca^{2+}-induced contractions in the umbilical artery, and at 4 mM the response was abolished (Figure 7). Diltiazem

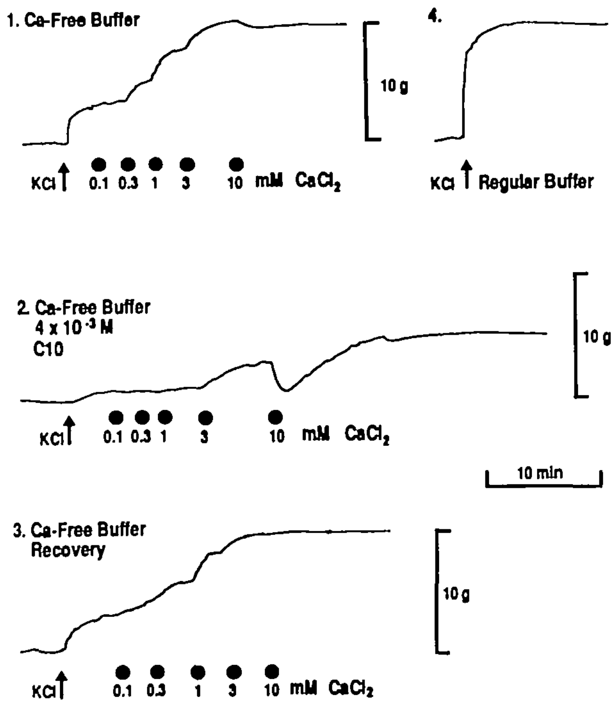

FIGURE 5. *Tracings showing inhibitory effect of caprate (C10) on contractions produced by $CaCl_2$ in human basilar arteries bathed in calcium-free buffer and depolarized with 40 mM KCl. 1, control response; 2, inhibition to $CaCl_2$ in artery exposed to 4 mM C10; 3, recovery; 4, response to 40 mM KCl in physiological buffer.*

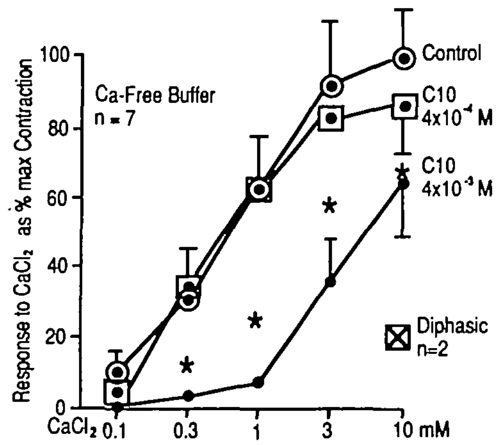

FIGURE 6. *Effect of caprate (C10) on dose–response curves for $CaCl_2$ obtained in human basilar arteries previously exposed to calcium-free buffer and depolarized with 40 mM KCl (control) or also exposed to C10. Only 4 mM C10 was inhibitory (*p<0.05 different from control).*

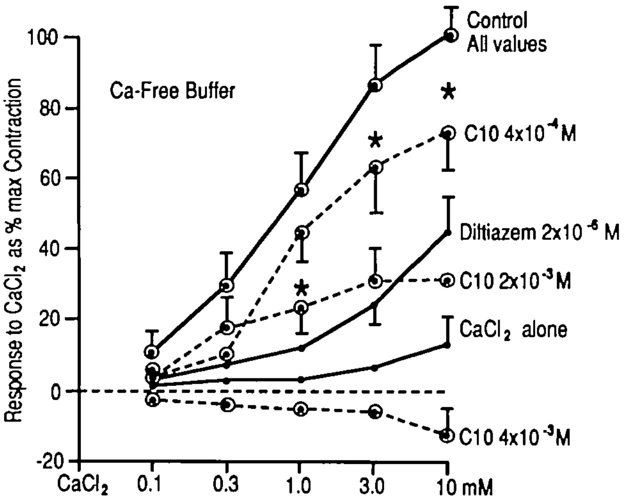

FIGURE 7. *Effect of caprate (C10) on dose–response curves for $CaCl_2$ obtained in human umbilical arteries previously exposed to calcium-free buffer and depolarized with 40 mM KCl (control) or also exposed to C10. At 400 μM C10 was inhibitory to $CaCl_2$, but diltiazem was approximately 1,000 times more effective. Each line represents five (diltiazem) to 11 observations. All points below asterisks differ significantly from control ($p<0.05$). Some SEMs not shown for clarity. Horizontal dashed line, basal tone.*

at 2 μM was as inhibitory as 2 mM C10 in this test, or about 1,000 times more potent (Figure 7).

Six basilar artery segments reamed to destroy the endothelium and unreamed control segments from the same individual responded in similar manners to 0.4 mM C10. When C10 was applied, contraction was 7.6±0.4 g in the reamed segments and 8.1±0.3 g in the controls. The reamed vessels relaxed 76.7±9.2% with C10 while the controls relaxed 79.3±8.7%. In contrast, 5 units/ml thrombin reduced the diameter of the precontracted reamed segments by only 3.4±1.3% (range 0–7%) but relaxed the controls by 69.8±7.4%, indicating that the endothelium was functional only in the control vessels.[18] Histological examination of the 4-mm segments stained with hematoxylin and eosin confirmed that the endothelium was removed by reaming but remained in the control vessels.

Discussion

These findings clearly demonstrate that fatty acids are vasorelaxants, that potency varies with carbon length and saturation, that caprate (C10) is the most potent, and that basilar arteries are more sensitive to C10 than are umbilical arteries, with EC_{50}s of 63 μM and 780 μM, respectively. Moreover, C10 was antagonistic to a variety of contractile agonists. Although less potent, two of four unsaturated fatty acids, myristoleate (C14:1) and oleate (C18:1), relaxed precontracted basilar arteries at EC_{50}s of approximately 1 mM (Table 1). Since the dilation produced by each fatty acid was prolonged, the nonesterified fatty acids normally synthesized and stored by arteries[7,8] could exert a tonic relaxant effect on blood vessels.

The remarkable sensitivity manifested by the basilar artery supports the hypothesis of others that fatty acids participate in the normal regulation of cerebral blood flow.[12] It is possible, however, that unknown postmortem changes contributed to the greater sensitivity since the umbilical arteries were in general prepared for use sooner than the basilar arteries. On the other hand, the responses to well-known contractile agonists of "fresh" bovine basilar arteries and human basilar arteries prepared for use 7–24 hours postmortem are similar, and there is little change in vasomotor activity as assessed by absolute contraction or molar sensitivity during the first 24 hours after death.[19] Likewise, the sensitivity to several agonists of "fresh" canine and postmortem human basilar arteries is remarkably similar; the sensitivity to 5-HT is identical.[20] The literature also indicates that "fresh" human pial arterioles removed during surgery and larger cerebral arteries removed postmortem respond in a similar manner to most agonists.[6] In addition, we have noted in preliminary reports that canine basilar arteries are as sensitive to C10 as human basilar arteries (EC_{50}s of 49 μM and 63 μM, respectively) and more sensitive than canine femoral arteries (EC_{50} of 440 μM).[21] Together these findings suggest that differences in sensitivity to C10 were not due to the "freshness" of the vessel nor to its size and that among the vessels studied cerebral arteries are the most sensitive, independent of species.

The mechanism involved in the efficacy of C10 as a dilator remains problematic. The endothelium was not a requirement as it is for many dilator agents.[22] Its potency as an inhibitor of $PGF_{2\alpha}$-induced contractions in umbilical arteries and as an inhibitor of Ca^{2+}-induced contractions suggests that C10 was producing calcium blockade in that artery. In the basilar artery, however, there was no such relation, with 400 μM C10 having no effect on Ca^{2+}-induced contractions. Although palmitate (C16) and palmitoylcarnitine have diametrically opposite effects on Ca^{2+}-induced responses of intestinal strips,[23] both C10 and its carnitine ester were vasorelaxant in basilar artery segments.

Membranous guanylate cyclase of human fibroblasts is one enzyme that is directly stimulated by either saturated or unsaturated fatty acids at physiological concentrations, 100–600 μM.[3,24] This stimulation is greatest in the presence of Mg^{2+},[3] a divalent cation that favors vasorelaxation.[25] In contrast, nitrovasodilators do not stimulate the enzyme,[3,4] which may explain why fatty acids relax the umbilical artery (Table 1) whereas sodium nitrite does not.[16] Although the vasorelaxation might be mediated by cGMP, the investigation of arteries is required because several saturated fatty acids, especially C14, stimulate the enzyme more effectively than does C10.[3] Also, unsaturated fatty acids are nearly as effective as C14 in the generation of cGMP, whereas C10 was far more vasorelaxant in the basilar artery (Table 1). Nevertheless, it is of special interest that fatty acids manifest a stereospecificity for the enzyme and as vasorelaxants.

The stereospecificity manifested by fatty acids in other tissues also seems unrelated to the vasodilator action. For instance, C14 is the most potent uncoupler of oxidative phosphorylation,[1] and C18:1 proved to be the best inhibitor of histamine release by mast cells.[5] Also, attempts to link the hypnotic effect of saturated fatty acids to specific enzymes have been unsuccessful.[2,26] Comparative studies show, however, that C8 and C10 are more potent in producing dose-dependent hypnosis and coma in animals than are C4 or C6.[27] This ranking roughly parallels the vasodilator potency pattern seen in arteries (Figure 1). On the other hand, C4 was not a potent dilator of human basilar arteries (Table 1) but reliably produces sleep and increases cerebral blood flow in cats.[12] The difference may be related to a central nervous system effect, a species effect, and/or a greater sensitivity of arterioles to fatty acids. Although the hypnotic effect might limit the clinical use of C10 as a vasodilator, in our experience femoral blood flow of dogs can be doubled by the intra-arterial injection of C10 without systemic effects or deepening anesthesia.[28]

The concept that nonesterified fatty acids influence vasomotion is further supported by the concentrations revealed in isolated studies. Thus, a group of cellular low-molecular-weight proteins bind up to 500 μM of nonesterified fatty acid and one binds only saturated fatty acid.[29] Feline serum normally contains 180 μM C4,[10] human serum 2–18 μM C8,[30] and rabbit brain 200 μM C8.[31] The concentration of nonesterified fatty acids in canine aortas varies with the layer studied, from 660 μM to 2.9 mM, while 680 μM is normally present in serum.[8] A fatty diet including butter (30% C4–C10) markedly increases the arterial fatty acid content, especially in the muscle layer.[8] Also, sympathetic nerves of rats fed saturated fats (C8–C18) store far more and release much less norepinephrine than rats fed other diets.[32] The tail arteries of rats fed saturated fats also respond on average less to norepinephrine. With ischemia, the brain concentration of saturated fatty acids exceeds by twofold that of arachidonate and in one animal reached 1.2 mM.[33] Electroconvulsive shock produces a similar free fatty acid profile, and these acids are derived from phospholipids, not triglycerides.[34] In Reye's syndrome plasma levels of 11.5 mM (170 mg/dl) have been reported for octanoate (C8), and the concentration of this fatty acid best reflected the clinical condition of the patient, including coma.[30] Also, alimentation of C8 to patients may yield serum values of 1.1 mM, will elevate the cerebrospinal fluid concentrations, and may produce coma.[11] Medium-chain (C8) and long-chain (C14) fatty acids are actively transported through the blood–brain barrier[35] so that the brain, plasma, and cerebrospinal fluid are sources of saturated fatty acids that, under pathological conditions, could alter cerebrovascular tone. Our findings support the posit that the increases in intracranial pressure observed in patients with Reye's syndrome could be due to cerebrovasodilation caused by elevated fatty acid levels.[36]

The dilator response may also reflect metabolic states as fat depots with the highest lipid turnover rates have the highest blood flows.[37] The type of fatty acid stored might also account for the fact that many obese individuals are normotensive.[37] Conversely, since arteries in diabetic patients do not synthesize fatty acids but do synthesize cholesterol,[38] the poor circulation often seen in such patients may reflect this deficiency. In any case, the comparison of reported concentrations present in arteries and other tissues with their potencies as vasodilators indicates that fatty acids could play a role in vasomotion in health and disease.

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KEY WORDS • basilar artery • fatty acids • vasodilation

Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION

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Stroke. 1991;22:469-476
doi: 10.1161/01.STR.22.4.469
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628