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Review

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

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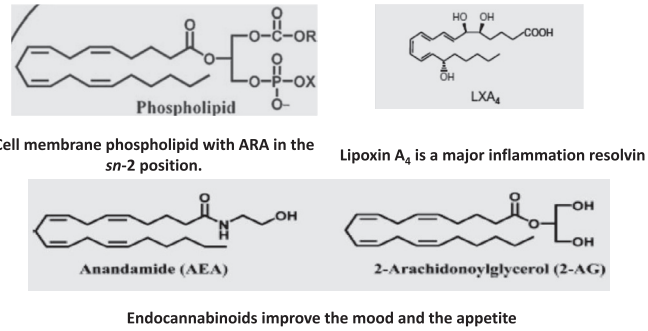
GRAPHICAL ABSTRACT



Cell membrane phospholipid with ARA in the *sn*-2 position.

Lipoxin A_4 is a major inflammation resolvin

Endocannabinoids improve the mood and the appetite

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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 carbond 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 perme-

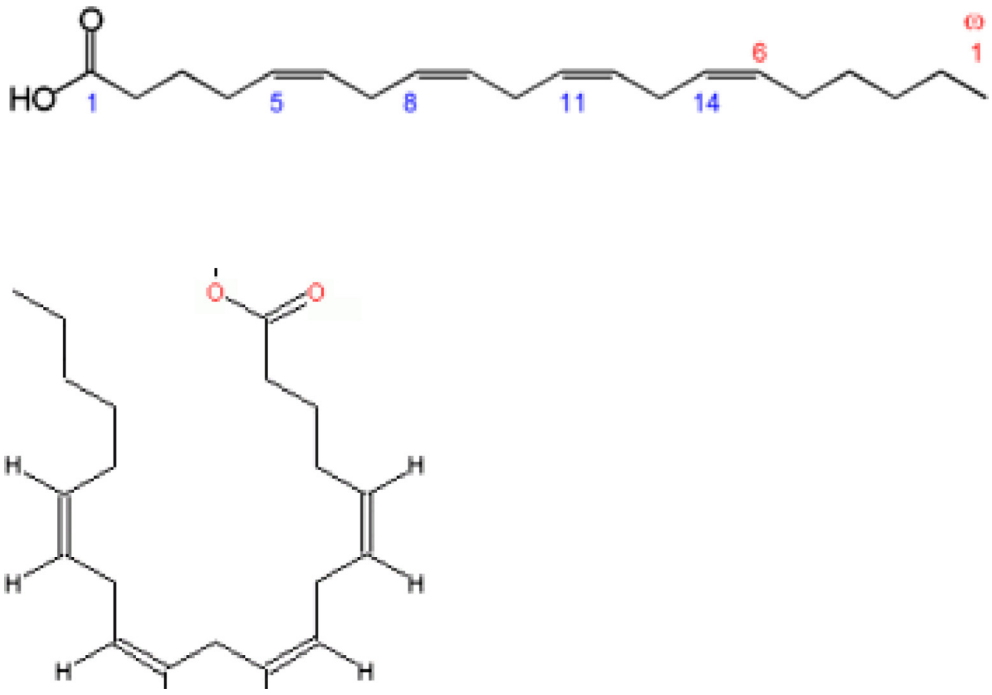

Fig. 1. Arachidonic acid structure showing linear and hairpin configuration.

ability to membranes [24,25]. ARA control of membrane fluidity influences the function of specific membrane proteins involved in cellular signaling [24,25] and plays a fundamental role in maintenance of cell and organelle integrity and vascular permeability [26]. These properties might explain ARA critical role in neuron function, brain synaptic plasticity, and long-term potentiation in the hippocampus [27–31].

Ion channels

Non-esterified, free ARA affects neuronal excitability and synaptic transmission via acting on most voltage-gated ion (Na_v, K_v, Ca_v, Cl_v, proton H_v) channels, responsible for regulating the electric activity of excitable tissues, such as the brain, heart and muscles. Ion channels are large families of integral membrane proteins that form a selective pore for ions to cross the lipid bilayer, via undergoing conformational changes in response to alteration in the cell transmembrane electrical potential. These channels gate passage of specific ions and thus control the propagation of nerve impulses, muscle contraction, and hormone secretion [32–39]. The homologous mon-, di- or tetrameric subunits of ARA-sensitive voltage-gated channels are composed of four transmembrane helices spanning the cell membrane lipid bilayer (S1-S4) making up the voltage-sensor domain, and/or 2 transmembrane segments constituting the central ion-conducting pore [34,35,39]. The gating charges are situated on helix S4, a positively charged voltage sensor, which responds to changes in voltage across the membrane by inducing movements of the helix relative to the remainder of the protein or the movement of the positive charges through the membrane toward the extracellular side [34–36]. Since S4 is in contact with the lipid bilayer, the ARA lipophilic, flexible acyl chain can position its carboxylate negative charge onto the voltage sensor, and modulate its activity, likely shifting the voltage dependency of activation via channel-activating electrostatic interactions [37–39].

Free ARA evoked K+ channel opening in neurons of the rat visual cortex, thus suggesting the existence of an ARA-activated type of K+ channel, which may play a critical role in modulating cortical neuronal excitability [40,41]. Arachidonic acid was previously reported to directly activate K+ channels in gastric, pulmonary artery, and vascular smooth muscle cells, and cardiac atrial cells likely via interacting with the ion channel protein itself [40–43]. Conversely, ARA is known to suppress the Kv4 family of voltage-dependent K+ channels, in a direct, fast, potent, and partially reversible mode [44]. The activity of the large-conductance Ca2+- dependent K+ (BK) channels, which control diverse functions in the central nervous system such as sleep and neural regulation of the heart, is increased up to 4 folds by ARA, consequent to direct interaction with the channel protein [43,45]. Conversely, ARA inhibited intermediate conductance, Ca++-activated K+ channels, which play crucial roles in agonist-mediated transepithelial Cl^- secretion across airway and intestinal epithelia, via interacting with the pore-lining amino acids (aa) threonine (aa 250) and valine (aa 275) [46]. Background, non-voltage-dependent two pore domain K(+) channels, which play an essential role in setting the neuronal membrane potential and potential duration are opened by ARA, and not its metabolites, provided the carboxyl end is not substituted with an alcohol or methyl ester [47,48]. Additionally, ARA was reported to inhibit the ATP- sensitive K+ channel in cardiac myocytes almost completely, while activated the ATP-insensitive K+ channel [49].

Free, non-esterified ARA prevents ischemia-induced heart arrhythmia, a major cause of sudden cardiac death in humans, by modulating the activity of cardiac Na+ channels, the major class of ion channels that determine cardiac excitability, causing a reduction in the electrical excitability and/or automaticity of cardiac myocytes [50]. Sodium channels consist of a large functional subunit and a smaller subunit, which interacts with a regulatory segment. Arachidonic acid, but not its metabolic products, was shown to voltage-dependent modulate muscle Na+ channel currents, displaying both activation and inhibitory effects depending on the depolarizing potential [51]. Arachidonic acid also displayed both activation and inhibitory effects on different Cl- channels, widely distributed especially in epithelial tissues, and thus, mediate increase or block of Cl- ions permeation [52–55]. The double bonds and hydrophilic head were recently reported to be responsible for the ARA mediated dramatic increases in proton current amplitude through the voltage-gated proton (Hv) channel. The latter lacks a pore domain but allows passage of proton through the center of each voltage sensor domain [39] and supports the rapid production of reactive oxygen species (ROS) in phagocytes through regulation of pH and membrane potential [56].

Receptors and enzymes

Exogenous or endogenously produced ARA was discovered to greatly enhance the functional activity of ligand-gated ion channels, namely the γ-amino butyric acid receptor (GABA-R) located on the neuronal membrane, via modulating the GABA-R interaction characteristics with its ligands [57–60]. Free ARA exposure essentially led to inhibiting the muscle and neuronal nicotinic acetylcholine receptor (nAChR), an integral membrane protein deeply embedded in the postsynaptic region, with two agonist binding sites and a central ion pore. The receptor inhibition resulted from ARA displacing lipids from their sites in the plasma membrane and direct acting as antagonist at the PUFA-protein interface [60–63].

Activation of eosinophils, neutrophils, and macrophages elicits powerful respiratory burst associated with reduction of molecular oxygen to superoxide via activation of the NADPH oxidase complex, which consists of five proteins residing in resting cells in the cytosol or membrane of intracellular vesicles, and in activated cells are assembled on the cell membrane [26,64]. Generated ROS induce membrane depolarization and cytoplasm pH decrease, thus restricting NADPH activity. Concentrations of ARA of 5–10 μM added to neutrophils enhanced NADPH oxidase stimulation due to ARA-mediated activation of the Hv channel, modulation of the membrane potential and pH, and efflux of the H^+ ions generated together with the superoxide anion, O_2- [56,65–67].

PUFA, especially ARA, are documented activators of membrane-associated, magnesium-dependent, neutral sphingomyelinases (nSMase) [68–73]. ARA was recently documented as activator of *Schistosoma mansoni* and *S. haematobium* tegument-associated neutral sphingomyelinase in a dose-dependent manner, eventually leading to their attrition *in vitro* and *in vivo* [74–77].

Cell death

Free ARA levels are kept very low in cells as uncontrolled accumulation of unesterified ARA decisively impaired cell survival via induction of apoptosis [8]. The apoptotic effect was attributed to free ARA and not its metabolites as it was recorded in the absence of lipoxygenase or cyclooxygenase enzyme activity, and was speculated to be associated with oxidative stress and/or changes in membrane fluidity [6,25,26,78–81]. Indeed, Pompeia et al. reported that the cytotoxicity of arachidonic acid is undeniable, but may well be one of its fundamental functions *in vivo* [81]. ARA concentrations of 50–100 μM are cytotoxic to most cell lines *in vitro*. In the majority of models 1–10 μM ARA is necessary to elicit any biological response but some activities require 100–300 μM [25]. This indicates that ARA apoptotic and physiological levels overlap and it is very possible that ARA cytotoxicity occurs *in vivo* because under

some pathologic conditions, human plasma ARA levels can increase from 0.1–50 μM to 100 and up to 500 μM [81].

A most needed nutritional supplement

Newborns

Polyunsaturated fatty acids (PUFAs), especially ARA, affect the function of numerous ion channels, the activity of various enzymes and are implicated in cell apoptosis, necrosis and death, events of critical importance during embryogenesis, thereby have significant physiological and pharmacological impact on the health of newborns [39–42]. ARA and docosahexaenoic acid (DHA, 22:6 ω3) are important components of human milk but are lacking in cow milk and most commercial infant formula in developing countries [82]. Due to its importance in development especially of the central nervous system and retina [82–84], the Food and Agricultural Organization (FAO)/World Health Organization (WHO) recommended that infant formula, unless specifically added, should be supplemented with ARA [85]. Decreased postnatal ARA and DHA blood levels in premature infants were found to be associated with neonatal morbidities, while adding DHA and ARA to preterm-infant formulas led to improved visual acuity, visual attention and cognitive development [82–85]. The ARA levels in human milk and ARA requirements, essentiality in pre- and neonatal life and during development, and inclusion in infant formulas have recently been reviewed [86–88], challenged and discussed [89].

Neurological disorders

ARA does not only influence cell membrane fluidity and the activity of ion channels, especially in the brain, it constitutes together with DHA 20% of the human brain dry weight, concentrated in the neurons outer membrane and in the myelin sheath [90]. Additionally, positron emission tomography was used to show that the brain of human healthy volunteers consumes ARA at a rate of 17.8 mg/d [91]. Accordingly, ARA was recommended for management of central nervous system, visual and auditory damage in preterm infants via supporting neurovascular membrane integrity [92]. Children with autism had lower levels of blood PUFA, especially ARA, than normal children [93], and showed notable improvement after dietary PUFA intake [94]. In the elderly too, ARA supplementation improved cognitive functions [31], perhaps via increasing the proliferation of neural stem/progenitor cells or newborn neurons and general hippocampal neurogenesis [30]. The charged ARA displayed beneficial effects on epileptic seizures and cardiac arrhythmia by electrostatically affecting the k_V channel's voltage sensor, thus regulating neuronal excitability [37,38].

Exercise

In skeletal muscles, ARA has been found to make up to 15–17% of total fatty acids, thus explaining why ARA supplementation affected body composition, muscle function and power output in strength-training individuals [86,95,96]. It is also possible that ARA modulates neuromuscular signaling through its incorporation into cell membranes, and/or increases neurotransmitter firing from nerve cells [91].

Schistosomicidal action

The first evidence relating PUFA to schistosomes came from the ability of corn oil to expose hitherto unavailable surface membrane antigens of *Schistosoma mansoni* lung-stage larvae to specific antibody binding, thus allowing serologic visualization [97]. Further studies indicated that among PUFA, ARA (10 μM, 30 min) was the most effective in allowing specific antibody binding to otherwise hidden surface membrane antigens of *S. mansoni* and *Schistosoma haematobium* lung-stage schistosomula [74]. Of importance, exposure to 20 μM ARA for 30 min elicited surface membrane disintegration and attrition of the schistosomula [74]. Studies aiming at clarifying these observations led to identification of surface membrane sphingomyelin (SM) instrumental role in schistosome immune evasion. Controlled SM hydrolysis by parasite tegument-associated neutral sphingomyelinase (nSMase) allows entry of nutrients but not host molecules >600 Da or antibodies. Excessive nSMase activation and consequent SM hydrolysis elicits exposure of surface membrane antigens and eventual larval death. ARA is a major nSMase activator. Accordingly, it was straightforward to predict that ARA possesses potentially potent schistosomicidal activity [75,77,86,98,99].

All adult worms of *S. mansoni* and *S. haematobium* exposed to 2.5 mM ARA in the presence of 100% fetal calf serum showed extensive damage, disorganization, and degeneration of the tegument and the subtegumental musculature followed by death of all worms within 5 h [100]. Pure ARA and different ARA formulations elicited notable, reproducible, and safe schistosomicidal activity against larval, juvenile and adult *S. mansoni* and *S. haematobium* infection of inbred and outbred mice and hamsters [100,101]. The ability of ARA to control infection with *S. mansoni* was demonstrated in Egyptian children. The chemotherapeutic activity of ARA and praziquantel (PZQ) was equally high in low infection settings and equally low in children with heavy infection living in high endemicity areas. The highest cure was consistently achieved in children with light or heavy infection when ARA was combined with PZQ [77,86,102,103].

A breakthrough regarding the usefulness of ARA in defense against schistosomes came from the demonstration of association between resistance of the water-rat, *Nectomys squamipes* to repeated infection with *S. mansoni* and accumulation of ARA in liver cells [104]. This pioneering study prompted us to examine the relation between susceptibility and resistance of rodents to *S. mansoni* or *S. haematobium* infection and ARA levels in serum and lung and liver cells before and weekly after infection. The results strongly suggested that ARA is a potent "natural" schistosomicide, and may be considered an endoschistosomicide [105].

The schistosomicidal action of ARA is based on excessive hydrolysis of parasite surface membrane SM. Interestingly, Miltefosine, a *hexa*-decyl-phosphocholine, which interferes with proper biosynthesis of SM, was recently documented as a potent schistosomicide *in vitro* and *in vivo* [106].

Tumoricidal potential

Reports decades earlier indicated that PUFA, and especially free unesterified ARA possess tumoricidal activity *in vitro* and *in vivo* [107]. The most important and consistent studies documenting the tumoricidal action of PUFA, namely ARA were reported by Undurti Das and Colleagues [108–115], who advocated ARA as a potential anti-cancer drug [108]. Thus, ARA was reported to kill tumor cells selectively *in vitro* via eliciting cell surface membrane lipid peroxidation, which can be blocked by vitamin E, uric acid, glutathione peroxidase and superoxide dismutase [109]. Free ARA was found to inhibit the *in vitro* growth of human cervical carcinoma (HELA) cells and methyl cholanthrene-induced sarcoma cells. Free ARA augmented the generation of superoxide anion and lipid peroxidation in the tumor cells indicating a possible correlation between the ability of unesterified PUFA to augment free radicals and their tumoricidal action [110,111]. Moreover, free unesterified ARA, independently of its metabolites, displayed

cytotoxic action on both vincristine-sensitive (KB-3-1) and resistant (KB-Ch(R)-8-5) cancer cells *in vitro* that appeared to be a free-radical dependent process [112]. At concentrations of 100–200 μM, ARA was more effective than mesotrexate in *in vitro* suppression of gastric carcinoma cells, as a result of lipid peroxidation processes [113], and inhibited proliferation of human prostate cancer and human prostate epithelial cells, independently of free radicals generation [114]. ARA-mediated apoptosis of colon cancer cells appeared to be essentially due to loss of mitochondrial membrane, accumulation of ROS, and caspase-3 and caspase-9 activation [115]. Accordingly, it was concluded that ARA suppresses proliferation of normal and tumor cells by a variety of mechanisms that may partly depend on the type(s) of cell(s) being tested and the way ARA is handled by the cells [111,112]. A contradictory effect of ARA on tumorigenesis was observed in mice with a germline mutation in the adenomatous polyposis coli gene [116].

We have recently proposed that ARA may inhibit proliferation and elicit death of tumor cells via its activating impact on cell membrane-associated neutral sphingomyelinase (nSMase) and increased outer leaflet SM hydrolysis [68–76]. Disruption of the tight SM-based hydrogen bond network around cancer cells may allow contact inhibition processes to proceed and cell proliferation to stop [77], whereby the primary SM catabolite, ceramide released following SM hydrolysis is a renowned secondary messenger involved in programmed cell death [117]. It is of importance to recall that Miltefosine, which has been approved for the treatment of breast cancer metastasis, and is currently used for the treatment of cutaneous metastases of mammary carcinoma significantly inhibits SM biosynthesis in human hepatoma and other tumor cells [106,118–121]. The likely mechanism of action of this phospholipid analogue is inhibition of phosphatidylcholine biosynthesis, thus hindering SM metabolism, and substantially increasing the levels of ceramide [120,121].

Arachidonic acid metabolites physiological roles

The four *cis* double bonds of ARA mediate its propensity to react with molecular oxygen through the actions of three types of oxygenases: cyclooxygenase (COX), lipoxygenase (LOX), and cytochrome P450, leading to the generation of inflammatory bioactive lipids or eicosanoids (prostanoids and leukotrienes). However, dietary ARA is a poor substrate for oxidation [11] and ARA processing occurs only following release from cell membrane by phospholipase A2 [122,123]. Moreover, ARA reacylation is very significant in cells whereby a large portion of the ARA that is released by phospholipase A2 is rapidly incorporated back into phospholipids and a minor portion only converted into oxygenated metabolites [8]. Additionally, several, if not all, ARA metabolites have a considerable role in maintaining normal health via regulating innumerable physiologic processes [122,123].

Resolution of inflammation

Not only free ARA, but its metabolites, prostaglandins (PG), namely PGF_{2a}, PGE_2, and PGI_2 display essential roles in skeletal muscle development and growth by controlling proliferation, differentiation, migration, fusion and survival of myoblasts [123]. Indeed, eicosanoids produced from ARA tend to promote muscle growth during and after physical activity in healthy humans. Yet, the major action of ARA metabolites is promotion of acute inflammatory response, characterized by the production of pro-inflammatory mediators such as PGE_2 and PGI_2, followed by a second phase in which lipid mediators with pro-resolution activities may be generated. Resolution of inflammation is no more considered a passive process, but rather an active programmed response regulated by mediators with pro-resolving capacity, prominent among which is ARA-derived lipoxin A_4 [124,125]. Lipoxin A_4 stimulates cessation of neutrophil infiltration, enhances macrophage uptake of apoptotic cells in pre-clinical animal models [124–130], attenuates leukotriene C4-induced bronchoconstriction in asthmatic subjects, decreases eczema severity and duration and improves patients' quality of life via inhibiting the activity of innate lymphoid cells type 2 [131,132].

Lipoxin A_4 (1 nM) was also reported to attenuate adipose inflammation, decreasing interleukin (IL)- 6 and increasing IL-10 expression in aged mice [129]. Recently, lipoxin A_4 encapsulated in poly-lactic-co-glycolic acid microparticles displayed considerable healing effects in topical treatment of dorsal rat skin lesions, provided interaction with its specific receptor on skin cells [130]. Other ARA metabolites, notably PGE_2, PGI_2 and leukotriene B_4 and leukotriene D4 readily promote wound healing via regulating the production of angiogenic factors and endothelial cell functions [133], and inducing stem cells' proliferation and angiogenic potential [134]. Furthermore, lipoxin A_4 was reported to have anti-diabetic potential via inhibiting IL-6, tumor necrosis factor and ROS generation [135,136].

Endocannabinoids

Endocannabinoids are so termed because they activate the same G protein-coupled, cannabinoid receptors (CB1 and CB2) as delta-9-tetrahydrocannabinol, the active component of marijuana (*Cannabis sativa*). Endocannabinoids are important modulators of brain reward signaling, motivational processes, emotion, stress responses, pain and energy balance [137–141]. The endocannabinoids, N-arachidonoyl-ethanolamine and 2-arachidonoylglycerol, are ARA-derived. ARA *Trans*-acylase-catalyzed transfer of ARA from the *sn*-1 position of phospholipids to the nitrogen atom of phosphatidylethanolamine generates N-arachidonoyl-phosphatidyle thanolamine (NAPE). NAPE can be hydrolyzed to arachidonylethanolamine (anandamide, AEA) in a one-step reaction catalyzed by NAPE-specific phospholipase D, or two-steps reaction catalyzed by a phospholipase C and a phosphatase. NAPE can be converted to anandamide via two further synthetic pathways [137, Fig. 2]. The importance of anandamide can be inferred from the redundancy of its precursor conversion pathways. 2-arachidonoylglycerol (2-AG) is produced from the hydrolysis of diacylglycerols (DAGs) containing arachidonate in the 2 position, catalyzed by a DAG lipase that is selective for the *sn*-1 position [137, Fig. 3].

Interaction of ARA-derived endocannabinoids with their specific receptors generate signals, which control neural processes that underpin key aspects of social behavior whereby endocannabinoid signaling dysregulation is associated with social impairment related to neuropsychiatric disorders [138,139]. Endocannabinoid-mediated signaling, especially in the brain, modulates a variety of pathophysiological processes, including appetite, pain and mood, whereby inhibition of endocannabinoid degradation is predicted to be instrumental in reducing pain and anxiety [140,141]. Additionally, anandamide appeared to modulate human sperm motility [142] and improve renal functions and chronic inflammatory disorders of the gastrointestinal tract by regulating gut homeostasis, gastrointestinal motility, visceral sensation, and inflammation [143–145].

Roles in type 2 immune responses

Allergens, cysteine peptidases and numerous helminth-derived excretory-secretory products disrupt the epithelial or endothelial barriers, eliciting release of the type 2 immunity master cytokines

and alarmins, TSLP (thymic stromal lymphopoietin), interleukin (IL)-25 and IL-33 [98,99]. These cytokines bind to receptors on innate lymphoid cells 2 (ILC2), tissue-resident sentinels, mainly found in the skin and at mucosal surfaces of intestine and lungs. Cytokine-receptors' interactions result into signals that induce ILC2 recruitment, proliferation and activation. The activated ILC2 produce type 2 cytokines, principally IL-5 and IL-13, which are instrumental in the recruitment and activation of eosinophils, basophils, and mast cells [146–148]. Major basic proteins, proteases, histamine, heparin, type 2 cytokines, and reactive ROS are not only produced inducing the various signs of inflammation, ARA is furthermore released from the activated cell membrane and oxidized to inflammatory metabolites (see review by Hanna and Hafez [149]). The ARA-derived metabolites are the road to generation of resolvins that help in resolving inflammation and wound and lesion healing [129–136]. Of considerable importance is the discovery that ILC2 share with airway and gut smooth muscle cells, and/or epithelial cells, eosinophils, mast cells, macrophages, dendritic cells, and T helper 2 (Th2) lymphocytes surface membrane receptors for ARA-derived metabolites. Chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2) is a receptor for prostaglandin D_2, CysLTR for cysteinyl leukotrienes D_4 and E_4 and ALXR for lipoxin A_4. Prostaglandin D_2, leukotriene D_4 and E_4 stimulate, while lipoxin A_4 inhibits ILC-2 expansion and effector functions [131,132,150–155], thus, implicating ARA metabolites as secondary inducers of type 2 immune responses' amplification, regulation and memory in airway and gut hyperresponsiveness and repair, and resistance to parasites [156].

Conclusions

In conclusion, it is recommended to monitor and supplement serum ARA levels in pregnant women, infants, children and the elderly in poor rural settings as dietary ARA is safe, being a poor substrate for beta-oxidation and is critically essential for the development and optimal performance of the nervous system, especially the brain and cognitive functions, the skeletal muscle and immune systems. Additionally, ARA promotes and regulates type 2 immune responses against intestinal and blood flukes and may well represent an invaluable endoschistsomicide and endotumoricide.

Conflict of interest

The authors have declared no conflict of interest.

Compliance with Ethics Requirements

This article does not contain any studies with human or animal subjects.

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