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Omega-3, Omega-6 and Omega-9 Fatty Acids: Implications for Cardiovascular and Other Diseases

Melissa Johnson[1]* and Chastity Bradford[2]

[1]College of Agriculture, Environment and Nutrition Sciences, Tuskegee University, Tuskegee, Alabama, USA
[2]Department of Biology, Tuskegee University, Tuskegee, Alabama, USA

Abstract

The relationship between diet and disease has long been established, with epidemiological and clinical evidence affirming the role of certain dietary fatty acid classes in disease pathogenesis. Within the same class, different fatty acids may exhibit beneficial or deleterious effects, with implications on disease progression or prevention. In conjunction with other fatty acids and lipids, the omega-3, -6 and -9 fatty acids make up the lipidome, and with the conversion and storage of excess carbohydrates into fats, transcendence of the glycome into the lipidome occurs. The essential omega-3 fatty acids are typically associated with initiating anti-inflammatory responses, while omega-6 fatty acids are associated with pro-inflammatory responses. Non-essential, omega-9 fatty acids serve as necessary components for other metabolic pathways, which may affect disease risk. These fatty acids which act as independent, yet synergistic lipid moieties that interact with other biomolecules within the cellular ecosystem epitomize the critical role of these fatty acids in homeostasis and overall health. This review focuses on the functional roles and potential mechanisms of omega-3, omega-6 and omega-9 fatty acids in regard to inflammation and disease pathogenesis. A particular emphasis is placed on cardiovascular disease, the leading cause of morbidity and mortality in the United States.

Keywords: Omega-3 fatty acids; Omega-6 fatty acids; Omega-9 fatty acids; Cardiovascular disease; Hypertension; Inflammation

Introduction

Strategic in pathophysiological homeostasis (following injury), as well as cellular, tissue and organismic protection are acute and chronic inflammatory responses [1,2]. Consequently, the pathogenesis and progression of cardiovascular and other diseases is initiated and perpetuated by this phenomenon. Efforts to normalize or control inflammatory processes include pharmacological, dietary and behavioral therapies, aimed at regulating biologically stimulatory molecules that may stimulate or suppress the synthesis of inflammatory triggers and subsequent byproducts [3-9]. The most recognizable potent bioactive lipid mediators are Arachidonic Acid (AA, C20:4n6), Eicosapentaenoic Acid (EPA, C22:5n3) and Docosahexaenoic Acid (DHA, C20:6n3), synthesized from their dietarly essential precursors linoleic (LA, C18:3n6) and α- linolenic (ALA, C18:3n3) acids (Figure 1). The omega-9 fatty acid, oleic acid, has been suggested to occupy a role in the metabolism of the essential fatty acids [10,11]. These bioactive lipid mediators regulate pro-and anti-inflammatory processes via their ability to stimulate enzymes and produce cytokines and other acute phase molecules [12]. Further, these mediators occupy a central role in the synthesis of lipoxins and resolvins that hinder inflammatory pathways, increase the production of anti-inflammatory cytokines and facilitate the resolution of acute inflammation [13-17]. Decreasing dietary omega-6 fatty acid (i.e. linoleic acid) intake increases the bioavailability of omega-3 fatty acids [18], which may in turn lower tissue concentrations of the omega-6/omega-3 fatty acid ratio, mitigate the intensity and duration of inflammatory responses and subsequently reduce disease risk [19-21].

The relationship between omega-3 and omega-6 fatty acids, inflammation and disease pathogenesis continues to be a topic of extensive study. To a lesser magnitude omega-9 fatty acids have been considered as potential disease mediators. These fatty acids may work individually, additively or synergistically as precursors and critical elements within metabolic pathways, thus actively influencing and/or altering membrane fluidity, cell structure, and disease pathogenesis (Table 1). Research has revealed the relationship between inflammation and the cellular lipidomic (i.e. lipid) and glycomic (i.e. sugar) profiles, genetic regulation and signaling, suggesting that these profiles may be useful clinical diagnostic and therapeutic tools [22-57]. This review provides a brief synopsis of the structure, function and physiological implications of the omega-3, omega-6 and omega-9 fatty acids in inflammation, hypertension, and Cardiovascular Disease (CVD).

Omega fatty acids and inflammation

Inflammation, resulting from various genetic, demographic, behavioral, environmental and nutritional interactions, is at the center of CVD and other vascular diseases (Figure 2). Potential triggers of increased risk for inflammation and subsequent endothelial and vascular injury are genetic characteristics [58], Western dietary patterns [59], environmental toxins [60], adaptive immune responses [61], the presence of other co-morbidities [62,63], and socioeconomic factors [64]. This is evident in the new paradigm shift of evaluation of heart failure patients with preserved ejection fraction. The emphasis shifts from solely using left ventricular afterload to evaluate heart failure patients, and now includes coronary microvascular inflammation [65] thus, changing the methods of patient evaluation. Omega fatty acids have been described as inflammation-modulating agents, which may stimulate or suppress the synthesis of pro- and/or anti-inflammatory cell signaling molecules. In a recent randomized controlled trial, omega-3 polyunsaturated fatty acid supplementation lowered the concentration of serum proinflammatory cytokines[66].

One of the omega-6 fatty acids, arachidonic acid, directly impacts inflammation. *Invitro* it enhanced the ability of endothelial cells to bind

***Corresponding author:** Melissa Johnson, College of Agriculture, Environment and Nutrition Sciences, Tuskegee University, Tuskegee, Alabama, USA, Tel: 334-727-8625; E-mail: mjohnson@mytu.tuskegee.edu

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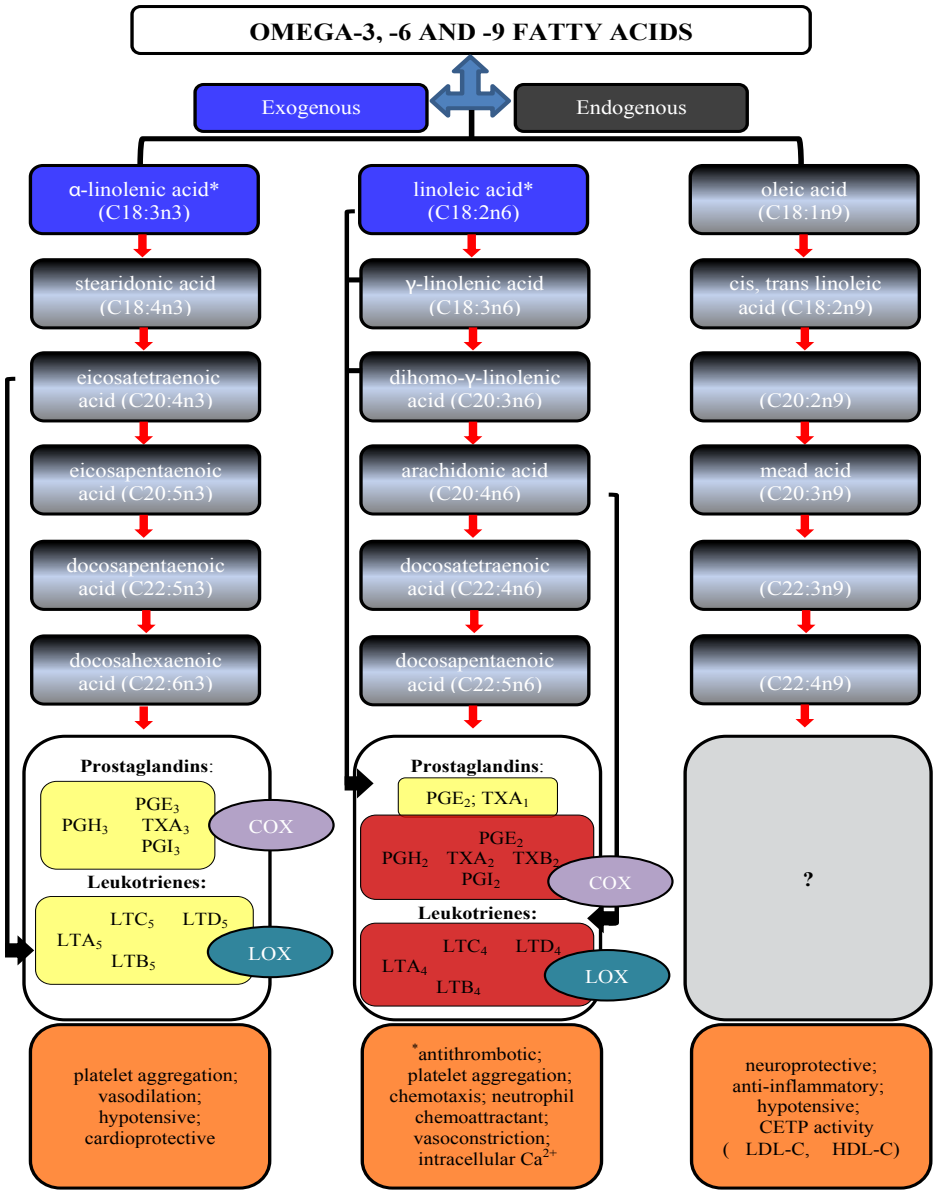

*essential fatty acids; PGE, PGH, PGI- prostaglandins (series indicated by subscript)- PGE_2- prostaglandin E2, PGH_2- prostaglandin H2, PGI_2- prostaglandin I2, PGE_3- prostaglandin E3, PGH_3- prostaglandin H3, PGI_3- prostaglandin I3; LTA, LTB, LTC, LTD- leukotrienes (series indicated by subscript)- LTA_4- leukotriene A4, LTB_4- leukotriene B4, LTC_4- leukotriene C4, LTD_4- leukotriene D4, LTA_5- leukotriene A5, LTB_5- leukotriene B5, LTC_5- leukotriene C5, LTD_5- leukotriene D5; thromboxanes (series indicated by subscript)- TXA_1- thromboxane A1, TXA_2- thromboxane A2, TXA_3- thromboxane A3; COX- cyclooxygenase pathway; LOX- lipoxygenase pathway; Ca^{2+}- calcium; CETP- cholesteryl ester transfer protein; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol

Figure 1: Summary of omega-3, omega-6 and omega-9 fatty acid metabolism and implications for disease.

monocytes- thus, facilitating the pro-inflammatory process. Linoleic and γ-linolenic, omega-6 fatty acids, and omega-9 oleic acids were able to indirectly provoke the synthesis of Reactive Oxygen Species (ROS) superoxide, a pro-inflammatory mediator, mainly by activating p47 and NADPH oxidase enzyme complex [67]. Oleic acid also induced foam cell formation in rat aorta smooth muscle cells and enhanced atherosclerotic lesion development [68]. This is of particular interest as macrophage foam cell has been suggested to be a potential target for therapeutic interventions [69], with the oxidative byproducts of cholesterol metabolism being found to influence the lipidome and transcriptome of the macrophage [70]. Others found the activation of macrophages to regulate the expression of genes involved in lipid metabolism, immunity and apoptosis [71,72].

An alternative study found that oleic acid exerted vascular antiatherogenic effects [54] Oleic acid was able to mitigate the effects of TNF-α-induced oxidative stress and injury in adult male Sprague-Dawley rat cardiomyocytes [73] as well as reduce the inflammation associated with saturated fatty acid-induced inflammation in human aortic endothelial cells [74]. Further, the incorporation of milks enriched with oleic acid into the diet has resulted in reductions in total cholesterol, LDL-cholesterol and triglyceride levels, the effects of which

Fatty Acid	Structure	Dietary Source	Function/Mechanism	Implication	References
Omega-3 Fatty Acids					
α-linolenic acid, ALA	C18:3n3	Plant oils linseed oil, kiwifruit oil, chia seed oil, flaxseed oil, canola (rapeseed) oil, soybean, purslane, walnuts	anti-inflammatory antioxidant hypocholesterolemic hypolipidemic hypotensive vasoconstrictive	↓ oxidative stress ↓ oxidation ↓ inflammation ↓ platelet aggregation	[26-33]
Eicosapentaenoic acid, EPA	C20:5n3	Oily fish, fish oil, certain seaweeds, human breast milk	antioxidant anti-inflammatory hypotensive improved insulin sensitivity	↓ oxidative stress ↓ oxidation ↓ inflammation	[34-38]
Docosahexaenoic acid, DHA	C22:6n3	Cold water fish, metabolic synthesis from EPA	anti-inflammatory hypolipidemic	↓ decline in mental function in Alzheimer's disease ↑ cognition ↑ visual acuity ↓ colon carcinoma cell growth	[39-46]
Omega-6 Fatty Acids					
Linoleic acid, LA	C18:3n6	Corn, peanut, soybean, cottonseed, other plant oils	↑ vascular adhesion molecule-1 expression ↑ oxidation	↑ inflammation	[47-51]
Arachidonic acid, AA	C20:4n6	Meat, eggs, dairy products	↑ platelet aggregation ↑ vasoconstriction ↑ eicosanoid synthesis	↑ inflammation ↑ vascular damage ↑ oxidative stress	[52,53]
Omega-9 Fatty Acids					
Oleic acid, OA	C18:1n9	Olive oil, macadamia oil	hypolipidemic hypotensive ↓ atherogenicity	↓ LDL cholesterol ↓ LDL cholesterol oxidation vasoprotective improved lipid profile	[54-56]
Nervonic acid	C24:1n9	King salmon, yellow mustard seed, flaxseed	nerve cell myelin biosynthesis	↓ obesity-related risk factors for CVD	[57]

Table 1: Structure, dietary source, mechanism and implications of select omega-3, omega-6 and omega-9 fatty acids.

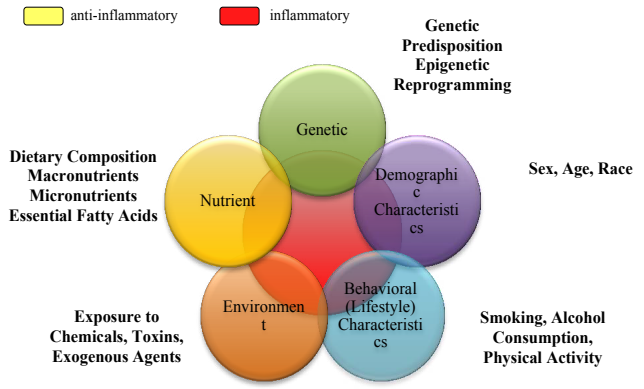

Figure 2: Interactions between and among factors contributing to inflammatory status and disease risk.

were observed among healthy individuals, those with increased risk for cardiovascular disease and individuals with CVD [75]. Although studied to a much lesser degree than oleic acid, another omega-9 fatty acid, nervonic acid, has demonstrated influence on CVD risk. Researchers found Body Mass Index (BMI), leptin, triglycerides, total cholesterol and fasting blood glucose to be significantly negatively correlated with serum nervonic acid. These findings illustrate the ability of nervonic acid to exert protective effects against obesogenic-linked risk factors and conditions such as insulin resistance, diabetes, dyslipidemia and metabolic syndrome.

The impact of fatty acids as inflammatory-modulators is crucial to the state of the vasculature.The vasculature is mainly comprised of endothelial cells, caveolae, smooth muscle cells, adventitia, and fibroblasts. Thus, the cellular responsiveness of the vasculature is vital to the endothelium.The endothelial cells are in direct contact with the red blood cells, and blood lipid profiles are tools of evaluating cardiovascular health. Fatty acid composition of a major component of the endothelium, caveolae, played a regulatory role in TNF-α-induced endothelial cell activation and inflammation. The major omega-6 unsaturated fatty acids in the American diet are atherogenic and enhance the endothelial inflammatory response [76]. One of them, arachidonic acid, directly impacted inflammation. *In vitro*, it enhanced the ability of endothelial cells to bind, a pro-inflammatory response [77]. In younger animals, estrogen inhibits the expression of proinflammatory mediators in vascular smooth muscle cells [78]. Therefore, in addition to the fatty acids, age and gender play a major role in the inflammatory response. Further, a higher eicosapentaenoic acid to arachidonic acid ratio was associated with decreased LV wall thickness among individuals with diabetes [79]. The ability of omega-3, 6, and 9 fatty acids to differentially modulate inflammatory stimuli, impact vascular composition, cellular responsiveness, and influence the structural integrity of the left ventricle underscore the implications of these fatty acids in chronic disease risk and prevention.

Omega fatty acids and hypertension

Chronic diseases such as hypertension, obesity, and diabetes are a national and international concern. Obesity prevalence has increased dramatically in recent years. The mortality of obese patients is more often a result of diabetes and hypertension [80]. Obesity is strongly associated with metabolic abnormalities, including insulin resistance, type 2 diabetes, hypertension, and dyslipidemia, mediated in part by the chronic inflammatory state induced by the secretion of adipocytokines, such as angiotensinogen, transforming growth factor–beta, tumor necrosis factor–alpha, and interleukin-six [81-83].

The cardioprotective mechanisms of the omega-3 fatty acids

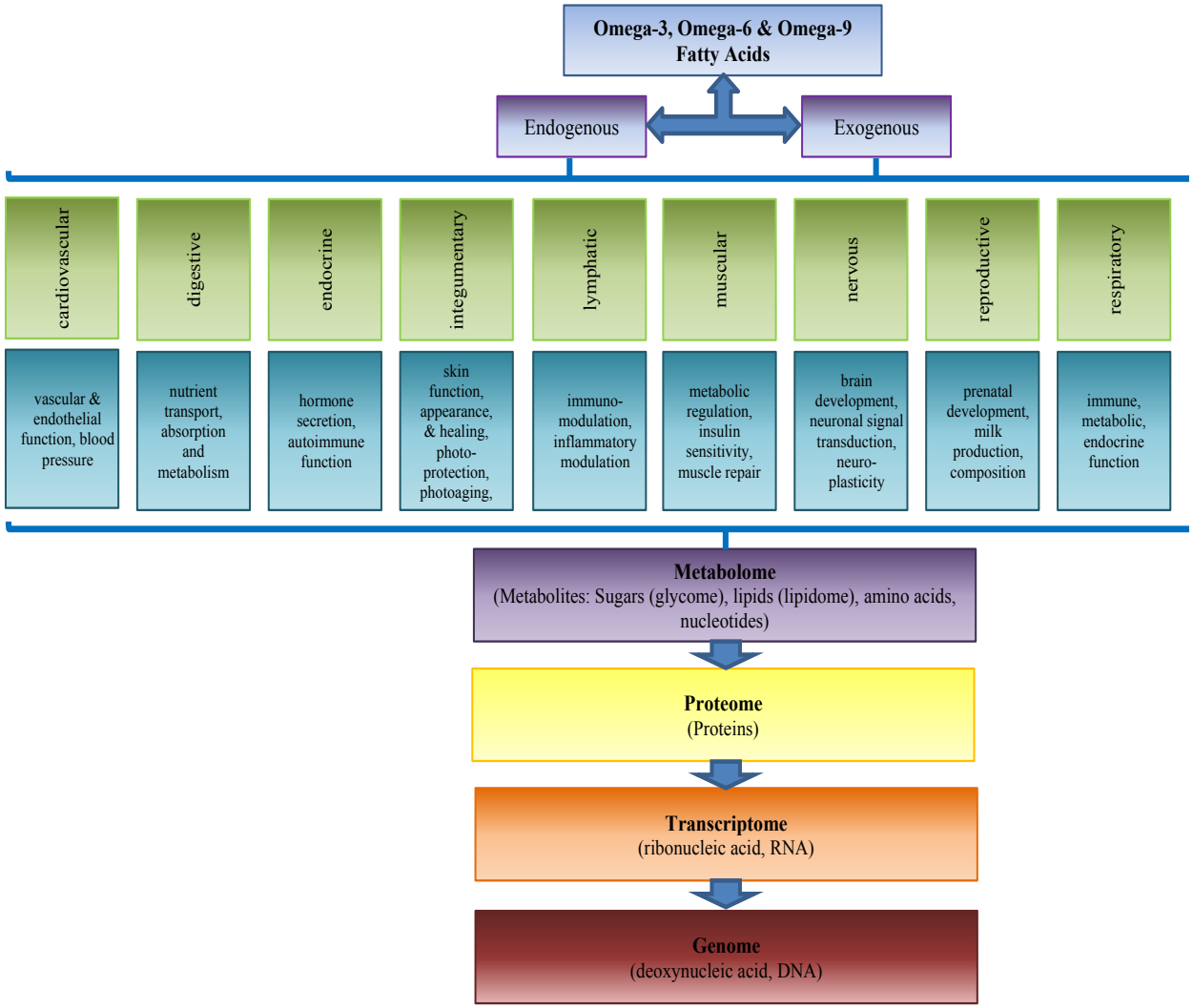

Figure 3: Potential cellular, molecular and genetic interactions and implications of omega-3, omega-6 and omega-9 fatty acids on biological systems and health/disease outcomes.

Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA) have been attributed to their ability to displace the omega-6 fatty acid, arachidonic acid [8], as molecular substrates during the cyclooxygenase and oxygenase pathways. The combined hypotensive effects of EPA and DHA have been demonstrated in randomized controlled trials [84]. However others found DHA and DHA epoxides to be effective in lowering blood pressure but not EPA [85]. The epoxides of an omega-6 fatty acid, arachidonic acid epoxyeicosatrienoic acids also exhibit antihypertensive and anti-inflammatory effects [86]. Actions of these fatty acids subsequently influence metabolism, β-oxidation, fatty acid synthesis, pro-inflammatory molecule synthesis and the transcription of genes coding for transcription factors (e.g. Peroxisome Proliferator-Activated Receptor [PPAR], Sterol-Response Element Binding Protein [SREBP] and Nuclear Factor jB [NF-jB] as well as enzymes implicated in cholesterol synthesis) [87,88]. Intake of EPA and DHA has been inversely associated with markers of inflammation in both men and women [89] In addition to influencing cytokine concentrations, EPA and DHA have been demonstrated to influence blood glucose and lipid profile [90]. The supplementation of DHA into the diet of hypertriglycemic men was found to decrease serum levels of c-reactive protein and other inflammatory biomarkers [91].

Studies suggest that there is a role for the renin-angiotensin system in the mechanistic blood pressure lowering effects of omega-3 fatty acids.The Ren-2 rat model is mediated by ANG II, and the data suggest that omega-3 PUFA may reduce hypertension via the renin-angiotensin system [92]. In models of Angiotensin-II induced hypertension, DHA epoxides reduce inflammation and systolic blood pressure partially via reduction of prostaglandins, MCP-1, and upregulation of angiotensin-converting enzyme-2. It has been proposed that the oleic acid constituent of olive oil may be responsible for the hypotensive and cardio protective effect associated with olive oil consumption [93-96]. Flaxseed, one of the richest sources of the plant-based omega-3 fatty acid, alpha-linolenic acid has been suggested to have a positive impact on CVD.There is strong scientific evidence from human trials that omega-3 fatty acids from fish or fish oil supplements (EPA and DHA) can significantly reduce risk factors for heart disease (such as reducing blood triglyceride [TG] levels, LDL-cholesterol, serum lipids, blood glucose), diabetes and metabolic syndrome [97-100], yet

using nutritional strategies to combat diseases is not the first line of therapeutic intervention [101,102]. Unfortunately, analysis of national observational data indicates that U.S. adults are not consuming the recommended intake of fish and omega-3 fatty acids [103].

Omega fatty acids and other diseases

In addition to suppressing or inhibiting the expression of specific genes implicated in lipid metabolism, dietary fatty acid intake influences cellular, molecular oxidative and inflammatory status [8]. In addition to occupying a role in immune function [104], oleic acid inhibits food intake and glucose production in male rats [105] and has been suggested to enhance insulin production in rat pancreatic beta cells in both in vivo and in vitro environments favoring the inhibition of insulin production by TNF-α [106]. Further, the presence of a rich supply of oleic acid within low density lipoprotein molecules was protective against oxidative modification in rabbits, suggesting the antiatherogenic propensity of oleic acid. Conversely oleic acid was able to facilitate increased macrophage concentrations in mesenteric adipose tissue [107] and attenuate renal fibrosis [108]. Although omega-3 fatty acids have been classified as anti-inflammatory mediators, there is conflicting evidence on the definite ability of these fatty acids to consistently reduce the risks, morbidities and mortalities associated with CVD, cancers and other inflammatory diseases and disorders [109]. There is also evidence for the role of omega-3 fatty acids in the stress response and cognitive function. Rats fed the omega-3 enriched diet had a lower stress-induced weight loss and plasma corticosterone peak, and reduced grooming [110]. These data suggest that the response to chronic restraint stress can also be altered by omega-3 fatty acids.

Conclusions

Central to the initiation, pathogenesis and progression of many disease states is inflammation. Conventional mechanisms of alleviating inflammation include pharmacological therapies, which often target specific key components of inflammatory pathways. Albeit not relatively novel, increased attention has been devoted to more aggressively reevaluating dietary approaches that mitigate inflammatory sequelae. Serving as mediators of lipid metabolism and foundational biomolecules of the lipidome, the character of omega-3, omega-6 and omega-9 fatty acids warrants further discussion. Omega-3 and omega-6 fatty acids have typically been associated with anti- and pro-inflammatory pathways, respectively, whereas the direct role of omega-9 fatty acids in inflammatory pathways remains unclear. In conjunction with other fatty acids and lipid classes, the omega-3, -6 and -9 fatty acids make up the lipidome, and within the conversion of excess carbohydrates into fats, transcendence of the glycome into the lipidome occurs.

More recently, lipidomics profiling has been used as an assessment and monitoring tool for cardiovascular and other disease risk [23,111]. Bioinformatical tools have been particularly useful in examining the lipidome [112]. The genetic, metabolic and phenotypic consequences of omega-3, omega-6 and omega-9 fatty acids range from undetectable to detectable, and may even endure throughout subsequent cellular and organismic generations (Figure 3). Although research affirms a relationship between omega-3, omega-6 and omega-9 fatty acids, both synergistically with the metabolism of the other fatty acids, as well as individually in modulating specific pathways, findings are conflicting. Together the anti-inflammatory exertions, along with the pro-inflammatory mechanisms, highlight the delicate, oftentimes calculated mercurial nature of these fatty acids in maintaining homeostasis. Additional research is needed to add credence to the emergence of omega-3, omega-6 and omega-9 fatty acids as modulators of metabolism, lipidomics and glycomics.

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