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Review

Arachidonic acid: Physiological roles and potential health benefits – A review

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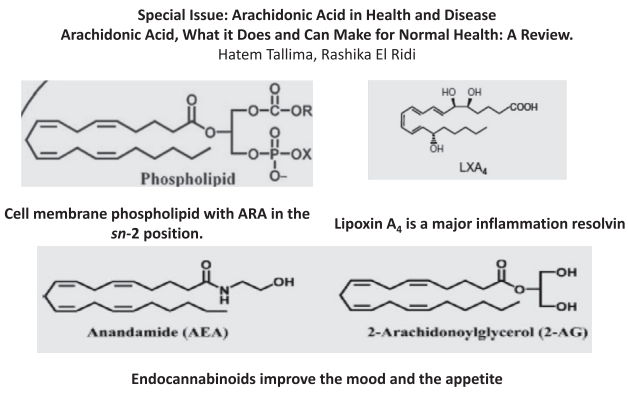
GRAPHICAL ABSTRACT



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ABSTRACT

It is time to shift the arachidonic acid (ARA) paradigm from a harm-generating molecule to its status of polyunsaturated fatty acid essential for normal health. ARA is an integral constituent of biological cell membrane, conferring it with fluidity and flexibility, so necessary for the function of all cells, especially in nervous system, skeletal muscle, and immune system. Arachidonic acid is obtained from food or by desaturation and chain elongation of the plant-rich essential fatty acid, linoleic acid. Free ARA modulates the function of ion channels, several receptors and enzymes, via activation as well as inhibition. That explains its fundamental role in the proper function of the brain and muscles and its protective potential against *Schistosoma mansoni* and *S. haematobium* infection and tumor initiation, development, and metastasis. Arachidonic acid in cell membranes undergoes reacylation/deacylation cycles, which keep the concentration of free ARA in cells at a very low level and limit ARA availability to oxidation. Metabolites derived from ARA oxidation do not initiate but contribute to inflammation and most importantly lead to the generation of mediators responsible for resolving inflammation and wound healing. Endocannabinoids are oxidation-independent ARA derivatives, critically important for brain reward signaling, motivational processes, emotion, stress responses, pain, and energy balance. Free ARA and metabolites promote and modulate type 2 immune responses, which are critically important in resistance to parasites and allergens insult, directly via action on eosinophils, basophils, and mast cells and

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indirectly by binding to specific receptors on innate lymphoid cells. In conclusion, the present review advocates the innumerable ARA roles and considerable importance for normal health.

Introduction

Arachidonic acid (ARA) is a 20-carbon chain fatty acid with four methylene-interrupted cis double bonds, the first with respect to the methyl end (omega, ω or n) is located between carbon 6 and 7. Hence, ARA belongs to the omega-6 (n-6) polyunsaturated fatty acids (PUFA), is designated as 20:4ω-6, with a biochemical nomenclature of all-*cis*-5,8,11,14-eicosatetraenoic acid, and usually assumes a hairpin configuration (Fig. 1) [1].

Arachidonic acid is obtained from food such as poultry, animal organs and meat, fish, seafood, and eggs [2–5], and is incorporated in phospholipids in the cells' cytosol, adjacent to the endoplasmic reticulum membrane that is studded with the proteins necessary for phospholipid synthesis and their allocation to the diverse biological membranes [6]. Of note, glycerophospholipids are composed of a glycerol backbone esterified to two hydrophobic fatty acids tails at *sn*- (stereospecifically numbered) 1 and 2 position and a hydrophilic head-group at *sn* 3. The membrane and cytosolic phospholipids of mammalian cells and tissues are rich in ARA, usually localized in the glycerol backbone *sn*-2 position. Platelets, mononuclear cells, neutrophils, liver, brain and muscle have up to 25% phospholipid fatty acids as ARA [7]. Arachidonic acid participates in the Lands cycle, a membrane phospholipids' reacylation/deacylation cycle, which serves to keep the concentration of free ARA in cells at a very low level [8]. Since ARA is a fundamental constituent of cell structure, it will particularly be needed for during development and growth and upon severe or widespread cell damage and injury.

Another ARA source, so important for herbivores and vegetarians, is linoleic acid, also an omega-6, 18 carbonde PUFA that contains only two *cis*- double bonds (18:2ω-6). Linoleic acid is an essential fatty acid for animals because they cannot synthesize it, in contrast to plants, which can synthesize it from oleic acid. Linoleic acid is abundant in many nuts, fatty seeds and their derived vegetable oils [5]. It is converted in animals cells cytosol to ARA, docosatetraenoic acid (22:4ω-6) and other fatty acids by stepwise desaturation and chain elongation. Linoleic acid conversion to ARA is, however, low. Linoleic acid is readily oxidized by delta 6-desaturase to γ-linolenic acid (18:3-n6), but several factors such as aging, nutrition, smoking impair the activity of the enzyme. Gamma linolenic elongation step to dihomo-γ-linolenic acid (20:3-n6) is rapid; yet, it is oxidized by delta-5 desaturase to yield ARA at a small percentage because delta-5 desaturase prefers the n-3 to n-6 fatty acids [9–13].

Arachidonic acid production

The filamentous fungus, *Mortierella*, especially of the species *alpina* (http://eol.org/collections/119317) is considered a predominant source for preparation of ARA on the industrial scale [14–22]. Additionally, ARA can be *in vitro* synthesized from 5-hexyn-1-ol as described in detail by Prakash et al. [23].

Arachidonic acid physiological functions

Cell membrane fluidity

Arachidonic acid four *cis* double bonds endow it with mobility and flexibility conferring flexibility, fluidity and selective permeability to membranes [24,25]. ARA control of membrane fluidity influences the function of specific membrane proteins involved in

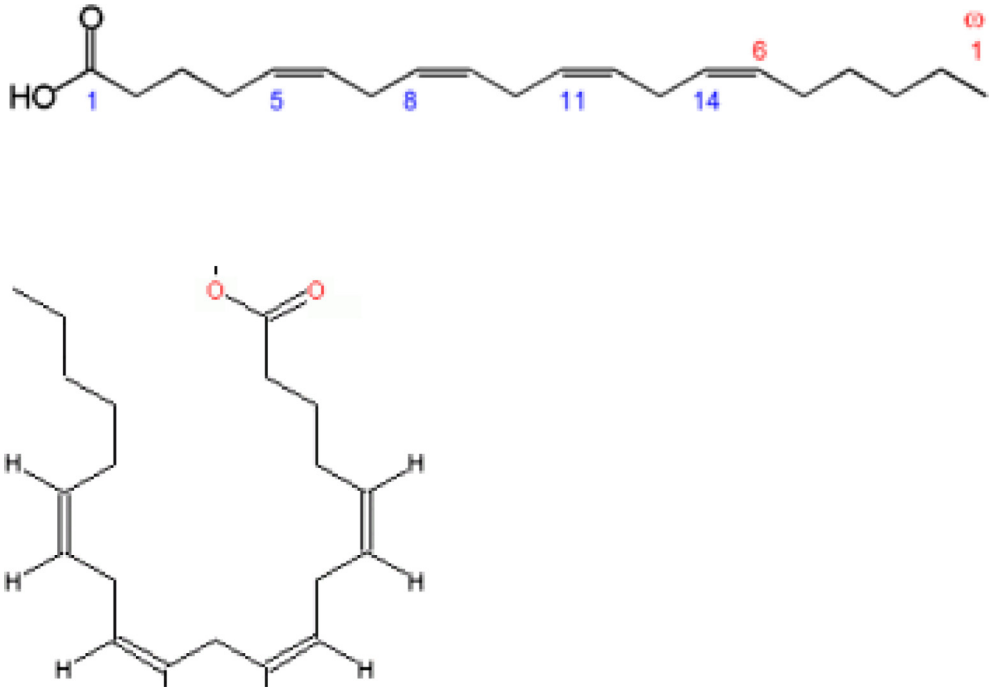

Fig. 1. Arachidonic acid structure showing linear and hairpin configuration.

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