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Editorial

Special Issue: Arachidonic acid in health and disease

The idea that arachidonic acid (ARA or AA, 20:4n-6) has a critical role in human health and several diseases is slowly gaining ground. Two important aspects of AA that are now rather well established include: its selective tumoricidal action and potential antimicrobial properties against a variety of infections. Since, our diet is not rich in AA, it is important that a major portion of AA needed for its various functions needs to be synthesized in the body. AA metabolism is complex and it is the precursor of both pro- and anti-inflammatory molecules. The current special issue on AA has been conceived to discuss not only its synthesis and metabolism but also its pivotal role in many physiological and pathological processes and conditions.

In the present issue, Sanaa M. Shanab, Rehab M. Hafez, and Ahmed S. Fouad discussed the algal and plant sources of AA and outlined the fact that fish do not produce polyunsaturated fatty acids (PUFAs) by themselves but do so by feeding on PUFA-producing microalgae, especially *Nannochloropsis.* In contrast to this, higher terrestrial plants, microorganisms, especially bacteria and fungi, and lower plant species such as mosses and hardy herbaceous plants and shrubs produce AA, because they possess all the genes and biochemical pathways necessary for its biosynthesis. Plants are the major source of linoleic (LA) and linolenic (ALA) acids, which the humans are able to metabolize to form AA, EPA (eicosapentaenoic acid, n-3), and DHA (docosahexaenoic acid, n-3). In general, fungi are used for AA commercial production. In their review, Shanab et al. discussed various aspects of PUFA biosynthesis in micro and macroalgae. The review by Hiroshi Kikukawa, Eiji Sakuradani, Akinori Ando, Sakayu Shimizu, and Jun Ogawa reiterates not only the health benefits of PUFAs, including AA but also the extraordinary capacity of *Mortierella alpina* for AA generation and accumulation. Indeed, the reviews by Shanab and her colleagues and Kikukawa et al. outline in a clear fashion the biochemical steps and enzymes involved in the synthesis of AA and other PUFAs. Both reviews also report on the advances in gene manipulation of plants, bacteria, algae, and the fungus, *M. alpina* IS-4 that resulted in the development of transgenic organisms displaying resistance to environmental lethal factors and enhanced productivity of AA and other specific and rare PUFAs. In addition to this, the review by Violette S. Hanna and Ebtisam A. Hafez discussed the fate of AA in humans after the fatty acid is released from the cell membrane phospholipids by phospholipases. The authors have discussed in a very detailed fashion AA oxidation by cyclooxygenases, COX-1 and COX-2, and the different lipoxygenases. In addition, the authors outline AA metabolism by non-enzymatic pathways, which lead to the formation of isoprostanes and mono-nitrated nitroalkenes, currently used as markers of oxidative stress and the role of free radicals in human diseases. Such intricacies became clear now after Hatem Tallima in his review entitled: "Chemical insights into arachidonic acid metabolic pathways" brought to light, with clear illustrations and explanations, the detailed chemical reaction mechanisms of the two major metabolic pathways of ARA.

Hatem Tallima and Rashika El Ridi maintained a more layman view as indicated by the title of their review: "Arachidonic acid: physiological roles and potential health benefits", and discussed the fact that there are very few adverse effects following ingestion of significant amounts of AA and AA-rich foods such as eggs and red meat that could be attributed to the poor oxidation of dietary AA. On the other side of the coin, adequate AA intake is needed for cognitive functions and proper health and development of newborns, pregnant women, elderly, and athletes, to resist development tumors, and protect against infection by schistosomes. In this review, the authors have discussed in detail the actions of unesterified AA on cell ion channels, receptors, and enzymes and that AA metabolites do not initiate but promote beneficial type 2 immune responses, and generate mediators that resolve inflammation and enhance wound healing. The role of endocannabinoids derived from AA in brain reward signaling, motivational processes, emotion, stress responses, pain and energy balance was also emphasized.

The three reviews by Undurti N. Das discussed the role of AA in the regulation of blood pressure and prevention of type 1 and type 2 diabetes mellitus that is rather thought-provoking. The action of

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and/or its metabolites on several enveloped viruses, including influenza and possibly human immunodeficiency virus, gram- negative and gram-positive bacteria, fungi, and protozoa implies its antimicrobial actions that need to be probed further. The review on ageing suggested that perhaps low activity of desaturases, and alterations in AA levels and its metabolism with potential decrease in the availability of anti-inflammatory lipoxins, resolvins, protectins, and maresins may have a significant role in tissue ageing.

The last article in this Special Issue on the role of endogenous AA in resistance to schistosome infection is indeed a very interesting one. In this manuscript, the authors documented rather convincingly relationship between the levels of AA in host serum, lung and liver and outcome of *Schistosoma mansoni* and *Schistosoma haematobium* infection in resistant and permissive species. This study implied that free, unesterified AA impacts parasites via activation of ion-gated channels or tegument-associated neutral sphingomyelinase. It was suggested that hydrolysis of sphingomyelin (SM) leads to parasite attrition via disintegration of the SM-based hydrogen bond network and lipid barrier leading to the release of the apoptosis-signaling ceramide. It is also interesting to note that AA may impact parasites via activation of the leukocytes NADPH (nicotinamide adenine phosphate) oxidase and enhancement of surface membrane lipids oxidation by reactive oxygen species. One of the fascinating question that needs to be addressed is the *in vivo* relevance of the ARA tumoricidal, microbicidal, and schistosomicidal effective concentrations recorded *in vitro*, usually some hundred times higher than those available as free, unesterified in the host circulation. On that note, the article discussed the importance of the *in vivo* continuous versus the *in vitro* few hours' exposure to ARA and the like hood of free ARA release from depots in cell membranes, platelets, and leukocytes upon infection and inflammation.

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