Linoleic Acid Induces Relaxation and Hyperpolarization of the Pig Coronary Artery

Silvia I. Pomposiello, Magaly Alva, Dixon W. Wilde, Oscar A. Carretero

Abstract—Linoleic acid, a polyunsaturated C₁₈ fatty acid (18:2n-6), is one of the major fatty acids in the coronary arterial wall. Although diets rich in linoleic acid reduce blood pressure and prevent coronary artery disease in both humans and animals, very little is known about its mechanism of action. We believed that its beneficial effects might be mediated by changes in vascular tone. We investigated whether linoleic acid induces relaxation of porcine coronary artery rings and the mechanism involved in this process. Linoleic acid and two of its metabolites, 13-hydroxyoctadecadienoic acid (13-HODE) and 13-hydroperoxyoctadecadienoic acid (13-HPDOE), induced dose-dependent relaxation of prostaglandin (PG) F₂α-precontracted rings that was not affected by indomethacin (10⁻³ mol/L), a cyclooxygenase inhibitor, or cinnamyl-3,4-dihydroxy-α-cyanocinnamate (CDC; 10⁻⁵ mol/L), a lipoxygenase inhibitor. Removal of endothelial cells had no effect on vasorelaxation, suggesting a direct effect on the vascular smooth muscle cells (VSMC). When rings were contracted with KCl, linoleic acid failed to induce relaxation. Although tetrabutylammonium (5×10⁻³ mol/L), a nonselective K⁺ channel blocker, slightly inhibited the relaxation caused by linoleic acid, glibenclamide (10⁻⁶ mol/L), an ATP-sensitive K⁺ channel blocker, and charybdotoxin (7.5×10⁻⁸ mol/L) or tetraethylammonium (5×10⁻³ mol/L), two different Ca²⁺-activated K⁺ channel blockers, had no effect. However, relaxation was completely blocked by ouabain (5×10⁻⁷ mol/L), a Na⁺/K⁺-ATPase inhibitor, or by a K⁺-free solution. In addition, linoleic acid (10⁻⁶ mol/L) caused sustained hyperpolarization of porcine coronary VSMC (from −49.5±2.0 to −60.7±4.2 mV), which was also abolished by ouabain. We concluded that linoleic acid induces relaxation and hyperpolarization of porcine coronary VSMC via a mechanism that involves activation of the Na⁺/K⁺-ATPase pump. (Hypertension. 1998;31:615-620.)

Key Words: linoleic acid • nitric oxide • prostaglandins • endothelium-derived hyperpolarizing factor • cyclooxygenase • Na⁺/K⁺-ATPase inhibitor

Linoleic acid, a polyunsaturated C₁₈ fatty acid (18:2n-6), is one of the main essential fatty acids, and is one of the major fatty acids in the arterial wall,¹ which can be liberated by phospholipase activity.²,³ Linoleic acid is the principal precursor of arachidonic acid (20:4n-6), which is the substrate for synthesis of prostaglandins and thromboxane A₂. Structurally related derivatives of arachidonic acid and linoleic acid have been demonstrated in blood vessels and related tissues. Linoleic acid can be enzymatically or nonenzymatically⁴ converted to 13-HPODE, which can be further reduced to 13-HODE. Production of these hydro(per)oxy metabolites has been reported in aortas from rats, rabbits, and humans,⁵ and unlike the fetal calf aorta⁶ their formation is independent of cyclooxygenase activity. Lipoxygenation of linoleic acid resulted in 13-HODE formation in endothelial cells.⁶ Linoleic acid metabolites are formed in larger quantities than the corresponding arachidonic acid metabolites,⁷ suggesting that they may be of biological significance.

Several studies have suggested that hypertension and cardiovascular disease are caused in part by a relative deficiency in polyunsaturated fatty acids, especially linoleic acid.⁸,⁹ Abnormal fatty acid metabolism has been observed during hypertension.⁷,¹⁰,¹¹ Saturated fatty acids have been shown to be hypertensive, whereas polyunsaturated fatty acids are hypotensive.¹²,¹³ Linoleic acid inhibits salt-induced hypertension¹⁴ as well as deoxycorticosterone acetate-salt hypertension in rats.¹⁵ It has also been shown that gamma-linolenic acid, a metabolite of linoleic acid, attenuates stress-induced hypertension.¹⁶ Diets enriched with linoleic or gamma-linolenic acid lower blood pressure in hypertensive humans¹⁷ and attenuate the development of hypertension in SHR.¹⁸-²⁰ These data suggest that linoleic acid may play a role in blood pressure regulation.

Although diets rich in linoleic acid reduce blood pressure and prevent coronary artery disease in both humans and animals, very little is known about its mechanism of action. Its beneficial effects might be mediated by changes in vascular tone. We investigated whether linoleic acid induces relaxation of porcine coronary artery rings and the mechanism involved in this process.

Methods

Vascular Reactivity

Pig hearts were obtained from a slaughterhouse and immediately immersed in ice-cold Krebs solution of the following composition (in mmol/L): NaCl 118.3, KCl 4.7, MgSO₄·7H₂O 1.2, KH₂PO₄ 1.2, CaCl₂·6H₂O 2.5, NaHCO₃ 25, and glucose 11.1. The left circumflex

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615
coronary artery was carefully removed and cleaned of fat and connective tissue. The arteries were cut into rings 3 to 5 mm wide, mounted on stainless steel stirrups (one fixed and the other movable), and suspended in an organ chamber (8 mL) filled with Krebs solution at 37°C which was gassed continuously with 95% O₂-5% CO₂ to maintain a pH of 7.4. The movable stirrup was attached to an isometric force transducer (model FT 03C, Grass Instruments) coupled to a polygraph (model 7D, Grass Instruments). The rings were stretched until basal tension reached 5g, since in preliminary studies this resulted in optimal responses. After a 60-minute stabilization period, rings were precontracted with PGF₂α (10⁻⁴ to 10⁻⁵ mol/L) or KCl (20 to 30 mmol/mL) to achieve a tension of approximately 80% of the contraction obtained with 60 mmol/L KCl. To test endothelial integrity, bradykinin (10⁻⁴ mol/L), two different Ca²⁺ channel blockers, and position of VSMC were carefully cleaned of fat and connective tissue and position of VSMC were carefully cleaned of fat and connective tissue and then minced. Vessel fragments were enzymatically digested according to previously described methods in a solution containing (in 0.1 mmol/L CaCl₂) Hanks’ 263 U/mL collagenase (type I), 22.5 U/mL papain, 0.5 mg/mL soybean trypsin inhibitor (SBTI) (type I), 15 mmol/L taurocholate, and 5 mg/mL bovine serum albumin (0.003% free fatty acid). After digestion, fragments were rinsed three times in Hanks’ solution, then resuspended in Hanks’ solution containing 0.005% bovine serum albumin, 0.5 mg/mL SBTI (type I), 15 mmol/L taurocholate, and 5 mg/mL bovine serum albumin (0.003% free fatty acid). Vessel fragments were triturated by Pasteur pipette to release single relaxed VSMC. Cells in suspension were placed in a 0.5-mL controlled-atmosphere recording chamber and heated to 35°C. Cells were superfused at 3 mL/min with bicarbonate-buffered PPS containing (in mmol/L) NaCl 120.0, KCl 5.0, MgCl₂ 1.2, CaCl₂ 1.8, NaHCO₃ 14.0, and glucose 5.0. PPS and chamber atmosphere were constantly gassed with 95% O₂-5% CO₂, and the pH of the superfusate was maintained at 7.4.

**Membrane Potential Recording**

Membrane potentials in the absence (control) or presence of 10⁻⁶ mol/L linoleic acid (with or without 5×10⁻⁷ mol/L ouabain) were recorded using the perforated patch pipette technique. Briefly, pipettes were pulled from type R-6 glass (Garnet Glass) using a Kopf 720 puller (David Kopf Instruments) and then coated with a nitrile-cellulose-butyaryl-toluene sulfonamide-formaldehyde resin mixture to minimize capacitance. Bath depth was 1 to 2 mm. Pipette tips were filled with a KCl-based solution by briefly dipping the tip into the solution. The internal solution contained (in mmol/L) KCl 100, NaCl 3.0, MgCl₂ 3.0, CaCl₂ 0.1, EGTA 1.1, HEPES 10, and KOH 31.5, at pH 7.37. Once the tips were filled, the pipette barrel was back-filled with the internal solution containing 100 μg/mL nystatin.

Pipettes were positioned on the membrane of single relaxed VSMC and allowed to spontaneously form a gigahm seal. Slight suction was applied to allow the cell to be raised off the bottom of the recording chamber. Current clamp recordings were obtained using an Axopatch 200A amplifier and pClamp version 6.0.3 software (both from Axon Instruments). Once the seal was established, pipette capacitance was canceled using the on-board circuitry of the Axopatch amplifier. As the nystatin diffused down to the pipette tip and was incorporated into the membrane patch, the capacitance transient of a test pulse increased until it reached a stable value, indicating perforation of the membrane by the antibiotic. Cells were maintained under a voltage clamp at a holding potential of ~60 mV during this period. Once the membrane patch was perforated, the recording mode was changed to the slow current clamp for measurement of cell membrane potential. Current clamp recordings were passed through a low-pass Bessel filter at 2 kHz. Only cells showing a stable resting potential for 1 to 2 minutes were used for these experiments. In some cases, such as with very long relaxed cells, the slow current clamp artifacts that correlated with instability in the membrane seal. These cells were not used. After a period of stabilization, cells were treated with either 10⁻⁶ mol/L linoleic acid, 5×10⁻⁷ mol/L ouabain, or a combination of both agents following a period of treatment in ouabain alone. Generally, 1 to 2 cells from each heart were used.

**Synthesis of 13-HPODE**

Free linoleic acid (10 mg in 100 mL 0.2 mol/L Tris buffer at pH 9.0 and 4°C) was incubated with 126 000 U soybean lipoxidase type I (linolate: oxygen oxidoreductase; EC 1.13.11.12) at 4°C. After a 30-minute incubation period, a second amount of lipoxidase (126 000 U) was added for 30 minutes at 4°C. After a total incubation period of 60 minutes, the mixture was acidified to pH 4.0 with a 2.3 mol/L citric acid solution. This mixture was extracted twice with cooled diethyl ether (100 mL each) and the collected ether fractions dried on anhydrous Na₂SO₄. After removal of the organic solvent, the residue was dissolved in a minimal volume of chloroform/methanol (2:1) and spotted on a silica gel plate for preparative thin-layer chromatography. The plate was developed in the organic fraction of an ethyl acetate/iso-octane/acetic acid/water mixture (100:50:20:100). Detection and identification of 13-HPODE were carried out with UV light (234 nm) or spraying with phosphomolybdic acid. The band was

**Selected Abbreviations and Acronyms**

CDC = cinnamyl-3,4-dihydroxy-α-cyanocinnamate
13-HODE = 13-hydroxy-9,11-octadecadienoic acid
13-HPODE = 13-hydroperoxy-9,11-octadecadienoic acid
L-NAME = Nω-nitro-L-arginine methyl ester
NO = nitric oxide
PGF₂α/PGF₁α = prostaglandin F₂α and I₂, respectively
SHR = spontaneously hypertensive rat(s)
TBA = tetra butyl ammonium
TEA = tetracyethylammonium
VSMC = vascular smooth muscle cell(s)
EC50, pretreated for 45 minutes with both indomethacin (10−5 mol/L) and L-NAME (10−4 mol/L). Effect of CDC (b; 10−5 mol/L) on linoleic acid–induced relaxation of PGF2α-precontracted porcine coronary artery rings. Results are expressed as mean±SEM.

Materials

Bradykinin was obtained from Biomol. Inorganic salts, PGF2α, linoleic acid (sodium salt), free linoleic acid, palmitic acid (sodium salt), L-NAME, indomethacin, ouabain, papain, taurine, bovine serum albumin, nystatin, collagenase, soybean lipoxidase (type I), SBTI (type I), diethyl ether, tetrahydrofuran, and 2,2,4-trimethylpentane (iso-octane) were purchased from Sigma. Glacial acetic acid and Baker flex silica gel IB-F (20 mesh octane) were purchased from Sigma. 13-HPODE and 13-HODE standards were obtained from Biomol. Chloroform, methanol, ethyl acetate, and acetonitrile were purchased from Aldrich. Glacial acetic acid and Baker flex silica gel IB-F (20×20×0.2 cm) for thin-layer chromatography were obtained from JT Baker. Indomethacin was dissolved in 0.2 mol/L Trizma base; palmitic acid, 13-HODE, and 13-HPODE were dissolved in 10% ethanol; glibenclamide was dissolved in 0.2 mol/L Trizma base; and charybdotoxin (7.5×10−8 mol/L) and the ATP-sensitive K+ channel blocker glibenclamide (10−6 mol/L) was used to analyze differences between groups, depending on whether assumptions of normality were met. For multiple comparisons, adjusted alpha levels were used to determine the significance of each test in order to ensure an overall testing level of 0.05.

Results

Effects of Linoleic Acid

Linoleic acid elicited dose-dependent relaxation of rings precontracted with PGF2α. Relaxation developed slowly (over 2 to 3 minutes) in a time-dependent fashion and was not affected by pretreatment with the cyclooxygenase inhibitor indomethacin (10−5 mol/L), the NO synthase inhibitor L-NAME (10−4 mol/L) (Fig 1a), or the lipoxygenase inhibitor CDC (10−5 mol/L) (Fig 1b); nor was it affected by removal of the endothelium (Table).

In rings precontracted with high extracellular concentrations of KCl (30 mmol/L), linoleic acid failed to cause relaxation (Fig 2a). TBA (5×10−3 mol/L), a nonselective K+ channel blocker, significantly inhibited relaxation at the maximum dose (Fig 2b), while the Ca2+-dependent K+ channel blockers TEA (5×10−3 mol/L) and charybdotoxin (7.5×10−8 mol/L) and the ATP-sensitive K+ channel blocker glibenclamide (10−6 mol/L)
had no effect (Fig 3 a, 3b, and 3c, respectively). However, relaxation was completely blocked by the Na\(^+/K^+\)-ATPase inhibitor ouabain (5 \times 10^{-7} \text{ mol/L}). When vessels were incubated in K\(^+\)-free solution, which is another way to inhibit the Na\(^+/K^+\)-ATPase pump, linoleic acid did not cause relaxation (Fig 4). Activation of the pump by the addition of K\(^+\) (5.9 mmol/L) produced total relaxation.

**Effects of 13-HPODE and 13-HODE**

Two metabolites of linoleic acid, 13-HPODE and 13-HODE, elicited dose-dependent relaxation of PGF\(_{2\alpha}\)-precontracted rings (Fig 5a and 5b), which was not affected by removal of the endothelium (Table). These metabolites were equipotent with linoleic acid (Table). As with linoleic acid, relaxation was abolished by high extracellular concentrations of KCl (30 mmol/L) or ouabain (5 \times 10^{-7} \text{ mol/L}) (Fig 5a and 5b). Glibenclamide, TEA, and charybdotoxin had no effect on 13-HPODE–induced relaxation (EC\(_{50}\), \mu \text{mol/L}: for glibenclamide 23.5 \pm 1.0; for TEA 23.3 \pm 1.9; and for charybdotoxin 24.2 \pm 4.7).

**Effects of Other Fatty Acids**

Palmitic acid, a saturated C\(_{16}\) fatty acid (16:0), failed to induce relaxation of porcine coronary artery rings; conversely, oleic acid, a monounsaturated fatty acid (18:1), linoleic acid (18:2), and eicosapentaenoic acid (20:5) induced dose-dependent relaxation with different potencies. Fatty acids with increasing degrees of \(\omega\)-unsaturation had higher potencies. The number of double bonds correlated with potency (Fig 5c). (Note: Palmitic acid was used instead of stearic acid (18:0), which is not soluble in the buffer solution.)

**Effects of Linoleic Acid on Membrane Potential**

Mean resting potential in pig coronary VSMC was 249.5 \pm 2.0 mV (n=20). In cells showing a stable resting potential, linoleic acid (10^{-6} \text{ mol/L}) induced mean hyperpolarization to -60.7 \pm 4.2 mV (P<.05; n=10) (Fig 6). The development of hyperpolarization was slow, requiring several minutes (2 to 3 minutes). In some experiments, periodic checks of the holding current needed to maintain a voltage-clamp holding potential of -60.0 mV indicated that linoleic acid did not alter seal resistance or nonspecific membrane leakage current. In contrast to linoleic acid, ouabain (5 \times 10^{-7} \text{ mol/L}) caused slight depolarization of the cell membrane, to -40.7 \pm 2.5 mV.

![Figure 4](image-url)  
**Figure 4.** Effect of the Na\(^+/K^+\)-ATPase inhibitor ouabain (5 \times 10^{-7} \text{ mol/L}) or K\(^+\)-free solution on linoleic acid–induced relaxation of PGF\(_{2\alpha}\)-precontracted porcine coronary artery rings. Results are expressed as mean\(\pm\)SEM.

![Figure 5](image-url)  
**Figure 5.** Effects of KCl and the Na\(^+/K^+\)-ATPase inhibitor ouabain (5 \times 10^{-7} \text{ mol/L}) on relaxation induced by 13-HPODE (a; 10^{-7} to 10^{-4} \text{ mol/L}) and 13-HODE (b; 10^{-7} to 10^{-4} \text{ mol/L}). c. Effect of different fatty acids on PGF\(_{2\alpha}\)-precontracted porcine coronary artery rings. PA indicates palmitic acid; OA, oleic acid; LA, linoleic acid; and EA, eicosapentaenoic acid. Results are expressed as mean\(\pm\)SEM.

![Figure 6](image-url)  
**Figure 6. a,** Effect of the Na\(^+/K^+\)-ATPase inhibitor ouabain (5 \times 10^{-7} \text{ mol/L}) on linoleic acid (10^{-6} \text{ mol/L})–induced hyperpolarization. b, Membrane potentials in the absence (control) or presence of 10^{-6} \text{ mol/L} linoleic acid (with or without 5 \times 10^{-7} \text{ mol/L} ouabain) were recorded using the perforated patch pipette technique. After a period of stabilization, cells were treated with either 10^{-8} \text{ mol/L} linoleic acid, 5 \times 10^{-7} \text{ mol/L} ouabain, or a combination of both agents following treatment with ouabain alone. Results are expressed as mean\(\pm\)SEM.
Subsequent superfusion of the cells with ouabain solution containing 10−7 mol/L linoleic acid failed to induce significant hyperpolarization (~40.8±6.8 mV; n=5) (Fig 6), suggesting that the hyperpolarizing action of linoleic acid was interrupted by blockade of Na+/K−-ATPase.

**Discussion**

Our study showed that linoleic acid induces relaxation and hyperpolarization of porcine coronary arteries via stimulation of the Na+/K−-ATPase pump. We found that linoleic acid–induced relaxation was not affected by the cyclooxygenase inhibitor indomethacin, the lipoxygenase inhibitor CDC, or the NO synthase inhibitor L-NAME. Removal of endothelial cells had no effect. These data suggest that linoleic acid has a direct effect on VSMC.

Relaxant effects of linoleic acid and related fatty acids, such as eicosapentaenoic acid (20:5n-3) and docosahexaenoic acid (22:6n-3), have been reported to be endothelium-independent in the aorta of normotensive rats and SHR and the cat coronary artery, but endothelium-dependent in rabbit and cat aortic rings. While none of them was affected by cyclooxygenase inhibition, only the relaxation induced by eicosapentaenoic acid in the cat coronary artery was affected by lipoxygenase inhibitors. We also found that 13-HPODE and 13-HODE, metabolites of linoleic acid, produced endothelium-independent relaxation of porcine coronary artery rings that was not affected by cyclooxygenase inhibition. Although similar results have been reported in canine splenic and coronary arteries, relaxation in response to 13-HODE but not 13-HPODE was partly endothelium-dependent and inhibited by indomethacin. The fact that linoleic acid and its metabolites have similar potencies suggests that they may share a similar mechanism of action; however, our study does not allow us to conclude whether the metabolites mediate relaxation or act via a similar mechanism. Since both are C18 fatty acids with similar number of cis-unsaturations, it could be that their effects are related to its hydrocarbon structure.

To determine whether these effects are specific for linoleic acid and its metabolites, we tested different fatty acids that vary in number and position of cis-unsaturations as well as carbon chain length. Interestingly, we observed that fatty acids with increasing degrees of cis-unsaturation were more potent: eicosapentaenoic acid (20:5n-3)>linoleic acid (18:2n-6), 13-HPODE (18:2n-6), and 13-HODE (18:2n-6)>oleic acid (18:1n-9)>palmitic acid (16:0). Similar results were obtained in the rat aorta. It is known that cis-unsaturated fatty acids increase fluidity by altering membrane structure, whereas saturated fatty acids have no effect. Based on this, it is possible that the vasorelaxant effect of polyunsaturated fatty acids may be mediated in part by changes in fluidity. Reduced fluidity and lowered linoleic acid and cis-unsaturated fatty acid content were found in platelet membranes of hypertensive patients, erythrocyte membranes of patients with essential hypertension, and SHR. SHR VSMC. It has also been shown that concentrations of saturated fatty acids such as palmitic and stearic acid are increased while unsaturated fatty acids such as linoleic and arachidonic acid are decreased in the plasma phospholipid fraction of hypertensive patients compared with normal individuals. In addition, abnormal essential fatty acid metabolism has been observed in myocyte cultures from newborn SHR. Thus, the beneficial effects of dietary linoleic acid could be related to changes in vascular tone, which may be mediated by increased fluidity.

Although we did not investigate changes in fluidity, it is known to modify enzyme activity as well as other biochemical and physiological functions such as ion transport, which are important determinants of membrane potential in VSMC. When rings were contracted by depolarizing them with high extracellular concentrations of KCl, linoleic acid failed to induce relaxation, suggesting that the vasorelaxant effects of linoleic acid may be mediated by changes in membrane potential. Besides PGI2 and NO, another known mechanism for vasodilation is membrane hyperpolarization. We found that linoleic acid caused sustained hyperpolarization in porcine VSMC. Development of both relaxation and hyperpolarization was slow, requiring several minutes. These data strongly suggest that linoleic acid–induced relaxation may be mediated by membrane hyperpolarization. To study the underlying mechanism, we first tested the effect of different channel blockers on relaxation in response to linoleic acid. TBA, a nonselective K+ channel blocker, slightly inhibited the relaxation induced by linoleic acid, whereas the ATP-sensitive K+ channel blocker glibenclamide or the Ca2+-activated K+ channel blockers TEA and charybdotoxin had no effect. Although linoleic acid caused relaxation of the porcine coronary artery by a K+–sensitive mechanism, this relaxation was not mediated by either an ATP-sensitive or Ca2+-activated K+ channel; however, the Na+/K+-ATPase inhibitor ouabain completely blocked the vasodilation elicited by linoleic acid. Because these data suggested that relaxation might be mediated by activation of the Na+/K+-ATPase pump, experiments were performed in the absence of K+, which is known to inhibit the pump. Linoleic acid did not cause relaxation when vessels were incubated in K+-free solution. At the end of the experiment, activity of the pump was demonstrated by total relaxation of the coronary rings produced by the addition of 5.9 mmol/L K+. Involvement of the pump in vasodilation and hyperpolarization has already been suggested. As expected, hyperpolarization was also blocked by ouabain, indicating that both relaxation and hyperpolarization are mediated by activation of the Na+/K+-ATPase pump. When ouabain was added, slight depolarization occurred, indicating that pump activity was blocked and that it may be involved in maintenance of the resting membrane potential. Several studies have shown that pump activity is inhibited in hypertensive humans and animals, suggesting that this pump may be implicated in the regulation of blood pressure. The hypotensive effect of linoleic acid in deoxycorticosterone acetate–salt hypertension in rats was correlated with increases in the activity of the Na+/K+-ATPase pump. Thus, it may be possible that linoleic acid, by increasing fluidity, activates the pump, which in turn alters the membrane potential of VSMC, causing vasodilation. Although arachidonic and linoleic acids have been reported to have an inhibitory effect on Na+/K+-ATPase, unsaturated fatty acids have recently been shown to activate the Na+/K+-ATPase pump, while saturated fatty acids such as palmitic acid had little or no effect. The difference between these studies may be related to assay methodology. On the other hand, these findings raise the possibility that fatty acids might exert both
inhibitory and stimulatory effects on the pump depending on the conditions. Finally, plasma concentrations of linoleic acid can increase from \( \approx 45 \) to \( 250 \mu\text{mol/L} \) 6 hours after ingestion of an enriched meal.\(^{3,4}\) In our study, physiological concentrations of linoleic acid induced relaxation of coronary arteries, indicating that linoleic acid may be important in the regulation of vascular tone.

In conclusion, linoleic acid produces relaxation and hyperpolarization of VSMC via a mechanism that involves stimulation of the Na\(^+\)/K\(^+\)-ATPase pump. The present study shows a potential mechanism for the action of linoleic acid, and we speculate that its relaxant properties may be partly responsible for its dietary effects on blood pressure.

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