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Fatty acid–induced changes in vascular reactivity in healthy adult rats

Raymond Christon[a,*], André Marette[b], Mylène Badeau[c], Frédéric Bourgoin[c], Sébastien Mélançon[c], Hélène Bachelard[c]

[a]*Nutrition Lipidique et Régulation Fonctionnelle du Cœur et des Vaisseaux, UMR INRA-Université Paris XI, Faculté de Pharmacie, 92290 Châtenay-Malabry, France*

[b]*Department of Anatomy and Physiology and Lipid Research Unit, Laval University Hospital Research Center, Ste-Foy, Québec, Canada G1V 4G2*

[c]*Department of Medicine and Lipid Research Unit, Laval University Hospital Research Center, Ste-Foy, Québec, Canada G1V 4G2*

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Abstract

Dietary fatty acids (FAs) are known to modulate endothelial dysfunction, which is the first stage of atherosclerosis. However, their exact role in this initial phase is still unclear. The effects of isolated or combined (by 2) purified FAs from the main FA families were studied on the vascular response of isolated thoracic aorta in healthy rats to get a better understanding of the mechanisms of action of dietary FAs in regulating vascular endothelial function. Cumulative contraction curves to phenylephrine and relaxation curves to carbachol and then to sodium nitroprusside were obtained in the absence or presence of the FAs studied allowing endothelium-dependent and endothelium-independent ability of the smooth muscle to relax to be assessed in each experimental group. The endothelium-dependent vasodilator response to carbachol was lowered by eicosapentaenoic acid, whereas it was not altered either by docosahexaenoic acid alone or by combined eicosapentaenoic acid–docosahexaenoic acid, oleic acid, or stearic acid, and it was increased by linoleic acid (LA). A decreased phenylephrine-induced contraction was observed after incubation with arachidonic acid and with stearic acid. On the other hand, the endothelium-dependent relaxation was reduced by the addition of combined LA–arachidonic acid and LA–oleic acid. In conclusion, these data point out the differential effects of different types of FAs and of FAs alone vs combined on vascular reactivity. The complex nature of these effects could be partially linked to metabolic specificities of endothelial cells and to interactions between some FAs.
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1. Introduction

Dietary lipids have an important impact on cardiovascular disease (CVD) risk, and research in this field has placed particular emphasis upon the role played by fatty acids (FAs) in modulating vascular function [1,2]. In addition, several studies in humans as well as rodents have demonstrated that an experimental elevation in circulating nonesterified FA concentrations in healthy subjects led to impairment of endothelium-dependent and insulin-mediated vasodilation because of a reduced nitric oxide (NO) production [3]. However, the exact role of different types of FA on atherosclerosis, particularly during its initial phase dealing with an endothelial dysfunction [4], is still unclear.

It is currently believed that a diet enriched in long-chain $n-3$ polyunsaturated FAs ($n-3$ PUFAs) reduces the risk of developing CVD [5,6], that a long-term feeding of olive oil (OO), rich in oleic acid (OA), highly contributes to the very low prevalence of CVD in people of the Mediterranean region [7], and that γ-linolenic acid may also modulate the atherosclerosis process by inhibiting smooth muscle cell proliferation [8]. Several studies have shown that the main long-chain $n-3$ PUFAs, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), can prevent the activation of endothelial cells (ECs) either by inhibiting the expression of adhesion molecules or by improving endothelial NO synthase (eNOS) activity [9,10]. It has even been suggested that these effects of $n-3$ PUFA could be related to EC membrane characteristics or redox status [11,12]. Moreover, OA has been shown to inhibit the endothelium-dependent vasodilator response to acetylcholine in rabbit femoral artery rings preconstricted with phenylephrine by inhibiting eNOS activity [13]. However, this FA has also been shown to increase the relaxant response to acetylcholine in aortic rings from spontaneously hypertensive (SHR) as well as normal Wistar-Kyoto (WK) rats [7]. Thus, the respective

* Corresponding author. Tel.: +33 1 4683 5959/5364; fax: +33 1 4683 5371.

E-mail address: raymond.christon@jouy.inra.fr (R. Christon).

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effects of FAs appear rather controversial, which may be attributed to particular experimental conditions (animal species, cultured cells, etc). Moreover, in most of the aforementioned in vitro or ex vivo studies, FAs are generally considered separately, their possible interactions being not taken into account. It should be noted, however, that Herrera et al [7] have compared the effects of 2 OA-rich diets, containing OO and high–OA sunflower oil (HOSO), on vascular reactivity, and the results of their study suggest that only the long-term feeding of OO diet modulated the vascular response of rat aorta. As the OA concentration of OO and HOSO was similar, these authors considered that other components of OO, such as polyphenols, not present in HOSO, might be responsible for the beneficial effects of OO on the cardiovascular system. Without excluding this possibility, it may be hypothesized that the observed modulation results from an interaction between OA and other FAs present in these oils. Indeed, linoleic acid (LA) (18:2$n-6$) level was higher in HOSO than in OO (9.4% vs 3.5%), and this FA has been shown to be proatherogenic by promoting endothelial activation with enhanced expression of adhesion molecules and decreased eNOS activity [14,15]. The results obtained in this study could also be explained by a possible interaction between the effects of OA and LA in the HOSO treatment, whereas the effect of OA was predominant in the OO treatment. However, the mechanisms behind these beneficial or detrimental effects remain poorly understood. Most studies have focused on the effects of FAs under diseased conditions and not in healthy individuals. Therefore, the present study was undertaken to investigate the effects of isolated or combined FAs on endothelial function within the context of atherosclerosis prevention. In this study, we hypothesized that the modulating effect of FA on vascular reactivity in a healthy control animal could be very different whether FA were alone or in combination. This study should help us choose the FA to be tested in further mechanistic investigations addressing current hypotheses and questions recently raised [16,17].

2. Materials and methods

2.1. Animals

All surgical and experimental procedures followed institutional animal care guidelines and the investigation conforms with the *Guide for the Care and Use of Laboratory Animals* published by the US National Institutes of Health (Publication No. 85-23, revised 1996). Male Sprague-Dawley rats (Charles River, St-Constant, Canada), weighing 300 to 350 g, were housed individually in stainless steel cages. They were placed in a temperature-controlled room (22°C ± 1°C) on a 12-hour light/dark cycle (lights on at 6:00 AM) and had free access to food and tap water. After the settling-in period, rats were anesthetized with a mixture of ketamine-xylazine (100 and 10 mg/kg IP, respectively).

2.2. Measurement of aorta reactivity

The thoracic aortas from the rats were quickly excised and placed in chilled Krebs buffer solution (in mmol/L: NaCl, 118; KCl, 4.7; $MgSO_4$, 1.18; KH_2PO_4, 1.18; $NaHCO_3$, 25; dextrose, 11.1; $CaCl_2$, 2.5; EDTA, 0.06) containing bovine serum albumin (90 μmol/L). The fat and adventitia were dissected free, and the aorta was cut into 3-mm rings. The rings were mounted under 2-g resting tension on stainless steel hooks in 15-mL organ baths filled with Krebs buffer and gassed with 95% O_2 and 5% CO_2 at 37°C. Tension was recorded with a Grass force transducers

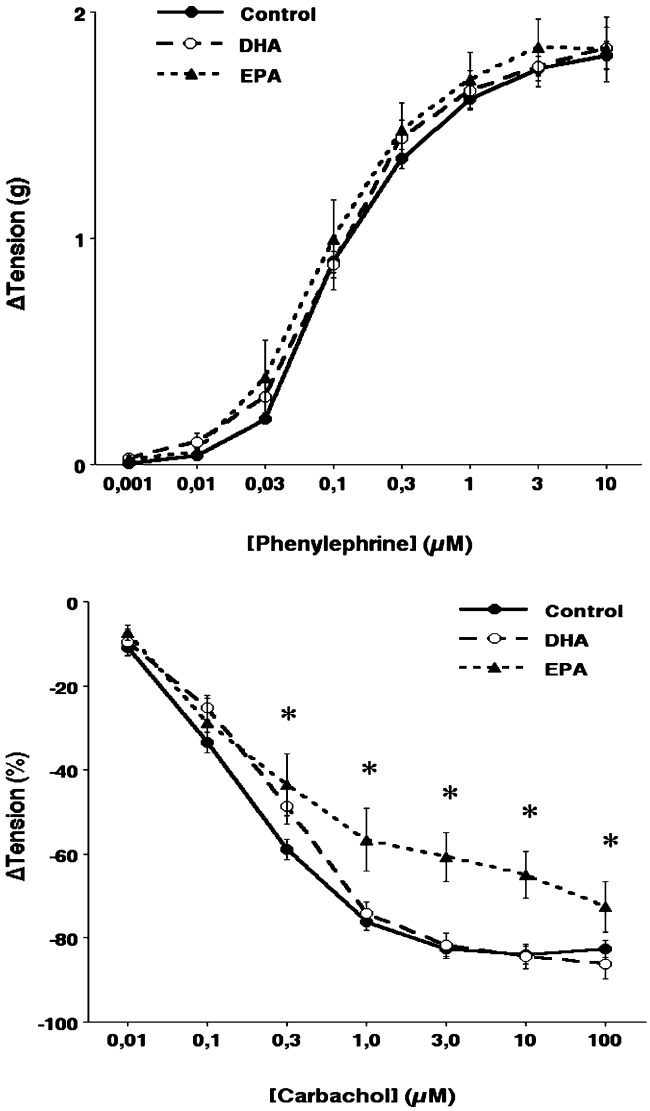

Fig. 1. Top, Cumulative DRCs to increasing concentrations of phenylephrine (10^{-9} to 10^{-5} mol/L) in rat isolated aortic rings incubated in the absence (control, n = 26) or presence of DHA (90×10^{-6} mol/L, n = 10) or EPA (90×10^{-6} mol/L, n = 9). Values are means ± SE shown by vertical lines. Bottom, Cumulative DRCs to increasing concentrations of carbachol (10^{-8} to 10^{-4} mol/L) in rat isolated aortic rings precontracted with phenylephrine (10^{-6} mol/L) and incubated in the absence (control, n = 26) or presence of DHA (90×10^{-6} mol/L, n = 9) or EPA (90×10^{-6} mol/L, n = 9). Values are means ± SE shown by vertical lines. *$P < .05$ indicates a significant difference between control and EPA-exposed aortic rings.

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