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Review

Vascular effects of the Mediterranean diet—Part II: Role of omega-3 fatty acids and olive oil polyphenols

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ABSTRACT

The lower occurrence of cardiovascular disease and cancer in populations around the Mediterranean basin as detected in the 1950s was correctly attributed to the peculiar dietary habits of those populations. Essentially, until the mid-20th century, typical Mediterranean diets were rich in fruits, vegetables, legumes, whole-wheat bread, nuts, fish, and, as a common culinary trait, the routine use of extra-virgin olive oil. Nowadays, the regular adoption of such dietary patterns is still thought to result in healthful benefits. Such patterns ensure the assumption of molecules with antioxidant and anti-inflammatory actions, among which ω-3 polyunsaturated fatty acids (PUFAs), ω-9 monounsaturated fatty acids (oleic acid), and phenolic compounds. The aim of this review is to provide an update of the vasculo-protective pathways mediated by ω-3 PUFAs and polyphenols in the context of the modern Mediterranean dietary habits, including the possible cross-talk and synergy between these typical components. This review complements a parallel one focusing on the role of dietary nitrates and alimentary fats.

Contents

1. Premise and Introduction

The beneficial effects of Mediterranean diets have been reported as due to the synergistic interaction of various constituents. Numerous studies have demonstrated that single components, i.e., inorganic nitrates, monounsaturated fatty acids, ω-3 polyunsaturated fatty acids (PUFAs) and polyphenols, have specific roles in the prevention of inflammatory and degenerative diseases, as well as of cancer. The metabolic roles of inorganic nitrates and monounsaturated fatty acids have been previously reviewed (*Capurso C et al, Vascular Pharmacology in press*). In this review, the biochemical and mechanistic properties of ω-3 PUFAs and olive oil polyphenols in the context of the Mediterranean dietary habits are discussed as a basis for a possible interplay between these nutritional components.

After the striking protective effects reported for a Mediterranean-type diet in the secondary prevention of coronary heart disease [1], the recently documented benefits of a Mediterranean diet supplemented

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in mixed nuts (as a source of ω-3 PUFAs besides to high-molecular-weight polyphenols, including proanthocyanidins and ellagitannins [2]) or extra-virgin olive oils (as a prominent source of low-molecular-weight polyphenols hydroxytyrosol and its derivatives, besides to monounsaturated fatty acids) in the primary prevention of major coronary events [3] also highlight the vasculo-protective potential of polyphenols and ω-3 PUFAs in the context of a Mediterranean dietary pattern. Such evidence, however, raises some questions, which will be addressed here: first, can the spontaneous adherence to a typical Mediterranean diet provide appreciable and biologically meaningful increases in plasma levels of polyphenols and ω-3 PUFAs? Second, are plant- and marine-derived polyphenols and ω-3 PUFAs endowed with shared or complementary vasculo-protective activities?

2. Role of ω-3 PUFAs in the Mediterranean diets

2.1. Structure, source and metabolism of ω-3PUFAs

In the last 50 years many epidemiological evidences have accumulated regarding the role of ω-3 PUFAs, namely α-linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), in the prevention and management of cardiovascular disease [4]. PUFAs are organic acids present in the diet and containing more than one double bonds in their aliphatic chain. Biologically relevant families of PUFAs are the omega-3 (ω-3) and the omega-6 (ω-6) PUFAs. Since the double bond in the ω-3 or ω-6 position cannot be inserted into FA by animal enzymes, but only by vegetable Δ12- and Δ15-desaturases, LA and ALA represent "essential fatty acids (EFAs)" for mammals [5]. Mammalian cells may indeed metabolize them (Fig. 1) through the action of a series of elongation and desaturation enzymes that insert double bonds into the molecules, with an additional final step for docosatetraenoic acid and DHA production that requires the translocation to peroxisomes for a β-oxidation reaction [6]. It is estimated that minimum human requirements are 1 and 0.2% of daily energy intake for ω-6 and ω-3 PUFAs, respectively [7]. Because LA and ALA are synthesized by plants, vegetables and vegetable oils are good sources of both FAs. Green plant tissues are especially rich in ALA, which typically comprises 55% of all FAs present in green vegetables. However such plant tissues are not rich in fat, and therefore, for most human diets, this source does not make a sufficient contribution to the minimum intake of ALA. In contrast, some plant oils, such as soybean, flaxseed, and rapeseed oil, as well as some kinds of dry fruits as nuts, contribute to a higher degree to ALA dietary intake, although, the absolute amount of LA is almost always superior to that of ALA [8]. Intervention studies with ALA in ω-3 PUFA-deficient patients have demonstrated marked increases in plasma concentrations of EPA [9–11]. In addition, vegans on a plant-based diet with no source of EPA and DHA in their diets have shown low but stable DHA levels in their blood [12,13]. Together, these findings preliminarily demonstrated the convertibility of ALA into EPA and DHA in humans. Such seminal evidence have been expanded using stable isotope-labeled ALA as tracer of ALA metabolism in humans [14]. These studies have shown that dietary ALA is mostly catabolized to carbon dioxide and ATP for energy production [15]. Only a small proportion of the administered ALA, estimated to be less than 5%, was metabolized to EPA and DHA [16], with greater capacity for ALA conversion in women than men [17]. ALA appears therefore to be a modest source of longer-chain ω-3 PUFAs in humans. In Europe, during the last two decades, the consumption of LA is increased by about 50%, passing from 10 to 15 g/day, while the consumption of ALA moved from 1 to 1.9 g/day [18]. Since dietary LA competes with ALA for Δ6-desaturase activity [19], the modest intakes of ALA and the high amounts of LA featuring in most western diets suggest that ALA cannot reliably replace EPA and DHA in many current diets, and therefore the direct dietary intake of EPA and DHA is by far the easiest way to increase the concentration of such FAs in human tissues [7]. Algae are the primary producers of DHA and EPA in the ecosystem, so that DHA and EPA enter the food chain through marine phytoplankton and accumulate in fish, especially oily fish (mackerel, trout, salmon, herring and sardines) [20].

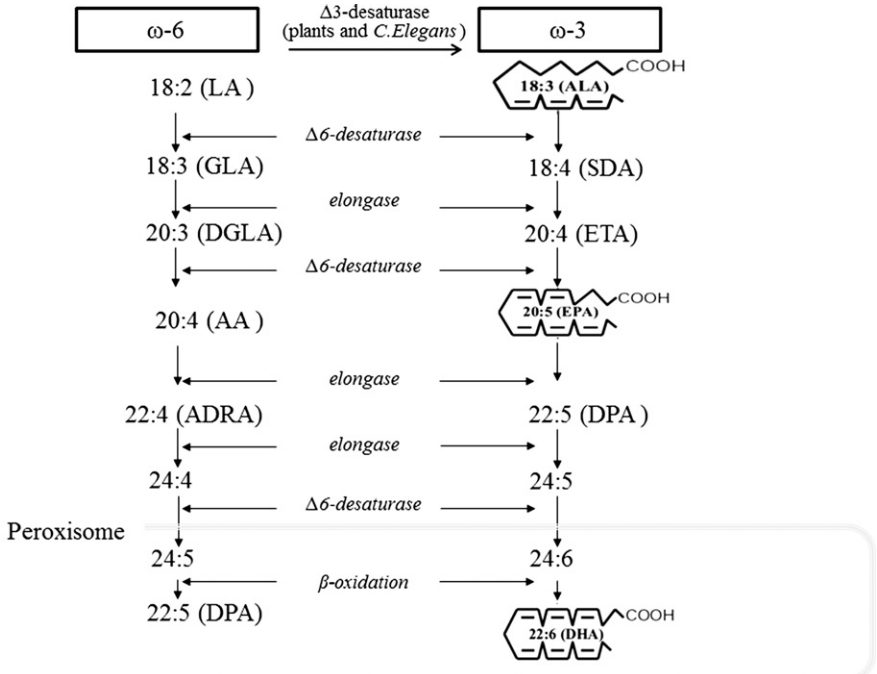

Fig. 1. Chemical structure and conversion pathway of linoleic (LA) and α-linolenic (ALA) acid into longer derivatives. In the omega-6 family, LA can be converted into γ-linolenic acid (GLA) (18: 3n-6) by Δ6-desaturase and then GLA can be elongated (by elongase) to dihomo-γ-linolenic acid (DGLA) (20: 3n-6). (DGLA) can be desaturated further by Δ5-desaturase to finally yield arachidonic acid (AA) (20: 4n-6). Using the same series of enzymes, ALA is converted into eicosapentaenoic acid (EPA) (20: 5n-3). The further conversion of EPA into docosahexaenoic acid (DHA) (22: 6n-3) involves a first addition of two carbon atoms to form docosapentaenoic acid (DPA) (22: 5n-3), of two further carbons to produce 24: 5, and a desaturation to form 24:6. The removal of two carbons from 24:6, by β-oxidation yields DHA (Sprecher's shunt). ETA, eicosatetraenoic acid; ADRA, adrenic acid.