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Research paper

Argan oil prevents down-regulation induced by endotoxin on liver fatty acid oxidation and gluconeogenesis and on peroxisome proliferator-activated receptor gamma coactivator-1α, (PGC-1α), peroxisome proliferator-activated receptor α (PPARα) and estrogen related receptor α (ERRα)

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Abstract

In patients with sepsis, liver metabolism and its capacity to provide other organs with energetic substrates are impaired. This and many other pathophysiological changes seen in human patients are reproduced in mice injected with purified endotoxin (lipopolysaccharide, LPS). In the present study, down-regulation of genes involved in hepatic fatty acid oxidation (FAOx) and gluconeogenesis in mice exposed to LPS was challenged by nutritional intervention with Argan oil. Mice given a standard chow supplemented or not with either 6% (w/w) Argan oil (AO) or 6% (w/w) olive oil (OO) prior to exposure to LPS were explored for liver gene expressions assessed by mRNA transcript levels and/or enzyme activities. AO (or OO) food supplementation reveals that, in LPS-treated mice, hepatic expression of genes involved in FAOx and gluconeogenesis was preserved. This preventive protection might be related to the recovery of the gene expressions of nuclear receptors peroxisome proliferator-activated receptor α (PPARα) and estrogen related receptor α (ERRα) and their coactivator peroxisome proliferator-activated receptor gamma coactivator-1α, (PGC-1α). These preventive mechanisms conveyed by AO against LPS-induced metabolic dysregulation might add new therapeutic potentialities in the management of human sepsis.

Keywords: Argan oil; Beta-oxidation; Coactivator; Gluconeogenesis; Nuclear receptor.

Abbreviations: ACADS, acyl CoA dehydrogenase short-chain; ACADM, acyl CoA dehydrogenase medium-chain; ACADL, acyl CoA dehydrogenase long-chain; AO, Argan oil; ACOX1, acyl-CoA oxidase 1; ERRα, estrogen related receptor α; G6PH, glucose-6-phosphatase; Glut2, glucose transporter 2; Glut4, glucose transporter 4; HNF-4α, hepatic nuclear factor-4α; OO, olive oil; LPS, lipopolysaccharide; PGC-1α, peroxisome proliferator-activated receptor γ coactivator-1α; PEPCK, phospoenolpyruvate carboxykinase; PPARα, peroxisome proliferator-activated receptor α.

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1. Introduction

Bacterial infection is a common cause of sepsis, a pathological state inducing a severe organ dysfunction and a high mortality rate, and requiring intensive care [1–3]. This acute syndrome is associated with systemic inflammation and disturbed metabolism [4,5]. During bacterial infection, release in the host of endotoxins (lipopolysaccharides, LPS) from gram-negative bacteria membrane generates a potent inflammatory cytokine response and severely impairs lipid metabolism, inducing reduced serum high density lipoprotein (HDL), increased plasma free fatty acids and triglycerides levels [3]. These metabolic changes are mainly accounted for by enhanced hepatic triglyceride synthesis and adipose tissue lipolysis combined with a drop in fatty acid oxidation (FAOx) in several tissues including heart, kidney, liver and skeletal muscle [3,6–10]. The downregulation of FAOx by LPS is correlated with decreased expressions of the nuclear receptor Peroxisome Proliferator-Activated Receptor (PPAR)α and its coactivator PPARγ Coactivator (PGC)-1α, which physiologically work in concert to regulate FAOx-related gene expressions [11,12]. In this respect, ligand-dependent activation of the nuclear receptor PPARα prompts its heterodimerization with Retinoid X Receptor (RXR)α [13,14]. The PPARα/RXRα complex binds to PPARα-response elements (PPRE) of target genes which may code for mitochondrial and peroxisomal enzymes involved in fatty acid β-oxidation pathways such as carnitine palmitoyl transferase 1 (CPT1a and CPT1b), short-, medium-, long- and very long-chain acyl CoA dehydrogenases (ACADS, ACADM, ACADL and ACADVL) [15–19], acyl-CoA oxidase 1 (ACOX1) [17,20,21] and other proteins [12,22]. On the other hand, Lipin-1, a phosphatidate phosphatase, has arisen as an additional transcriptional co-regulator of PPARα–PGC-1α-directed gene expression [23]. Its interaction with PPARα-PGC1α complex promotes the induction of FAOx genes [24]. Beside PPARα, estrogen related receptor (ERR) α or (ESRRα), an orphan nuclear receptor, has been also shown to regulate energy metabolism gene expression [25,26], particularly genes involved in FAOx [27,28]. This transcriptional regulation involves interaction with PCG-1α coactivator through a protein motif specifically dedicated to ERRα [29,30]. In liver, another interaction of PGC-1α is also observed for hepatic nuclear factor-4α (HNF-4α) to control genes coding gluconeogenesis proteins (phospoenolpyruvate carboxykinase (PEPCK), glucose-6-phosphatase (G6PH)) and glucose transporter 4 (Glut4) [31].

More than 20% of patients with sepsis develop liver dysfunction [1] and hence dysregulation of hepatic metabolism and reduced energy supply for other organs. In mouse models of sepsis, injection of purified LPS triggers many pathophysiological changes resembling those described in human patients [32]. Though down-regulatory mechanisms by which LPS impacts FAOx have been extensively studied, little attention has been actually paid to mechanisms capable of preserving normal FAOx and inflammation status. Interestingly, supplementation of parenteral nutrition with fish oil to patients, during the postoperative period, revealed lowest levels of circulating inflammatory mediators [33–35]. Accordingly, polyunsaturated fatty acid-rich diet has been reported to reduce acute inflammation and to promote anti-inflammatory process in mice [36]. Therefore, lipid nutritional support might help the prevention of not only inflammatory damages but also disrupted lipid homeostasis.

Argan edible oil (AO) is obtained by cold-pressure of roasted kernels from *Argania spinosa [L.] Skeels*, a singular Mediterranean species growing in the southwestern region of Morocco. Argan oil is used as a traditional food ingredient in the 'Amazigh diet', bringing almost 25% of total diet fat intake to indigenous consumers [37]. Accordingly, early clinical studies on Argan oil reported a decrease in plasma low density lipoprotein-cholesterol (LDL-cholesterol) and lipid hydroperoxides along with a rise in plasma tocopherol concentration [38]. Health benefits of this delectable virgin oil have been highlighted by several studies documenting its cardiovascular protective potential including hypocholesterolemic and hypotriglyceridemic properties in consumer populations [39–41]. AO has been also shown to reduce circulating LDL-cholesterol and ApoB and, in AO consumers, to increase HDL and ApoAI [40,41] whereas in human macrophages it increases HDL-mediated cholesterol efflux and reduces LDL-lipid peroxidation [38,39].

Therefore, in an attempt to test our hypothesis regarding the preventive effects of Argan oil against LPS-induced FAOx downregulation, mice pretreated with AO were subsequently injured by LPS to determine whether an experimental support may be or not given to this working hypothesis. The effects of AO against sepsis-associated liver hyperlipidemia are compared to those of olive oil (OO), a more usual ingredient in Mediterranean diets. We report here that, in fact, AO-enriched diet prevents LPS-associated hyperlipidemic effect through the induction of the hepatic expressions of PPARα, ERRα and their coactivator PGC-1α along with the up-regulation of their mitochondrial (*ACADS, ACADM, ACADVL*) and peroxisomal (*ACOX1*) target genes.

2. Material and methods

2.1. Argan oil treatment

Swiss OF1 mice (12–16 week-old) were obtained from IFFA CREDO (Casablanca). They were acclimatized in the laboratory for 10 days at 22 ± 2 °C with standard chow and water *ad libitum*. Animal studies were conducted in accordance with the protocols of Animal Use and Care of the University of Hassan 1st, Settat, Morocco. The virgin Argan oil used in this work was obtained from the Aklim area in the northeast of Morocco. Six groups of mice (5 mice/group) received during 25 days: a standard chow (2 groups, control); a standard chow supplemented with 6% (w/w) of Argan oil (2 groups, AO) or a standard chow supplemented with 6% (w/w) of olive oil (2 groups, OO). Oils were included in the diets by direct mixing with the standard animal chow. Sixteen hours before euthanasia and during the fed state, one group from control (+LPS), AO (AO + LPS) and OO (OO + LPS) respectively received (5 mg/kg) intraperitoneal injections of 100 μg of *Escherichia coli* 0111:B4 LPS (Sigma) resuspended in phosphate-buffered saline (PBS) or an equal volume of PBS alone.