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REVIEW | *Advances in Cardiovascular Geroscience*

Dietary modulation of oxylipins in cardiovascular disease and aging

Stephanie P. B. Caligiuri,[1] Mihir Parikh,[1] Aleksandra Stamenkovic,[1] Grant N. Pierce,[1] and Harold M. Aukema[2,3]

[1]*Department of Physiology and Pathophysiology, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba, Canada;* [2]*Department of Human Nutritional Sciences, Faculty of Agriculture and Food Sciences, University of Manitoba, Winnipeg, Manitoba, Canada; and* [3]*Canadian Centre for Agri-food Research in Health and Medicine, Albrechtsen Research Centre, St. Boniface Hospital, Winnipeg, Manitoba, Canada*

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Caligiuri SPB, Parikh M, Stamenkovic A, Pierce GN, Aukema HM. Dietary modulation of oxylipins in cardiovascular disease and aging. *Am J Physiol Heart Circ Physiol* 313: H903–H918, 2017. First published August 11, 2017; doi: 10.1152/ajpheart.00201.2017.—Oxylipins are a group of fatty acid metabolites generated via oxygenation of polyunsaturated fatty acids and are involved in processes such as inflammation, immunity, pain, vascular tone, and coagulation. As a result, oxylipins have been implicated in many conditions characterized by these processes, including cardiovascular disease and aging. The best characterized oxylipins in relation to cardiovascular disease are derived from the ω-6 fatty acid arachidonic acid. These oxylipins generally increase inflammation, hypertension, and platelet aggregation, although not universally. Similarly, oxylipins derived from the ω-6 fatty acid linoleic acid generally have more adverse than beneficial cardiovascular effects. Alternatively, most oxylipins derived from 20- and 22-carbon ω-3 fatty acids have anti-inflammatory, antiaggregatory, and vasodilatory effects that help explain the cardioprotective effects of these fatty acids. Much less is known regarding the oxylipins derived from the 18-carbon ω-3 fatty acid α-linolenic acid, but clinical trials with flaxseed supplementation have indicated that these oxylipins can have positive effects on blood pressure. Normal aging also is associated with changes in oxylipin levels in the brain, vasculature, and other tissues, indicating that oxylipin changes with aging may be involved in age-related changes in these tissues. A small number of trials in humans and animals with interventions that contain either 18-carbon or 20- and 22-carbon ω-3 fatty acids have indicated that dietary-induced changes in oxylipins may be beneficial in slowing the changes associated with normal aging. In summary, oxylipins are an important group of molecules amenable to dietary manipulation to target cardiovascular disease and age-related degeneration.

NEW & NOTEWORTHY Oxylipins are an important group of fatty acid metabolites amenable to dietary manipulation. Because of the role they play in cardiovascular disease and in age-related degeneration, oxylipins are gaining recognition as viable targets for specific dietary interventions focused on manipulating oxylipin composition to control these biological processes.

aging; cardiovascular disease; heart disease; oxylipins

ALL TISSUES IN THE BODY contain oxylipins, which are bioactive lipids that are endogenously produced via the oxygenation of polyunsaturated fatty acids. Their involvement in cardiovascular disease and aging includes their roles in innate immunity, inflammation, cardiac function, blood coagulation, and vascular tone regulation. Because they are derived from polyunsaturated fatty acids, dietary interventions involving these (e.g., ω-6 and ω-3 fatty acids) may prove to be an effective strategy in altering concentrations of deleterious or beneficial oxylipins. The recent advances in mass spectrometry techniques have increased the awareness of the vast number of oxylipins that are present and those that are altered by dietary manipulations. In addition, the enzymes responsible for their production, as well as the receptors to which they bind, are also potential targets for manipulating oxylipin levels. This review will highlight the physiological and pathophysiological role of oxylipins in cardiovascular disease and aging as well as how concentrations of oxylipins can be altered nutritionally.

Address for reprint requests and other correspondence: H. M. Aukema, Albrechtsen Research Centre, St Boniface Hospital, 351 Taché Ave., Winnipeg, MB, Canada R2H 2A6 (e-mail: harold.aukema@umanitoba.ca).

Enzymes in the Production of Oxylipins

Upon cell activation, oxylipin formation begins when fatty acids are released from membrane phospholipids by cytosolic phospholipase A_2 ($cPLA_2$). Although phospholipids are thought to be the primary source of fatty acid for oxylipin formation, lack of $cPLA_2$ does not completely abolish oxylipin formation (2, 153). Oxylipins may be formed by other means, such as through triacylglycerol lipase, as evidenced in mast cells (44). Once released, these fatty acids are converted to oxylipins via three main pathways: cyclooxygenase (COX), lipoxygenase (LOX), and cytochrome *P*-450 (CYP) epoxygenase and ω-hydroxylase. COX enzymes have dioxygenase activity, thus donating two oxygen molecules to the fatty acid substrate to form a 5-carbon ring structure at the 8- to 12-carbon positions of 20-carbon fatty acids. This process forms PGH, which is then further metabolized to several prostanoids [PGs and thromboxanes (TXs)] via enzymes specific for these prostanoids. The most well known of COX-derived oxylipins are the eicosanoids derived from arachidonic acid (AA), but prostanoids also are formed from dihomo-γ-linolenic acid (e.g., PGE_1), eicosapentaenoic acid (EPA) (e.g., PGE_3), and adrenic acid (e.g., dihomo-PGE_2) (58, 98). These prostanoids are produced via two different isomers of COX, namely, COX-1 and COX-2. COX-1 is constitutively expressed in most tissues, whereas COX-2 can be induced by inflammation to produce oxylipins that can propagate the inflammatory response. Inhibitors of COX such as acetaminophen, ibuprofen, and acetylsalicylic acid reduce the concentration of COX products and thus reduce fever, pain, and coagulation (57, 98, 165).

Many other enzymes that further metabolize COX oxylipins are also targets for pharmaceutical development. For example, TX synthase is responsible for converting PGH_2 to TXA_2, which is a potent vasoconstrictor. Ozagrel is a pharmaceutical TX synthase inhibitor that improves neurological function after an acute ischemic stroke in humans (220). However, the use of Ozagrel is not supported by the Food and Drug Administration, as its clinical safety and efficacy are still being investigated (196). Another enzyme of interest in oxylipin metabolism is PGI_2 synthase. PGI_2 synthase converts PGH_2 to PGI_2, which is a vasodilator. An experimental agonist of PGI_2 and a TX synthase inhibitor (ONO-1301) was tested in an animal model of hypertension and resulted in a decrease in blood pressure (130).

LOX is similar to COX, as it donates two oxygen molecules to its substrate in the formation of hydroperoxy derivatives of fatty acids. LOX enzymes are typically classified based on their formation of the resulting hydroxy derivatives of AA (e.g., 5-LOX, 12-LOX, and 15-LOX). However, the hydroxylation site varies with different fatty acids and often displays some promiscuity. The same homolog can have different positional specificities in different species, so the hydroxylation site naming system is limited; an alternate nomenclature has been proposed based on the gene names (18, 104). Further metabolism of LOX oxylipins (sometimes including epoxygenase and LOX activities) results in the formation of many other oxylipins, including leukotrienes (LTs), eoxins, hepoxilins, lipoxins (LXs), maresins (MaRs), protectins (PDs), and resolvins (Rvs) (17, 142, 160, 162). Pharmaceuticals have been developed to target LOX enzymes, such as Zileuton, to reduce the concentration of hydroxy-eicosatetraenoic acids (HETEs) and LT. This LOX inhibitor was developed to reduce inflammatory conditions, such as asthma (177).

The third oxylipin pathway includes the epoxygenase and ω-hydroxylase activities of a large number of CYP enzymes. Epoxygenase activity results in the formation of epoxygenated fatty acids such as epoxy-eicosatrienoic acid (EpETrE; often abbreviated as EET) derived from AA (134). These epoxy fatty acids are further metabolized by soluble epoxide hydrolase (sEH) to the dihydroxy form [e.g., dihydroxy-eicosatetraenoic acid (DiHETrE); often abbreviated as DHET]. Analogs of oxylipins from linoleic acid (LA), α-linolenic acid (ALA), γ-linolenic acid, dihomo-γ-linolenic acid, adrenic acid, EPA, and docosahexaenoic acid (DHA) also are formed by CYP epoxygenase activity (58, 100, 164, 182). ω-Hydroxylase activity results in hydroxylation of the carbons close to the methyl (ω) end of the fatty acid. For example, oxylipins formed from AA via this activity result in 16- to 20-HETE. Inhibitors of sEH have been developed for antihypertensive and cardioprotective effects. sEH is ubiquitously expressed and in particularly high concentrations in the liver, kidney, and blood vessels (48, 181). The latest pharmaceutical inhibitors of sEH are derived from urea and amides that are active site transition state mimetics. Inhibition of sEH increases concentrations of the more vasodilatory EpETrEs by preventing their metabolism to the DiHETrEs that have less vasodilatory activity (81, 91).

Oxylipins are generally formed in situ by these three major enzymatic pathways and act as autocrine and paracrine mediators. They also can be formed transcellularly, thus allowing cells that do not have the complete set of enzymes available to produce oxylipins (29). Their effects are mediated by binding to G protein-coupled receptors or to intracellular effectors, such as peroxisome proliferator-activated receptor-γ, among others that are still being elucidated (14, 18, 57, 100, 164, 182). Many oxylipins interact with multiple receptors that are characterized by their most potent biological ligand. Receptor isoforms also exist and often have differing effects. For example, PGE_2 can bind to the EP_3 receptor, which has prothrombotic effects, or to EP_4, which has antithrombotic effects (84). Further details on oxylipin receptors, enzymes, and further metabolism of oxylipins to more metabolites can be found in available reviews (14, 17, 18, 57, 58, 100, 104, 142, 160, 162, 164, 165, 182). Nonenzymatically derived oxylipins also can be formed, with many being used as markers of oxidative stress (e.g., isoprostanes). Further discussion of these in relation to health and disease can be found elsewhere (128).

Roles of Oxylipins in Cardiovascular Disease

Oxylipins, and more specifically the eicosanoids produced from AA, have long been implicated in atherosclerosis, platelet aggregation, vascular constriction, and cardiac injury and dysfunction. For select examples of oxylipins with cardiovascular functions, see Table 1. Eicosanoids therefore have been and continue to be targets for the treatment and prevention of heart disease. A well-researched inhibitor of eicosanoids is the COX inhibitor acetylsalicylic acid (i.e., aspirin), as the association of COX products with cardiovascular disease has been well documented. For example, patients with stable angina pectoris compared with normal subjects exhibit significantly higher concentrations of circulating TXB_2, and those with variant

Table 1. *Select oxylipins and physiological/pathophysiological effects associated with cardiovascular disease*

Oxylipin	Physiological/Pathophysiological Effect
	Linoleic acid
9-HODE 13-HODE	HODEs are produced via the LOX pathway. They are present in human monocyte-oxidized LDL and associated with oxidative stress (54, 79). 9-HODE induces macrophage IL-1β (102). 9-HODE and 13-HODE activate plasminogen activator inhibitor type-1 via PPAR-γ activation in endothelial cells (116). 13-HODE prevents platelets from adhering to human vascular endothelial cells (16, 191).
9,10-DiHOME 12,13-DiHOME	DiHOMEs are produced by the metabolism of EpOMEs (also known as leukotoxins) by sEH and are associated with oxidative stress and inflammation in endothelial cells (124, 204). Plasma concentrations of the DiHOMEs are decreased after flaxseed ingestion in patients with peripheral artery disease and hypertension (21).
	Dihomo-γ-linolenic acid
15-HETrE	15-HETrE is produced via 15-LOX and can inhibit 5-LOX in human polymorphonuclear leukocytes (145).
	Arachidonic acid
PGD_2	PGD_2 is produced via the COX pathway and can inhibit platelet aggregation (19, 211). PGD_2 either has no effect on vascular tone or can constrict and dilate mesenteric arteries in dogs (61). PGD_2 has been implicated in the innate immune response (172). PGD_2 inhibits human platelet aggregations and polymorphonuclear neutrophil degranulation (39).
15-deoxy-PGJ_2	15-Deoxy-PGJ_2 is a PGD_2 metabolite that activates plasminogen activator inhibitor type-1 via PPAR-γ activation in endothelial cells (116).
PGE_2	PGE_2 is produced via the COX pathway and can induce renal vascular resistance in rats (8). PGE_2 can either be proinflammatory and vasoconstrictive or anti-inflammatory and vasodilatory depending on which EP receptor it binds (34). PGE_2 is involved in cardiac hypertrophy and ischemia (77, 119).
6-keto-$PGF_{1\alpha}$	6-Keto-$PGF_{1\alpha}$ is the stable metabolite and marker of PGI_2 that is produced via the COX pathway. 6-Keto-$PGF_{1\alpha}$ in human plasma is inversely related to cardiovascular events and high central blood pressure (22, 27). PGI_2 is an endothelium-derived oxylipin with vasodilatory and antiaggregatory activity (33, 45). PGI_2 reduces pulmonary vascular resistance in humans (118).
$PGF_{2\alpha}$	$PGF_{2\alpha}$ is produced via the COX pathway and induces vasoconstriction in bovine, canine, and human coronary arteries (104). $PGF_{2\alpha}$ is associated with dysfunction in the stressed heart and with cardiac hypertrophy (1, 71).
TXB_2	TXB_2 is the stable metabolite and marker of the short-lived TXA_2 that is produced via the COX pathway. TXA_2 is an endothelium-derived oxylipin that potently induces vasoconstriction and aggregation of platelets (33). TXB_2 is positively associated with high central blood pressure and multiple cardiovascular events (22, 27).
LTs	LTs are produced via the 5-LOX pathway and are associated with atherosclerosis, endothelial dysfunction, intimal hyperplasia, and cytokine release (7). LTB_4 is chemotactic and stimulates neutrophil lysosomal degranulation of human neutrophils (66).
5-HETE 8-HETE 9-HETE 11-HETE 12-HETE 15-HETE	HETEs are produced via LOX pathways. 5-HETE is chemotactic for human neutrophils (62, 64) and inhibits PGI_2 production in porcine coronary artery endothelial cells (68). 5-, 8-, 9-, 11-, and 12-HETE stimulate migration, chemotaxis, and chemokinesis in multiple leukocytes (63, 65, 96, 184), whereas 15-HETE appears to have opposite effects (179, 189). 12- and 15-HETE have both pro- and antiaggregatory effects, depending on the model system and aggregant (35, 55, 86, 169, 170, 173). 15-HETE also can be converted to the LXs, which play a role in the resolution of inflammation (17).
5,12-DiHETE	5,12-HETE is produced via by sequential 5- and 12-LOX activity and is chemotactic for human neutrophils (64).
5,6-EpETrE 8,9-EpETrE 11,12-EpETrE 14,15-EpETrE	EpETrEs are formed via the CYP epoxygenase pathway and are endothelial-derived hyperpolarizing factors. EpETrEs vasodilate isolated canine coronary arterioles and preconstricted pressurized mouse arteries (76, 138). EpETREs induce hyperpolarization and relaxation of the vasculature (97). 11,12-EpETrE improve recovery of cardiac contractility in a rat model of ischemia/reperfusion (214). 14,15-EpETrE reduces postischemic electrocardiogram abnormalities (9).
5,6-DiHETrE 8,9-DiHETrE 11,12-DiHETrE 14,15-DiHETrE	DiHETrEs are produced by sEH from EpETrEs. The conversion of the EpETrE to the DiHETrEs causes a concomitant loss of vasodilation (76, 100) in some, but not all, cases (76). DiHETrEs in plasma decrease following flaxseed ingestion in patients with peripheral artery disease and hypertension (21). DiHETrEs vasodilate isolated canine coronary arterioles and preconstricted pressurized mouse arteries (76, 138). Plasma 5,6-DiHETrE is associated with high central blood pressure (27), and 11,12-DiHETrE is associated with multiple cardiovascular events (22) in patients with peripheral artery disease.
16-HETE 18-HETE 19-HETE 20-HETE	16-HETE through 20-HETE are produced by CYP ω-hydroxylase activity. 16-HETE is produced by polymorphonuclear leukocytes and is released upon ANG II stimulation (10). When administered intravenously, 16-HETE lowers intracranial pressure after a thromboembolic stroke in New Zealand White rabbits (11). 16-HETE, 18-HETE, and 19-HETE and metabolites of 20-HETE can promote vasodilation (30, 50, 88, 113). 20-HETE is a vasoconstrictor in small porcine coronary arteries (150).
	Eicosapentaenoic acid
PGD_3	PGD_3 inhibits human platelet aggregation with similar or greater activity than PGD_2 (211).
PGI_3	PGI_3 inhibits aggregation in human and rabbit platelets (99, 132).
LTB_5	LTB_5 is produced via the 5-LOX pathway and is much less chemotactic but stimulates neutrophil lysosomal degranulation with similar potency as LTB_4 in human neutrophils (66). LTB_5 is less inflammatory than LTB_4 in polymorphonuclear leukocytes, lungs, and transplanted tissue (107, 121, 122).

Continued

Table 1.—*Continued*

Oxylipin	Physiological/Pathophysiological Effect
5-HEPE	5-HEPE and 12-HEPE are produced via the LOX pathway.
12-HEPE	5-HEPE promotes bovine neutrophil chemotaxis in vitro but is less potent than 5-HETE (75). 12-HEPE inhibits human platelet aggregation similarly to 12-HETE (188).
5-oxo-EPE	5-Oxo-EPE is produced from 5-HEPE and is 10% as potent in stimulating neutrophils as 5-oxo-eicosatetraenoic acid formed from arachidonic acid (146).
8,9-EpETE 11,12-EpETE 14,15-EpETE 17,18-EpETE	EpETEs are produced via the CYP epoxygenase pathway. They inhibit platelet aggregation, display vasodilatory effects, and exhibit antiarrhythmic effects in neonatal cardiomyocytes (6, 98, 105, 216).
18-HEPE	18-HEPE is produced via the CYP ω-hydroxylase pathway and is a precursor to E-series resolvins, which can reduce neutrophil migration and inflammatory responses (136).
	Docosahexaenoic acid
14-HDoHE 17-HDoHE	14-HDoHE and 17-HDoHE are produced by the LOX pathway and are precursors to maresin, protectin, and D-series resolvins, respectively, which are inflammation-resolving mediators. 14-HDoHE can antagonize platelet activation (35). 17-HDoHE vasodilates bovine coronary arterial smooth muscle cells (110). HDoHEs can also be produced via autooxidation in vitro and therefore have been implicated as potential markers of oxidative stress (201). HDoHE plasma levels decreased with flaxseed ingestion (23, 27).
7,8-EpDPE 10,11-EpDPE 13,14-EpDPE 16,17-EpDPE 19,10-EpDPE	EpDPEs are produced via the CYP epoxygenase pathway and inhibit platelet aggregation and TXA_2 synthesis (98). EpDPEs dilate porcine coronary arterioles (216). 19,20-EpDPE decreases human platelet aggregation (87).
MaR	Maresin, protectin, and D-series resolvins are produced from 14-HDoHE and 17-HDoHE.
PD	These mediators are antiaggregatory (32, 212), resolve inflammation, and prevent neutrophil transmigration (136, 171, 172).
RvD	Resolvin D can increase the production of nitric oxide and PGI_2 in endothelial cells (182). Protectin DX exhibits antiaggregatory effects (32, 150)

HODE, hydroxy-octadecadienoic acid; LOX, lipoxygenase; PPAR, peroxisome proliferator-activated receptor; DiHOME, dihydroxy-octadecenoic acid; EpOME, epoxy-octadecenoic acid; sEH, soluble epoxide hydrolase; HETrE, hydroxy-eicosatrienoic acid; COX, cyclooxygenase; TX, thromboxane; LT, leukotriene; HETE, hydroxy-eicosatetraenoic acid; CYP, cytochrome *P*-450; HEPE, hydroxy-eicosapentaenoic acid; 5-oxo-EPE, 5-oxo-eicosapentaenoic acid; EpETE, epoxy-eicosatetraenoic acid; HDoHE, hydroxy-docosahexaenoic acid; EpDPE, epoxy-docosapentaenoic acid.

angina exhibit markedly elevated levels of TXB_2 during an episode of angina (187). In addition, patients with genetic variations for TX and PGI_2 synthases are at a higher risk for developing a myocardial infarction or ischemic stroke (109). Aspirin has been implicated in lowering cardiovascular disease risk because it alters several COX oxylipins involved. For example, it decreases the concentration of the proaggregatory and vasoconstrictive TXA_2 while having less effect on the antiaggregatory and vasodilatory PGI_2 (183a, 193, 199). Other COX oxylipins also have cardiovascular effects, such as PGE_2, which is involved in cardiac hypertrophy and ischemia (78, 120), and $PGF_{2\alpha}$, which is produced and associated with dysfunction in the stressed heart and also plays a role in cardiac hypertrophy (1, 72). In comparison, PGD_2 can inhibit platelet aggregation and polymorphonuclear neutrophil degranulation (19, 39, 212) and may be protective against ischemia-reperfusion injury (92).

In two landmark trials, aspirin significantly reduced the incidence of myocardial infarction and cardiovascular events (47). The Physician's Health Study and the British Doctor's Trial both observed an average 32% reduction in the incidence of a first myocardial infarction and a 15% reduction in vascular events with aspirin (47). In a trial including nearly 40,000 women, low-dose aspirin (100 mg), provided every second day for 10 yr, did not lower the risk of cardiovascular events in women aged >45 yr but did reduce the risk of cardiovascular events in women aged >65 yr (154). It is important to note that selective COX-2 inhibitors such as rofecoxib have resulted in a greater risk of developing cardiovascular events compared with naproxen. This is thought to be due to a reduction in the production of the protective antiaggregatory PGI_2 by rofecoxib (125). It appears that this increased risk of cardiovascular events with this drug is not found with other COX-2 inhibitors, however. Nevertheless, prolonged NSAID use is associated with gastrointestinal, renal, and cardiovascular side effects that need to be considered with their use, as reviewed in many recent publications (71, 144, 203). This provides evidence for the importance of the COX oxylipins in cardiovascular disease.

Another group of oxylipins that have been investigated for their impact on cardiovascular disease via proinflammatory effects are LTs derived via the LOX pathway. There is a clear association of inflammatory disease and cardiovascular disease; atherosclerosis is characterized frequently as a chronic inflammatory condition (42). The mechanisms whereby inflammatory reactions and infectious disease are involved in atherosclerotic cardiovascular disease can include endothelial interactions, foam cell formation, smooth muscle cell proliferation, promotion of atherothrombosis, and via cytokine and chemokine production (42). LTs have been implicated in the progression of atherosclerosis because of their role in inflammation as well as in endothelial dysfunction, intimal hyperplasia, and cytokine release (7). LTB_4 is chemotactic and stimulates neutrophil lysosomal degranulation of human neutrophils (65), and inhibition of LTs by competitive exclusion from their respective receptors reduces infarct size, intimal hyperplasia, and atherosclerosis in experimental models (157).

Like the LTs, several HETEs are also produced by the LOX pathway and have been implicated in platelet aggregation,

vasoconstriction, and inflammation. For example, 12- and 15-HETE have both pro- and antiaggregatory effects, depending on the model system and aggregant (35, 55, 87, 170, 171, 174), and 5-HETE inhibits PGI_2 production in porcine coronary artery endothelial cells (69). Many HETE isomers (5-, 8-, 9-, 11-, and 12-HETE) stimulate migration, chemotaxis, and chemokinesis in multiple leukocytes (62, 64, 185, 198), whereas 15-HETE may have the opposite effects (180, 190). 15-HETE also can be converted to LXs, which play a role in the resolution of inflammation (17).

Other HETEs are produced via the CYP ω-hydroxylase pathway, including 16- to 20-HETE produced from AA. The production of 20-HETE is stimulated by angiotensin II and endothelin-1 in vascular smooth muscle cells, and inhibition of the formation of 20-HETE reduces the impact of angiotensin II and endothelin-1 on the vasculature (134). 20-HETE induces vasoconstriction in canine renal arteries and porcine coronary arteries (151). On the other hand, 16-, 18-, and 19-HETE and metabolites of 20-HETE can promote vasodilation (30, 50, 89, 114). Therefore, the balance of the various isomers of HETE is of key importance in vascular tone regulation and thus cardiovascular disease.

The role of CYP-derived EpETrEs is a rapidly developing area of research because of their impact on vasodilation. They are endothelium-derived hyperpolarizing factors that increase the open state probability of Ca^{2+}-activated K^+ channels in coronary smooth muscle cells (28). EpETrEs accomplish this by activating the transient receptor potential (TRP)V4 channel to import Ca^{2+}, which activates the ryanodine receptor to induce a Ca^{2+} spark. Ca^{2+} sparks activate the Ca^{2+}-activated K^+ channel to induce hyperpolarization and relaxation of the vasculature (98). EpETrEs are quickly metabolized by sEH to DiHETrEs, in which a concomitant loss of vasodilation occurs. Maintaining EpETrE concentrations by reducing the production of DiHETrE through pharmacological sEH inhibition (83) induces a reduction in blood pressure in models of hypertension (82, 83, 132), reduces vascular smooth muscle cell proliferation (101), and inhibits inflammatory pain processes (135). Interestingly, however, DiHETrE can have similar or even greater vasodilatory activity than EpETrE under some conditions (77, 139), and polymorphisms in the EpETrE-producing CYP enzymes do not always correlate with effects on hypertension; more remains to be understood in this regard, as reviewed elsewhere (12).

EpETrEs also have protective effects directly on the heart, such as improving recovery from ischemia and electrocardiogram abnormalities in isolated rodent hearts (9, 163, 215) and suppressing the endoplasmic reticulum stress response in heart failure (208). They also have many other cardioprotective effects on heart injury related to ischemia-reperfusion injury, drug-induced cardiotoxicity, pressure overload, and cardiac hypertrophy, as previously reviewed (85, 161, 210).

Thus, although AA-derived oxylipins generally have proaggregatory, vasoconstrictive, and inflammatory effects that would have detrimental effects on cardiovascular health, not all (e.g., CYP products above) function in this way, and a comprehensive evaluation of the oxylipin profile is needed to assess the overall effects. In a recent investigation of nearly 100 patients with cardiovascular disease (22), the prevalence of transient ischemic attacks, strokes, angina, and acute coronary syndrome was studied to determine whether plasma oxylipins or fatty acids were related to cardiovascular/cerebrovascular events. None of the 24 fatty acids quantified were associated with any of these cardiovascular events. However, 8 of the nearly 40 plasma oxylipins identified known to regulate vascular tone were significantly associated with these clinical events. For example, plasma 16-HETE was more than four times higher in patients that suffered from a cerebrovascular accident versus those that did not. Plasma 8,9-DiHETrE increased the odds by 92-fold of acute coronary syndrome. Only the stable PGI_2 metabolite 6-keto-$PGF_{1\alpha}$ was associated with a protective effect with an odds ratio of <1 for the prevalence of transient ischemic attacks. For every one-unit increase in the TXB_2 to 6-keto-$PGF_{1\alpha}$ ratio and every 1 nM increase in plasma 16-HETE, TXB_2, or 11,12-DiHETrE, the odds of having had at least two events versus no event increased. Although the conclusions from this study are limited by the relatively small sample size in both patient population and the overall number of clinical events, the results clearly warrant further, more extensive study of the relationship of oxylipins with clinical events.

Nutritional Interventions Altering Oxylipins in Cardiovascular Diseases

The oxylipin profile in tissues is determined not only by the relative abundance of the oxylipin-synthesizing and -metabolizing enzymes but also by the polyunsaturated fatty acids present, which is influenced greatly by the composition of dietary fatty acids. The correlation between dietary polyunsaturated fatty acid intake and tissue concentrations of these same fatty acids is relatively high; one report indicated a ρ value of 0.96 between dietary ALA:LA to renal concentrations of ALA:LA (24).

Although oxylipins derived from AA are the best characterized and primarily the ones described above, oxylipins derived from other polyunsaturated fatty acids also must be considered in dietary recommendations. For example, LOX and CYP oxylipins derived from LA have been associated with atherosclerosis and inflammation (103, 141, 219) but also have been related to anti-inflammatory, antiproliferative, and antiplatelet effects (16, 79, 176, 192, 223). The LA oxylipin 13-hydroxyoctadecadienoic acid (13-HODE) is enriched in oxidized LDL and may contribute to the accumulation of macrophages in atherosclerotic plaques (175), suggesting a detrimental role for this oxylipin in atherosclerosis progression. This may be relevant to the ongoing debate regarding recommendations to increase dietary LA to reduce the risk of cardiovascular disease by reducing blood lipids (20). Indeed, increasing the levels of LA in the diet not only increases the levels of LA oxylipins (which can make up more than half of all oxylipins by mass) but also may increase the levels of AA-derived oxylipins, as has been illustrated in rat tissues (110, 150, 188).

Dietary interventions with ω-3 fatty acids are more commonly recommended for reduction in cardiovascular disease risk. With respect to oxylipins, those derived from ω-3 fatty acids tend to have less activity or opposite effects than ω-6-derived oxylipins, although this is not always the case. Because they can compete with the same enzymes and receptors as their ω-6 counterparts, further diminution of the biological effects of ω-6 oxylipins can occur (74, 102, 133). For example, TXA_3 derived from EPA is produced less efficiently than TXA_2

derived from AA, as EPA is generally a poorer substrate for COX and inhibits production of AA oxylipins (133, 206). On the other hand, PGI_3 has similar vasodilatory and antiaggregatory activity as PGI_2, resulting in a less aggregatory and vasoconstrictive state when EPA is present in the diet (133). With respect to LOX metabolites, LTB_5 derived from EPA is less inflammatory than LTB_4 (108, 122, 123), 5-oxo-eicosapentaenoic acid (5-oxo-EPE) derived from EPA is 10% as potent in stimulating neutrophils as its AA oxylipin counterpart (191), and 14-hydroxy-docosahexaenoic acid (14-HDoHE) can antagonize platelet activation (35). CYP-derived epoxy-eicosatetraenoic acids (EpETEs; often abbreviated as EEQ) formed from EPA and epoxy-docosapentaenoic acids (EpDPEs, often abbreviated as EDP) formed from DHA also inhibit platelet aggregation and TXA_2 synthesis with greater potency than their counterparts formed from AA (200), and EpETEs display similar or greater vasodilatory activity than EpETrEs in some vascular beds (106, 217). EpETEs also exhibit antiarrhythmic effects in neonatal cardiomyocytes by inhibiting Ca^{2+} and isoproterenol-induced contractility in these cells (6). The recently discovered MaRs and Rvs derived from DHA and EPA also are involved in the resolution of inflammation by preventing neutrophil transmigration in murine models of inflammation (137, 172, 173). Rv also can increase the production of nitric oxide and PGI_2 as well as decrease the production of adhesion molecules and reactive oxygen species in endothelial cells (183). A similar molecule, protectin DX (PDX), exhibits antiaggregatory effects (32, 151).

Oxylipins in the blood can be rapidly altered with dietary fat, as shown with the presence of increased levels of oxylipins in the circulation in as little as 2–6 h after consumption of a ω-3 fatty acid-enriched milkshake or supplementation (169, 184) or in longer-term studies with fish oil supplements (52, 93, 166, 168). Therefore, there is great potential through dietary intervention to alter the endogenous oxylipin profile and through this mechanism reduce the risk of proinflammatory conditions, such as hypertension and cardiovascular disease. Much evidence exists for the protective effects of ω-3 fatty acids derived from fish oils on risk for cardiovascular disease, as discussed in a recent science advisory from the American Heart Association (178), which concluded that ω-3 fatty acids were beneficial in patients with prevalent coronary heart disease. However, many studies also have failed to find a protective effect of ω-3 fatty acid supplementation in cardiovascular disease, as discussed in several recent reviews (15, 152, 155). These findings are confounded by a number of limitations in many studies, such as small sample size, short treatment periods, use of low dosages, and effects of high use of cardiovascular drugs for those at highest risk. Several of these limitations are presently being tested in several large randomized clinical trials that should provide more clarity to this issue (NCT00135226, NCT01169259, NCT01492361, and NCT02104817). The protective effects of oxylipins derived from 20- and 22-carbon ω-3 fatty acids as outlined above are considered an important component of the mechanism by which these fatty acids would mediate their protective effects and have been reviewed in further detail elsewhere (49, 70, 86, 211).

In addition, oxylipins derived from the 18-carbon ω-3 fatty acid ALA may also reduce the risk of cardiovascular disease. Although several studies have provided evidence of the protective effect of dietary ALA in cardiovascular disease (reviewed in Refs. 53, 70, and 95), little is known regarding its effects on oxylipins. In the FLAX effects in Peripheral Arterial Disease (FlaxPAD) trial (156), patients who received 30 g of ground flaxseed daily for 6 mo demonstrated a significant reduction in brachial systolic (−10 mmHg) and diastolic (−7 mmHg) blood pressure. A strong inverse relationship of blood pressure with plasma levels of ALA (the main fatty acid in flaxseed) was observed in this study (156). Interestingly, subsequent analyses revealed that ALA exhibited a significant inhibitory effect on the activity of sEH (21). sEH is a rate-limiting enzyme in the generation of several key dihydroxy-octadecenoic acids (DiHOMEs; also known as leukotoxin diols) and DiHETrEs. These oxylipins increase inflammation and cytotoxicity and generally have less vasodilatory activity than their epoxy precursors. Dietary flaxseed reduced the levels of all six of the DiHOMEs and DiHETrEs examined. Thus, as shown in Fig. 1, the reduction in blood pressure by dietary flaxseed may have been induced by an elevation in circulating ALA, which would inhibit sEH activity and thereby *1*) reduce the levels of inflammatory DiHOME (inflammation is thought to induce hypertension) and *2*) decrease the loss of vasodilation by decreasing the conversion of DiHETrE from EpETrE (21). These actions are consistent with ongoing studies testing the antihypertensive efficacy of drugs that inhibit sEH (40, 83, 132).

Another potential antihypertensive action of ALA is the ability to reduce the concentration of other proinflammatory oxylipins. Consumption of ground flaxseed by older healthy adults for 4 wk reduced the circulating levels of 5-HETE and two LA-derived oxylipins, 9,10,13- and 9,12,13-trihydroxy-octadecenoic acid (TriHOMEs), which are characterized by

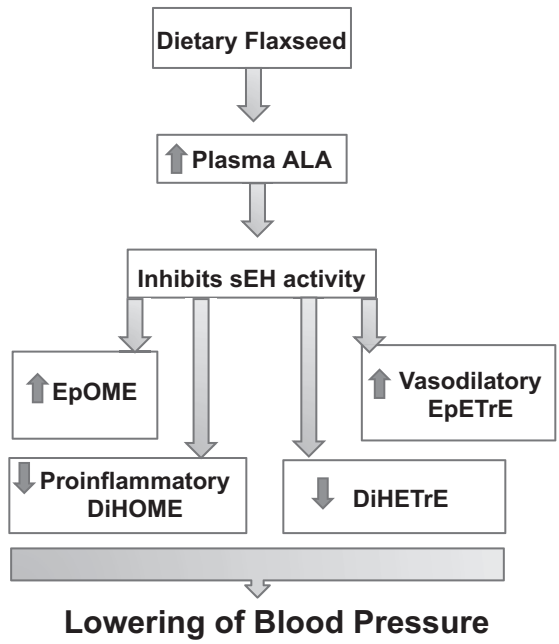

Fig. 1. Proposed mechanism whereby dietary flaxseed reduces blood pressure through the modulation of circulating oxylipin levels. ALA, α-linolenic acid; sEH, soluble epoxide hydrolase; EpOME, epoxy-octadecenoic acid (also known as leukotoxin); DiHOME, dihydroxy-octadecenoic acid (also known as leukotoxin diols); EpETrE, epoxy-eicosatrienoic acid (also abbreviated as EET); DiHETrE, dihydroxy-eicosatrienoic acid (also abbreviated as DHET). [Modified from Caligiuri et al. (21).]

their proinflammatory properties (175). Indeed, 5-HETE is reported to be the most chemotactic of the HETE family and promotes neutrophil recruitment (62). This may in part explain the capacity of an ALA-enriched diet maintained for 6 wk to reduce peripheral blood mononuclear cell production of interleukin-6, interleukin-1, and tumor necrosis factor-α in hypercholesterolemic patients (105).

In addition to effects on peripheral blood pressure, the effects of dietary flaxseed on central blood pressure were also examined in the FlaxPAD study (27). In patients with diagnosed hypertension, average decreases in central systolic and diastolic blood pressure versus the control were 10 and 6 mmHg, respectively. The circulating concentrations of several oxylipins such as TXB_2, 6-keto-$PGF1_\alpha$, and 5,6-DiHETrE were associated with central systolic blood pressure, central diastolic blood pressure, and central mean blood pressure. These oxylipins are known to have vascular tone-regulating properties and thus likely explain their relationship to hypertension. Plasma HDoHEs, which are oxidative products of DHA, were elevated in hypertensive patients. It was suggested that these oxylipins may have been elevated during hypertension in response to an increase in oxidative stress (27). Dietary flaxseed resulted in a decrease in plasma levels of 16-HETE, DiHETrE, and HDoHEs. However, the changes in central or brachial blood pressure induced by supplementing the diet with flaxseed were not associated with any alterations in cardiac contractile function or arterial stiffness. Thus, although ALA-derived oxylipins appear to play a role in protection from some aspects of cardiovascular disease, further delineation of its functions is required.

Oxylipins in Aging

Inflammation, oxidative stress, and vascular constriction are thought to be the causative processes of both cardiovascular disease and age-related degeneration (195). As a result, it is not surprising that the number one cause of death among older adults is cardiovascular disease. Because oxylipins influence and regulate these processes, they are important targets in aging research. AA and LA have been shown to contribute most to vasoconstriction, inflammation, oxidative stress, and tissue damage (62, 68, 105, 175, 207). Although there is growing literature on the effects of oxylipins associated with neuroinflammation and associated brain disorders such as Alzheimer's disease (43), there is less information on the role of oxylipins in normal aging, especially in humans. For select examples of oxylipins in aging, see Table 2.

In humans, the expression of several genes associated with oxylipin formation, such as several PLA_2 and LOX isoforms, increases with aging in human brain (158). A study on the postmortem frontal cortex found elevated levels of two PLA_2 isoforms [$sPLA_2$(IIA) mRNA and $iPLA_2$(VIA) protein] and CYP mRNA and protein in brains from older subjects, suggesting that oxylipin levels could differ in 41- versus 70-yr-old patients (94). In a recent report, the plasma oxylipin profile in younger (19–28 yr old) versus older (45–64 yr old) healthy men and women was shown to be different (23). Thirteen oxylipins were twofold or greater in older subjects than in younger subjects. Included in these were the more proinflammatory oxylipins 5-HETE, 9,10,13-TriHOME, and 9,12,13-TriHOME as well as the ω-3-derived oxylipins 5-HEPE and 11-HDoHE, which also were significantly higher in plasma of the older group compared with the younger group (23). Diet at baseline, in particular the intake of polyunsaturated fatty acids, was not significantly different among the two groups, nor was the presence of disease, medications, or body mass index. In muscle, PGE synthase levels are higher, whereas PGE receptor (EP) levels are lower in 79-yr-old compared with 25-yr-old men and women, indicating potential differences in PGE_2 effects in muscle (112). Levels of $PGF_{2\alpha}$ and PGE_2 are lower in the stomach and duodenum of older (>50 yr) compared with younger (<40 yr) subjects (36). TXB_2 and 6-keto-$PGF_{1\alpha}$ and their metabolites, 2,3-dinor TXB_2 and 2,3-dinor-6-keto-$PGF_{1\alpha}$, are elevated in the urine of older (78–94 yr) compared with young (25–35 yr) individuals (204), whereas LXA_4 levels are lower in older men and women (59). Thus, several studies in humans have demonstrated differences in oxylipin levels in blood, muscle, the gastrointestinal tract, and urine in older subjects.

In animal studies, the brain has been examined for oxylipin changes in aging. In the brain cortex of the senescence-accelerated prone mouse (SAMP8) model of accelerated senescence, several alterations were observed with aging, including higher levels of COX-derived AA oxylipins (PGE_2 and TXB_2) and the CYP-derived LA oxylipin 9,10-DiHOME and lower levels of the CYP-derived AA oxylipin 20-HETE and several LOX-derived DHA oxylipins (11-, 14-, and 20-HDoHE) (37). Other studies have indicated that increased brain 5-LOX is associated with aging (115, 149, 197). Other studies of oxylipins in brain have also reported higher levels of TXB_2 and 6-keto-$PGF_{1\alpha}$ in the rat hippocampus and cerebral cortex (4, 116) and higher levels of brain PD1-like metabolites in older mice (3). Whether these changes in oxylipins are associated with increased pathology or are protective against age-related degeneration remains to be determined.

The vasculature is another tissue that appears to have age-related changes in function associated with oxylipins. SAMP8 mice exhibit enhanced aorta contraction when exposed to a TXA_2 analog, and this effect increases with aging (136). Serum and aorta levels of TXB_2 are elevated in older rats (96), as is the expression of COX isoforms in the aorta and mesenteric arteries (118). In hamsters, $PGF_{2\alpha}$ causes greater contractions and vascular sensitivity in aortas exposed to acetylcholine in older compared with younger animals (214). 12-HETE induces higher rates of migration of aortic smooth muscle cells from older rats, and 20-HETE increases α_1-adrenergic vasoconstriction in older rat systemic arteries (13). On the other hand, rat aortic endothelial cells produce less of the vasodilatory 6-keto-$PGF_{1\alpha}$ when derived from older rats (67, 129), but serum and aorta levels were higher in older rats in another study (96). In rat mesenteric arteries, the vasodilatory response and expression of EP_2 receptors were reduced in response to 14,15-EpETrE in normotensive older rats (216), whereas arteries in aged rats with spontaneous hypertension demonstrate greater reactivity associated with TXA_2 and other COX products (56, 99). Based on human cell culture studies, increasing 11,12-EpETrE with the use of sEH inhibitors has been proposed as a potential treatment of endothelial dysfunction associated with aging, an important component of cardiovascular disease (186). On the other hand, another study in aging mice found few changes in plasma CYP oxylipins, although there were some changes in CYP expression in the kidney, liver, and aorta

Table 2. *Select oxylipins and physiological/pathophysiological effects associated with aging*

Oxylipin	Physiological/Pathophysiological Effect
	Linoleic acid
9,10-DiHOME	9,10-DiHOME is formed via the CYP epoxygenase pathway. 9,10-DiHOME levels are higher in the brain cortex of the SAMP8 model of accelerated senescence (37).
9,10,13-TriHOME	TriHOMEs are produced via sequential LOX and CYP activity.
9,12,13-TriHOME	9,10,13-TriHOME and 9,12,13-TriHOME were higher in plasma of 45- to 64-yr-old vs. 19- to 28-yr-old healthy men and women (23).
	Arachidonic acid
PGD_2	PGD_2 is produced via the COX pathway. Binding capacity of PGD_2 to synaptic membranes decreases with age in Wistar rats (93).
PGE_2	PGE_2 is produced via the COX pathway.
	PGE_2 production is higher in stimulated splenocytes and peritoneal macrophages obtained from 24- vs. 4-mo-old C57BL/6NIA mice and in stimulated splenocytes from similarly aged DBA mice (74).
	Blood PGE_2 is elevated in 24- vs. 6-mo-old Fischer-344 rats (95) but not in aging C57BL/6NNia mice (142).
	PGE_2 production in the rat liver decreases after 72 wk of age (125).
	PGE_2 levels are higher in the brain cortex of the SAMP8 model of accelerated senescence (37).
	Ex vivo lung production of PGE_2 is elevated in 24- vs. 3-mo-old mice (120).
6-keto-$PGF_{1\alpha}$	6-Keto-$PGF_{1\alpha}$ is the stable metabolite of PGI_2 that is produced via the COX pathway.
	6-Keto-$PGF_{1\alpha}$ levels are lower, and production in response to thrombin is less in cultured rat aortic endothelial cells derived from 100- vs. 6-wk-old Wistar rats (128).
	PGI_2-mediated responses to forskolin and isoproterenol are reduced in isolated aortic rings obtained from old compared with younger Wistar-Kyoto rats (67).
	6-Keto-$PGF_{1\alpha}$ in the serum and aorta is elevated in 24- vs. 6-mo-old rats (95).
	6-Keto-$PGF_{1\alpha}$ levels are higher in the hippocampus of 18- and 24- vs. 3-mo-old rats (115).
$PGF_{2\alpha}$	$PGF_{2\alpha}$ is produced via the COX pathway. It causes greater ACh-stimulated contractions and vascular sensitivity in aortas from aged (18 mo) compared with young (3 mo) hamsters.
	$PGF_{2\alpha}$ production in the rat liver decreases after 72 wk of age (125).
	$PGF_{2\alpha}$ and PGE_2 levels are lower in the stomach and duodenum of older (>50 yr) compared with younger (<40 yr) people (36). $PGF_{2\alpha}$ is elevated in peritoneal lavages of old (20 mo) compared with young (2 mo) rats (5).
TXB_2	TXB_2 is the stable metabolite of TXA_2 produced via the COX pathway. Hippocampus and cerebral cortex TXB_2 levels are higher in older (24 and 30 mo) compared with young (3−4 mo) rats (4, 115).
	TXB_2 in the serum and aorta are elevated in 24- vs. 6-mo-old rats (95).
	TXB_2 levels are higher in the brain cortex of the SAMP8 model of accelerated senescence (37). These mice also exhibit enhanced aorta contraction when exposed to a TXA_2 analog, which increases with aging (135).
	Arteries in aged rats with spontaneous hypertension demonstrate greater reactivity associated with TXA_2 and other COX products (56, 98). TXB_2 production from the lung ex vivo is elevated in 24- vs. 3-mo-old mice (120).
2,3-dinor TXB_2	2,3-Dinor TXB_2 and 2,3-dinor-6-keto-$PGF_{1\alpha}$ are urinary metabolites of TXB_2 and 6-keto-$PGF_{1\alpha}$.
2,3-dinor-6-keto-$PGF_{1\alpha}$	2,3-Dinor TXB_2 and 2,3-dinor-6-keto-$PGF_{1\alpha}$, along with their parent compounds, are elevated in the urine of older (78−94 yr) compared with young (25−35 yr) individuals (203).
LTB_4	LTB_4 and LTC_4 are produced via the LOX pathway and are higher in stimulated splenocytes obtained from 24-
LTC_4	compared with 4-mo-old mice (74).
	LTB_4 is elevated in peritoneal lavages of old (20-mo) compared with young (2 mo) rats (5).
5-HETE	5-HETE is produced via the LOX pathway. Plasma levels of 5-HETE were higher in plasma of 45- to 64-yr-old vs. 19- to 28-yr-old healthy males and females (23).
12-HETE	12-HETE is produced via the LOX pathway.
	12-HETE-induced migration rate of aortic smooth muscle cells is higher in tissue from 25- compared with 2-mo-old rats (130).
LXA_4	LXA_4 is produced via the LOX pathway and is involved in the resolution of inflammation.
	LXA_4 is inversely correlated with age in urine from 26- to 105-yr-old men and women (60).
LXB_4	LXB_4 is produced via the LOX pathway and is involved in the resolution of inflammation. LXB_4 levels were lower in peritoneal lavages of old (20 mo) compared with young (2 mo) rats (5).
14,15-EpETrE	EpETrEs are produced via the CYP epoxygenase pathway and exhibit vasodilatory effects.
	In rat mesenteric arteries, the vasodilatory response is reduced in response to 14,15-EpETrE in normotensive older rats (215).
19-HETE	19-HETE and 20-HETE are produced via the CYP ω-hydroxylase pathway.
20-HETE	
	20-HETE appears to be a greater contributor to α_1-adrenergic vasoconstriction in systemic arteries of aging rats (13).
	20-HETE levels were lower in the brain cortex of the SAMP8 model of accelerated senescence (37).
	Eicosapentaenoic acid
5-HEPE	5-HEPE is produced via the LOX pathway.
	5-HEPE levels are higher in plasma of 45- to 64-yr-old vs. 19- to 28-yr-old healthy men and women (23).
	Docosahexaenoic acid
11-HdoHE	HDoHE is produced via the LOX pathway. Plasma levels of 11-HDoHE were higher in plasma of 45- to 64-yr-old vs. 19- to 28-yr-old healthy men and women (23).
	11-HDoHE levels are lower in the brain cortex of the SAMP8 model of accelerated senescence (37).
14-HdoHE	14-HDoHE is produced via the LOX pathway.
	14-HDoHE levels are lower in the brain cortex of the SAMP8 model of accelerated senescence (37).

Continued

Table 2.—*Continued*

Oxylipin	Physiological/Pathophysiological Effect
20-HdoHE	HDoHE is produced via the CYP ω-hydroxylase pathway.
	20-HDoHE levels are lower in the brain cortex of the SAMP8 model of accelerated senescence (37).
PD1	PD1 (also known as neuroprotectin D1) is produced via the LOX pathway and is a proresolving mediator. Brain PD1-like metabolites are higher in 24- vs. 3-mo-old female NMRI mice (3).
MaR1	MaR and Rv belong to a class of proresolving mediators that are produced via the LOX pathway from 14-
RvD1	HDoHE and 17-HDoHE, respectively.
	MaR1 and RvD1 levels are lower in peritoneal lavages of old (20 mo) compared with young (2 mo) rats (5).

DiHOME, dihydroxy-octadecenoic acid; CYP, cytochrome *P*-450; SAMP8, senescence-accelerated prone mouse; TriHOME, trihydroxy-octadecenoic acid; COX, cyclooxygenase; TX, thromboxane; LT, leukotriene; LOX, lipoxygenase; EpETrE, epoxy-eicosatrienoic acid; HETE, hydroxy-eicosatetraenoic acid; HEPE, hydroxy-eicosapentaenoic acid; HDoHE, hydroxy-docosahexaenoic acid; PD, protectin; MaR, maresin; Rv, resolvin.

(108). Therefore, in many, but not all, studies, oxylipin changes in aging appear to be associated with decreased functionality, raising the possibility that manipulation of oxylipin levels may be a strategy for counteracting aging effects of the vasculature.

Besides the brain and vasculature, fewer studies in other tissues in aging have been studied. Splenocyte and macrophage production of PGE_2, LTB_4, and LTC_4 are elevated in response to stimulation in older mice (75), and peritoneal lavages from older mice have higher levels of $PGF_{2\alpha}$ and LTB_4 and lower levels of the proresolving LXB_4, MaR1, and RvD1 (5), providing a potential link between aging and inflammation involving oxylipins. In the kidney, increased 19- and 20-HETE generation in cortex homogenates from older rats has been observed (140), and a decrease in renal PGI_2 biosynthesis and renal 15-hydroxy-prostaglandin dehydrogenase activity in aging has been suggested as a potential factor in the progressive decrease in renal functions in the elderly (31). PGE_2 and $PGF_{2\alpha}$ also decrease in the rat liver after 72 wk of age (126), whereas ex vivo lung production of TXB_2 and PGE_2 was elevated in 24- compared with 3-mo-old mice (121). The implications of these age-related changes in these tissues remain to be investigated.

Nutritional Interventions Altering Oxylipins in Aging

It is possible that the oxylipin profile changes observed in aging may be modified through dietary intervention. After 4 wk of daily supplementation with 30 g of milled flaxseed, the oxylipin profile became less inflammatory in both younger and older groups, but the improvement in the older group was greater (23). In another study, EPA and DHA supplementation decreased plasma 5-HETE in younger and older healthy men (224). In aged rats, supplementation with EPA and DHA resulted in higher levels of oxylipins derived from these fatty acids and lower levels of AA-derived oxylipins, changes that were associated with improved reference memory-related learning ability (73). In contrast to ω-3 fatty acid supplementation, providing 21-mo-old Wistar rats with dietary AA had the opposite effects on renal oxylipins, which may increase the inflammatory state, although no adverse reactions under normal conditions were observed (90). Despite these interesting initial results from this small number of reports, larger dietary studies of aging populations are required before conclusions regarding the roles of dietary manipulation of oxylipins in aging can be reached. Dietary improvements and modifications even in very old age are possible and should be implemented to reduce inflammation and risk of cardiovascular disease. In the longest running longitudinal study in Canada, dietary improvements were observed in those around 85 yr old, and this was associated with better mental and physical functional scores and successful aging (25). The exact quantities and ratios of polyunsaturated fatty acids necessary to create the ideal oxylipin profile for aging and prevention of cardiovascular disease has yet to be identified. However, for older adults, the addition of ω-3 fatty acids is strongly supported for the prevention of cardiovascular disease and may aid in slowing age-related inflammation.

Summary and Future Directions

In conclusion, the effect of dietary ω-3 fatty acids on the production of oxylipins plays an important role in the mechanisms by which these dietary fatty acids reduce cardiovascular risk. Recent findings of dietary ALA effects on oxylipins in hypertensive patients suggest that this ω-3 fatty acid also may affect cardiovascular risk via unique effects on oxylipins. Fewer studies on the role of oxylipins in aging have been done, but they do implicate oxylipins in the aging process. These also are potentially altered by dietary fatty acids, but more studies are needed to continue to delineate the roles of oxylipins in age-related changes. Given the diverse functions and potencies of the different oxylipins and those derived from different fatty acids, comprehensive profiling of oxylipins in multiple tissues is necessary to appreciate the overall biological effects of the balance of these bioactive lipids. In this regard, studies comparing the biological effects of individual and combined oxylipins in multiple organ systems will enhance understanding of oxylipin functions in whole organisms. In particular, future discoveries on the effects of the oxylipins derived from LA and ALA, which make up the bulk of oxylipins in most tissues, will lead to a greater understanding of their effects in cardiovascular diseases and aging.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

S.P.B.C. and G.N.P. conceived and designed research; S.P.B.C. analyzed data; S.P.B.C., M.P., A.S., G.N.P., and H.M.A. drafted manuscript; S.P.B.C.,

G.N.P., and H.M.A. edited and revised manuscript; G.N.P. prepared figures; G.N.P. and H.M.A. approved final version of manuscript.

REFERENCES

1. **Adams JW, Sah VP, Henderson SA, Brown JH.** Tyrosine kinase and c-Jun NH_2-terminal kinase mediate hypertrophic responses to prostaglandin F2alpha in cultured neonatal rat ventricular myocytes. *Circ Res* 83: 167–178, 1998. doi:10.1161/01.RES.83.2.167.
2. **Adler DH, Cogan JD, Phillips JA III, Schnetz-Boutaud N, Milne GL, Iverson T, Stein JA, Brenner DA, Morrow JD, Boutaud O, Oates JA.** Inherited human cPLA(2alpha) deficiency is associated with impaired eicosanoid biosynthesis, small intestinal ulceration, and platelet dysfunction. *J Clin Invest* 118: 2121–2131, 2008. doi:10.1172/JCI30473.
3. **Afshordel S, Hagl S, Werner D, Röhner N, Kögel D, Bazan NG, Eckert GP.** Omega-3 polyunsaturated fatty acids improve mitochondrial dysfunction in brain aging−impact of Bcl-2 and NPD-1 like metabolites. *Prostaglandins Leukot Essent Fatty Acids* 92: 23–31, 2015. doi:10.1016/j.plefa.2014.05.008.
4. **Aïd S, Bosetti F.** Gene expression of cyclooxygenase-1 and Ca^{2+}-independent phospholipase A_2 is altered in rat hippocampus during normal aging. *Brain Res Bull* 73: 108–113, 2007. doi:10.1016/j.brainresbull.2007.02.015.
5. **Arnardottir HH, Dalli J, Colas RA, Shinohara M, Serhan CN.** Aging delays resolution of acute inflammation in mice: reprogramming the host response with novel nano-proresolving medicines. *J Immunol* 193: 4235–4244, 2014. doi:10.4049/jimmunol.1401313.
6. **Arnold C, Markovic M, Blossey K, Wallukat G, Fischer R, Dechend R, Konkel A, von Schacky C, Luft FC, Muller DN, Rothe M, Schunck WH.** Arachidonic acid-metabolizing cytochrome P450 enzymes are targets of omega-3 fatty acids. *J Biol Chem* 285: 32720–32733, 2010. doi:10.1074/jbc.M110.118406.
7. **Bäck M.** Leukotriene signaling in atherosclerosis and ischemia. *Cardiovasc Drugs Ther* 23: 41–48, 2009. doi:10.1007/s10557-008-6140-9.
8. **Baer PG, McGiff JC.** Comparison of effects of prostaglandins E_2 and I_2 on rat renal vascular resistance. *Eur J Pharmacol* 54: 359–363, 1979. doi:10.1016/0014-2999(79)90065-7.
9. **Batchu SN, Law E, Brocks DR, Falck JR, Seubert JM.** Epoxyeicosatrienoic acid prevents postischemic electrocardiogram abnormalities in an isolated heart model. *J Mol Cell Cardiol* 46: 67–74, 2009. doi:10.1016/j.yjmcc.2008.09.711.
10. **Bednar MM, Gross CE, Balazy MK, Belosludtsev Y, Colella DT, Falck JR, Balazy M.** 16(*R*)-hydroxy-5,8,11,14-eicosatetraenoic acid, a new arachidonate metabolite in human polymorphonuclear leukocytes. *Biochem Pharmacol* 60: 447–455, 2000. doi:10.1016/S0006-2952(00)00345-2.
11. **Bednar MM, Gross CE, Russell SR, Fuller SP, Ahern TP, Howard DB, Falck JR, Reddy KM, Balazy M.** 16(*R*)-hydroxyeicosatetraenoic acid, a novel cytochrome P450 product of arachidonic acid, suppresses activation of human polymorphonuclear leukocyte and reduces intracranial pressure in a rabbit model of thromboembolic stroke. *Neurosurgery* 47: 1410–1419, 2000.
12. **Bellien J, Joannides R.** Epoxyeicosatrienoic acid pathway in human health and diseases. *J Cardiovasc Pharmacol* 61: 188–196, 2013. doi:10.1097/FJC.0b013e318273b007.
13. **Berezan DJ, Dunn KM, Falck JR, Davidge ST.** Aging increases cytochrome P450 4A modulation of alpha1-adrenergic vasoconstriction in mesenteric arteries. *J Cardiovasc Pharmacol* 51: 327–330, 2008. doi:10.1097/FJC.0b013e318160b415.
14. **Bos CL, Richel DJ, Ritsema T, Peppelenbosch MP, Versteeg HH.** Prostanoids and prostanoid receptors in signal transduction. *Int J Biochem Cell Biol* 36: 1187–1205, 2004. doi:10.1016/j.biocel.2003.08.006.
15. **Bowen KJ, Harris WS, Kris-Etherton PM.** Omega-3 fatty acids and cardiovascular disease: are there benefits? *Curr Treat Options Cardiovasc Med* 18: 69, 2016. doi:10.1007/s11936-016-0487-1.
16. **Buchanan MR, Haas TA, Lagarde M, Guichardant M.** 13-Hydroxyoctadecadienoic acid is the vessel wall chemorepellant factor, LOX. *J Biol Chem* 260: 16056–16059, 1985.
17. **Buckley CD, Gilroy DW, Serhan CN.** Proresolving lipid mediators and mechanisms in the resolution of acute inflammation. *Immunity* 40: 315–327, 2014. doi:10.1016/j.immuni.2014.02.009.
18. **Buczynski MW, Dumlao DS, Dennis EA.** Thematic Review Series: Proteomics. An integrated omics analysis of eicosanoid biology. *J Lipid Res* 50: 1015–1038, 2009. doi:10.1194/jlr.R900004-JLR200.
19. **Bundy GL, Morton DR, Peterson DC, Nishizawa EE, Miller WL.** Synthesis and platelet aggregation inhibiting activity of prostaglandin D analogues. *J Med Chem* 26: 790–799, 1983. doi:10.1021/jm00360a003.
20. **Calder PC, Deckelbaum RJ.** Harmful, harmless or helpful? The *n*-6 fatty acid debate goes on. *Curr Opin Clin Nutr Metab Care* 14: 113–114, 2011. doi:10.1097/MCO.0b013e328343d895.
21. **Caligiuri SP, Aukema HM, Ravandi A, Guzman R, Dibrov E, Pierce GN.** Flaxseed consumption reduces blood pressure in patients with hypertension by altering circulating oxylipins via an α-linolenic acid-induced inhibition of soluble epoxide hydrolase. *Hypertension* 64: 53–59, 2014. doi:10.1161/HYPERTENSIONAHA.114.03179.
22. **Caligiuri SPB, Aukema HM, Ravandi A, Lavallée R, Guzman R, Pierce GN.** Specific plasma oxylipins increase the odds of cardiovascular and cerebrovascular events in patients with peripheral artery disease. *Can J Physiol Pharmacol* 95: 961–968, 2017. doi:10.1139/cjpp-2016-0615.
23. **Caligiuri SP, Aukema HM, Ravandi A, Pierce GN.** Elevated levels of pro-inflammatory oxylipins in older subjects are normalized by flaxseed consumption. *Exp Gerontol* 59: 51–57, 2014. doi:10.1016/j.exger.2014.04.005.
24. **Caligiuri SP, Blydt-Hansen T, Love K, Grégoire M, Taylor CG, Zahradka P, Aukema HM.** Evidence for the use of glomerulomegaly as a surrogate marker of glomerular damage and for alpha-linolenic acid-rich oils in the treatment of early obesity-related glomerulopathy in a diet-induced rodent model of obesity. *Appl Physiol Nutr Metab* 39: 951–959, 2014. doi:10.1139/apnm-2013-0476.
25. **Caligiuri S, Lengyel C, Tate R.** Changes in food group consumption and associations with self-rated diet, health, life satisfaction, and mental and physical functioning over 5 years in very old Canadian men: the Manitoba Follow-Up Study. *J Nutr Health Aging* 16: 707–712, 2012. doi:10.1007/s12603-012-0055-7.
26. **Caligiuri SP, Love K, Winter T, Gauthier J, Taylor CG, Blydt-Hansen T, Zahradka P, Aukema HM.** Dietary linoleic acid and α-linolenic acid differentially affect renal oxylipins and phospholipid fatty acids in diet-induced obese rats. *J Nutr* 143: 1421–1431, 2013. doi:10.3945/jn.113.177360.
27. **Caligiuri SPB, Rodriguez-Leyva D, Aukema HM, Ravandi A, Weighell W, Guzman R, Pierce GN.** Dietary flaxseed reduces central aortic blood pressure without cardiac involvement but through changes in plasma oxylipins. *Hypertension* 68: 1031–1038, 2016. doi:10.1161/HYPERTENSIONAHA.116.07834.
28. **Campbell WB, Gebremedhin D, Pratt PF, Harder DR.** Identification of epoxyeicosatrienoic acids as endothelium-derived hyperpolarizing factors. *Circ Res* 78: 415–423, 1996. doi:10.1161/01.RES.78.3.415.
29. **Capra V, Rovati GE, Mangano P, Buccellati C, Murphy RC, Sala A.** Transcellular biosynthesis of eicosanoid lipid mediators. *Biochim Biophys Acta* 1851: 377–382, 2015. doi:10.1016/j.bbalip.2014.09.00.
30. **Carroll MA, Balazy M, Margiotta P, Huang DD, Falck JR, McGiff JC.** Cytochrome *P*-450-dependent HETEs: profile of biological activity and stimulation by vasoactive peptides. *Am J Physiol Regul Integr Comp Physiol* 271: R863–R869, 1996.
31. **Chang WC, Tai HH.** Changes in prostacyclin and thromboxane biosynthesis and their catabolic enzyme activity in kidneys of aging rats. *Life Sci* 34: 1269–1280, 1984. doi:10.1016/0024-3205(84)90550-2.
32. **Chen P, Véricel E, Lagarde M, Guichardant M.** Poxytrins, a class of oxygenated products from polyunsaturated fatty acids, potently inhibit blood platelet aggregation. *FASEB J* 25: 382–388, 2011. doi:10.1096/fj.10-161836.
33. **Cheng Y, Austin SC, Rocca B, Koller BH, Coffman TM, Grosser T, Lawson JA, FitzGerald GA.** Role of prostacyclin in the cardiovascular response to thromboxane A_2. *Science* 296: 539–541, 2002. doi:10.1126/science.1068711.
34. **Coleman RA, Smith WL, Narumiya S.** International Union of Pharmacology classification of prostanoid receptors: properties, distribution, and structure of the receptors and their subtypes. *Pharmacol Rev* 46: 205–229, 1994.
35. **Croset M, Sala A, Folco G, Lagarde M.** Inhibition by lipoxygenase products of TXA_2-like responses of platelets and vascular smooth muscle. 14-Hydroxy from 22:6*n*-3 is more potent than 12-HETE. *Biochem Pharmacol* 37: 1275–1280, 1988. doi:10.1016/0006-2952(88)90782-4.
36. **Cryer B, Lee E, Feldman M.** Factors influencing gastroduodenal mucosal prostaglandin concentrations: roles of smoking and aging. *Ann Intern Med* 116: 636–640, 1992. doi:10.7326/0003-4819-116-8-636.
37. **Currais A, Goldberg J, Farrokhi C, Chang M, Prior M, Dargusch R, Daugherty D, Armando A, Quehenberger O, Maher P, Schubert D.**

A comprehensive multiomics approach toward understanding the relationship between aging and dementia. *Aging (Albany NY)* 7: 937–955, 2015. doi:10.18632/aging.100838.

38. **Dahan A, Altman H.** Food-drug interaction: grapefruit juice augments drug bioavailability−mechanism, extent and relevance. *Eur J Clin Nutr* 58: 1–9, 2004. doi:10.1038/sj.ejcn.1601736.
39. **Darius H, Michael-Hepp J, Thierauch KH, Fisch A.** Inhibition of human platelets and polymorphonuclear neutrophils by the potent and metabolically stable prostaglandin D_2 analog ZK 118.182. *Eur J Pharmacol* 258: 207–213, 1994. doi:10.1016/0014-2999(94)90482-0.
40. **Davis BB, Thompson DA, Howard LL, Morisseau C, Hammock BD, Weiss RH.** Inhibitors of soluble epoxide hydrolase attenuate vascular smooth muscle cell proliferation. *Proc Natl Acad Sci USA* 99: 2222–2227, 2002. doi:10.1073/pnas.261710799.
41. **De la Fuente M, Miquel J.** An update of the oxidation-inflammation theory of aging: the involvement of the immune system in oxi-inflamm-aging. *Curr Pharm Des* 15: 3003–3026, 2009. doi:10.2174/138161209789058110.
42. **Deniset JF, Pierce GN.** Possibilities for therapeutic interventions in disrupting *Chlamydophila pneumoniae* involvement in atherosclerosis. *Fundam Clin Pharmacol* 24: 607–617, 2010. doi:10.1111/j.1472-8206.2010.00863.x.
43. **Devassy JG, Leng S, Gabbs S, Monirujjaman M, Aukema H.** Omega-3 polyunsaturated fatty acids and oxylipins in neuroinflammation and management of Alzheimer disease. *Adv Nutr* 7: 905–916, 2016. doi:10.3945/an.116.012187.
44. **Dichlberger A, Schlager S, Maaninka K, Schneider WJ, Kovanen PT.** Adipose triglyceride lipase regulates eicosanoid production in activated human mast cells. *J Lipid Res* 55: 2471–2478, 2014. doi:10.1194/jlr.M048553.
45. **Dusting GJ, Moncada S, Vane JR.** Prostacyclin (PGX) is the endogenous metabolite responsible for relaxation of coronary arteries induced by arachindonic acid. *Prostaglandins* 13: 3–15, 1977. doi:10.1016/0090-6980(77)90037-5.
46. **Earles SM, Bronstein JC, Winner DL, Bull AW.** Metabolism of oxidized linoleic acid: characterization of 13-hydroxyoctadecadienoic acid dehydrogenase activity from rat colonic tissue. *Biochim Biophys Acta* 1081: 174–180, 1991. doi:10.1016/0005-2760(91)90023-B.
47. **Eidelman RS, Hebert PR, Weisman SM, Hennekens CH.** An update on aspirin in the primary prevention of cardiovascular disease. *Arch Intern Med* 163: 2006–2010, 2003. doi:10.1001/archinte.163.17.2006.
48. **Enayetallah AE, French RA, Barber M, Grant DF.** Cell-specific subcellular localization of soluble epoxide hydrolase in human tissues. *J Histochem Cytochem* 54: 329–335, 2006. doi:10.1369/jhc.5A6808.2005.
49. **Endo J, Arita M.** Cardioprotective mechanism of omega-3 polyunsaturated fatty acids. *J Cardiol* 67: 22–27, 2016. doi:10.1016/j.jjcc.2015.08.002.
50. **Fang X, Faraci FM, Kaduce TL, Harmon S, Modrick ML, Hu S, Moore SA, Falck JR, Weintraub NL, Spector AA.** 20-Hydroxyeicosatetraenoic acid is a potent dilator of mouse basilar artery: role of cyclooxygenase. *Am J Physiol Heart Circ Physiol* 291: H2301–H2307, 2006. doi:10.1152/ajpheart.00349.2006.
52. **Fischer R, Konkel A, Mehling H, Blossey K, Gapelyuk A, Wessel N, von Schacky C, Dechend R, Muller DN, Rother M, Luft FC, Weylandt K, Schunck WH.** Dietary omega-3 fatty acids modulate the eicosanoid profile in man primarily via the CYP-epoxygenase pathway. *J Lipid Res* 55: 1150–1164, 2014. doi:10.1194/jlr.M047357.
53. **Fleming JA, Kris-Etherton PM.** The evidence for a-linolenic acid and cardiovascular disease benefits: Comparisons with eicosapentaenoic acid and docosahexaenoic acid. *Adv Nutr* 5: 863S–876S, 2014. doi:10.3945/an.114.005850.
54. **Folcik VA, Cathcart MK.** Predominance of esterified hydroperoxylinoleic acid in human monocyte-oxidized LDL. *J Lipid Res* 35: 1570–1582, 1994.
55. **Fonlupt P, Croset M, Lagarde M.** 12-HETE inhibits the binding of PGH2/TXA2 receptor ligands in human platelets. *Thromb Res* 63: 239–248, 1991. doi:10.1016/0049-3848(91)90287-7.
56. **Fujii K, Onaka U, Abe I, Fujishima M.** Eicosanoids and membrane properties in arteries of aged spontaneously hypertensive rats. *J Hypertens* 17: 75–80, 1999. doi:10.1097/00004872-199917010-00012.
57. **Funk CD.** Prostaglandins and leukotrienes: advances in eicosanoid biology. *Science* 294: 1871–1875, 2001. doi:10.1126/science.294.5548.1871.
58. **Gabbs M, Leng S, Devassy JG, Monirujjaman M, Aukema HM.** Advances in our understanding of oxylipins derived from dietary PUFAs. *Adv Nutr* 6: 513–540, 2015. doi:10.3945/an.114.007732.
59. **Gangemi S, Pescara L, D'Urbano E, Basile G, Nicita-Mauro V, Davì G, Romano M.** Aging is characterized by a profound reduction in anti-inflammatory lipoxin A4 levels. *Exp Gerontol* 40: 612–614, 2005. doi:10.1016/j.exger.2005.04.004.
60. **Giles H, Leff P.** The biology and pharmacology of PGD2. *Prostaglandins* 35: 277–300, 1988. doi:10.1016/0090-6980(88)90093-7.
61. **Goetzl EJ.** A role for endogenous mono-hydroxy-eicosatetraenoic acids (HETEs) in the regulation of human neutrophil migration. *Immunology* 40: 709–719, 1980.
62. **Goetzl EJ, Brash AR, Tauber AI, Oates JA, Hubbard WC.** Modulation of human neutrophil function by monohydroxy-eicosatetraenoic acids. *Immunology* 39: 491–501, 1980.
63. **Goetzl EJ, Pickett WC.** The human PMN leukocyte chemotactic activity of complex hydroxy-eicosatetraenoic acids (HETEs). *J Immunol* 125: 1789–1791, 1980.
64. **Goetzl EJ, Weller PF, Sun FF.** The regulation of human eosinophil function by endogenous mono-hydroxy-eicosatetraenoic acids (HETEs). *J Immunol* 124: 926–933, 1980.
65. **Goldman DW, Pickett WC, Goetzl EJ.** Human neutrophil chemotactic and degranulating activities of leukotriene B_5 (LTB_5) derived from eicosapentaenoic acid. *Biochem Biophys Res Commun* 117: 282–288, 1983. doi:10.1016/0006-291X(83)91572-3.
67. **Gomez E, Schwendemann C, Roger S, Simonet S, Paysant J, Courchay C, Verbeuren TJ, Félétou M.** Aging and prostacyclin responses in aorta and platelets from WKY and SHR rats. *Am J Physiol Heart Circ Physiol* 295: H2198–H2211, 2008. doi:10.1152/ajpheart.00507.2008.
68. **González-Peña D, Checa A, de Ancos B, Wheelock CE, Sánchez-Moreno C.** New insights into the effects of onion consumption on lipid mediators using a diet-induced model of hypercholesterolemia. *Redox Biol* 11: 205–212, 2017. doi:10.1016/j.redox.2016.12.002.
69. **Gordon EE, Gordon JA, Spector AA.** HETEs and coronary artery endothelial cells: metabolic and functional interactions. *Am J Physiol Cell Physiol* 261: C623–C633, 1991.
70. **Guichardant M, Calzada C, Bernoud-Hubac N, Lagarde M, Véricel, E.** Omega-3 polyunsaturated fatty acids and oxygenated metabolism in atherothrombosis. *Biochim Biophys Acta* 1851: 485–495, 2015. doi:10.1016/j.bbalip.2014.09.013.
71. **Gunter BR, Butler KA, Wallace RL, Smith SM, Harirforoosh S.** Non-steroidal anti-inflammatory drug-induced cardiovascular adverse events: a meta-analysis. *J Clin Pharm Ther* 42: 27–38, 2017. doi:10.1111/jcpt.12484.
72. **Gupte SA, Okada T.** Prostaglandins and nitric oxide mediate superoxide-induced myocardial contractile dysfunction in isolated rat hearts. *J Mol Cell Cardiol* 33: 1107–1117, 2001. doi:10.1006/jmcc.2001.1371.
73. **Hashimoto M, Katakura M, Tanabe Y, Al Mamun A, Inoue T, Hossain S, Arita M, Shido O.** n-3 fatty acids effectively improve the reference memory-related learning ability associated with increased brain docosahexaenoic acid-derived docosanoids in aged rats. *Biochim Biophys Acta* 1851: 203–209, 2015. doi:10.1016/j.bbalip.2014.10.009.
74. **Hawcroft G, Loadman PM, Belluzzi A, Hull MA.** Effect of eicosapentaenoic acid on E-type prostaglandin synthesis and EP4 receptor signaling in human colorectal cancer cells. *Neoplasia* 12: 618–627, 2010. doi:10.1593/neo.10388.
75. **Hayek MG, Meydani SN, Meydani M, Blumberg JB.** Age differences in eicosanoid production of mouse splenocytes: effects on mitogen-induced T-cell proliferation. *J Gerontol* 49: B197–B207, 1994. doi:10.1093/geronj/49.5.B197.
76. **Heidel JR, Taylor SM, Laegreid WW, Silflow RM, Liggitt HD, Leid RW.** In vivo chemotaxis of bovine neutrophils induced by 5-lipoxygenase metabolites of arachidonic and eicosapentaenoic acid. *Am J Pathol* 134: 671–676, 1989.
77. **Hercule HC, Schunck WH, Gross V, Seringer J, Leung FP, Weldon SM, da Costa Goncalves AC, Huang Y, Luft FC, Gollasch M.** Interaction between P450 eicosanoids and nitric oxide in the control of arterial tone in mice. *Arterioscler Thromb Vasc Biol* 29: 54–60, 2009. doi:10.1161/ATVBAHA.108.171298.
78. **Hohlfeld T, Zucker TP, Meyer J, Schrör K.** Expression, function, and regulation of E-type prostaglandin receptors (EP3) in the nonischemic and ischemic pig heart. *Circ Res* 81: 765–773, 1997. doi:10.1161/01.RES.81.5.765.

79. **Honn KV, Nelson KK, Renaud C, Bazaz R, Diglio CA, Timar J.** Fatty acid modulation of tumor cell adhesion to microvessel endothelium and experimental metastasis. *Prostaglandins* 44: 413–429, 1992. doi:10.1016/0090-6980(92)90137-I.
80. **Horie M, Fukui H, Endoh S, Maru J, Miyauchi A, Shichiri M, Fujita K, Niki E, Hagihara Y, Yoshida Y, Morimoto Y, Iwahashi H.** Comparison of acute oxidative stress on rat lung induced by nano and fine-scale, soluble and insoluble metal oxide particles: NiO and TiO_2. *Inhal Toxicol* 24: 391–400, 2012. doi:10.3109/08958378.2012.682321.
81. **Imig JD, Walsh KA, Hye Khan MA, Nagasawa T, Cherian-Shaw M, Shaw SM, Hammock BD.** Soluble epoxide hydrolase inhibition and peroxisome proliferator activated receptor γ agonist improve vascular function and decrease renal injury in hypertensive obese rats. *Exp Biol Med (Maywood)* 237: 1402–1412, 2012. doi:10.1258/ebm.2012.012225.
82. **Imig JD, Zhao X, Zaharis CZ, Olearczyk JJ, Pollock DM, Newman JW, Kim IH, Watanabe T, Hammock BD.** An orally active epoxide hydrolase inhibitor lowers blood pressure and provides renal protection in salt-sensitive hypertension. *Hypertension* 46: 975–981, 2005. doi:10.1161/01.HYP.0000176237.74820.75.
83. **Inceoglu B, Schmelzer KR, Morisseau C, Jinks SL, Hammock BD.** Soluble epoxide hydrolase inhibition reveals novel biological functions of epoxyeicosatrienoic acids (EETs). *Prostaglandins Other Lipid Mediat* 82: 42–49, 2007. doi:10.1016/j.prostaglandins.2006.05.004.
84. **Iyú D, Jüttner M, Glenn JR, White AE, Johnson AJ, Fox SC, Heptinstall S.** PGE_1 and PGE_2 modify platelet function through different prostanoid receptors. *Prostaglandins Other Lipid Mediat* 94: 9–16, 2011. doi:10.1016/j.prostaglandins.2010.11.001.
85. **Jenkins CM, Cedars A, Gross RW.** Eicosanoid signalling pathways in the heart. *Cardiovasc Res* 82: 240–249, 2009. doi:10.1093/cvr/cvn346.
86. **Jiang J, Li K, Wang F, Yang B, Fu Y, Zheng J, Li D.** Effect of Marine-derived *n*-3 polyunsaturated fatty acids on major eicosanoids: a systematic review and meta-analysis from 18 randomized controlled trials. *PloS One* 11: e0147351, 2016. doi:10.1371/journal.pone.0147351.
87. **Johnson EN, Brass LF, Funk CD.** Increased platelet sensitivity to ADP in mice lacking platelet-type 12-lipoxygenase. *Proc Natl Acad Sci USA* 95: 3100–3105, 1998. doi:10.1073/pnas.95.6.3100.
88. **Jung F, Schulz C, Blaschke F, Muller DN, Mrowietz C, Franke RP, Lendlein A, Schunck WH.** Effect of cytochrome P450-dependent epoxyeicosanoids on Ristocetin-induced thrombocyte aggregation. *Clin Hemorheol Microcirc* 52: 403–416, 2012. doi:10.3233/CH-2012-1614.
89. **Kaduce TL, Fang X, Harmon SD, Oltman CL, Dellsperger KC, Teesch LM, Gopal VR, Falck JR, Campbell WB, Weintraub NL, Spector AA.** 20-hydroxyeicosatetraenoic acid (20-HETE) metabolism in coronary endothelial cells. *J Biol Chem* 279: 2648–2656, 2004. doi:10.1074/jbc.M306849200.
90. **Katakura M, Hashimoto M, Inoue T, Mamun AA, Tanabe Y, Arita M, Shido O.** Chronic arachidonic acid administration decreases docosahexaenoic acid-and eicosapentaenoic acid-derived metabolites in kidneys of aged rats. *PLoS One* 10: e0140884, 2015. doi:10.1371/journal.pone.0140884.
91. **Kato Y, Fuchi N, Saburi H, Nishimura Y, Watanabe A, Yagi M, Nakadera Y, Higashi E, Yamada M, Aoki T.** Discovery of 2,8-diazaspiro[4.5]decane-based trisubstituted urea derivatives as highly potent soluble epoxide hydrolase inhibitors and orally active drug candidates for treating hypertension. *Bioorg Med Chem Lett* 23: 5975–5979, 2013. doi:10.1016/j.bmcl.2013.08.054.
92. **Katsumata Y, Shinmura K, Sugiura Y, Tohyama S, Matsuhashi T, Ito H, Yan X, Ito K, Yuasa S, Ieda M, Urade Y, Suematsu M, Fukuda K, Sano M.** Endogenous prostaglandin D2 and its metabolites protect the heart against ischemia-reperfusion injury by activating Nrf2. *Hypertension* 63: 80–87, 2014. doi:10.1161/HYPERTENSIONAHA.113.01639.
93. **Keenan A, Pedersen TL, Fillaus K, Larson MK, Shearer GC, Newman JW.** Basal omega-3 fatty acid status affects fatty acid and oxylipin responses to high-dose *n*3-HUFA in healthy volunteers. *J Lipid Res* 53: 1662–1669, 2014. doi:10.1194/jlr.P025577.
94. **Keleshian VL, Modi HR, Rapoport SI, Rao JS.** Aging is associated with altered inflammatory, arachidonic acid cascade, and synaptic markers, influenced by epigenetic modifications, in the human frontal cortex. *J Neurochem* 125: 63–73, 2013. doi:10.1111/jnc.12153.
95. **Khalesi S, Irwin C, Schubert M.** Flaxseed consumption may reduce blood pressure: a systematic review and meta-analysis of controlled trials. *J Nutr* 145: 758–765, 2015. doi:10.3945/jn.114.205302.
96. **Kim JW, Zou Y, Yoon S, Lee JH, Kim YK, Yu BP, Chung HY.** Vascular aging: molecular modulation of the prostanoid cascade by calorie restriction. *J Gerontol A Biol Sci Med Sci* 59: B876–B885, 2004. doi:10.1093/gerona/59.9.B876.
97. **Kobzar G, Mardla V, Järving I, Samel N.** Comparison of anti-aggregatory effects of PGI_2, PGI_3 and iloprost on human and rabbit platelets. *Cell Physiol Biochem* 11: 279–284, 2001. doi:10.1159/000047814.
98. **Koeppen B, Stanton B.** Cellular physiology. In: *Berne & Levy Physiology* (6th ed.), edited by Koeppen B, Stanton B. Philadelphia, PA: Mosby Elsevier, 2010, p. 1–51.
99. **Koga T, Takata Y, Kobayashi K, Takishita S, Yamashita Y, Fujishima M.** Age and hypertension promote endothelium-dependent contractions to acetylcholine in the aorta of the rat. *Hypertension* 14: 542–548, 1989. doi:10.1161/01.HYP.14.5.542.
100. **Konkel A, Schunck WH.** Role of cytochrome P450 enzymes in the bioactivation of polyunsaturated fatty acids. *Biochim Biophys Acta* 1814: 210–222, 2011. doi:10.1016/j.bbapap.2010.09.009.
101. **Kopkan L, Husková Z, Sporková A, Varcabová Š, Honetschlägerová Z, Hwang SH, Tsai HJ, Hammock BD, Imig JD, Kramer HJ, Bürgelová M, Vojtíšková A, Kujal P, Vernerová Z, Červenka L.** Soluble epoxide hydrolase inhibition exhibits antihypertensive actions independently of nitric oxide in mice with renovascular hypertension. *Kidney Blood Press Res* 35: 595–607, 2012. doi:10.1159/000339883.
102. **Krämer HJ, Stevens J, Grimminger F, Seeger W.** Fish oil fatty acids and human platelets: dose-dependent decrease in dienoic and increase in trienoic thromboxane generation. *Biochem Pharmacol* 52: 1211–1217, 1996. doi:10.1016/0006-2952(96)00473-X.
103. **Ku G, Thomas CE, Akeson AL, Jackson RL.** Induction of interleukin 1 beta expression from human peripheral blood monocyte-derived macrophages by 9-hydroxyoctadecadienoic acid. *J Biol Chem* 267: 14183–14188, 1992.
104. **Kuhn H, Banthiya S, van Leyen K.** Mammalian lipoxygenases and their biological relevance. *Biochim Biophys Acta* 1851: 308–330, 2015. doi:10.1016/j.bbalip.2014.10.002.
105. **Kulkarni PS, Roberts R, Needleman P.** Paradoxical endogenous synthesis of a coronary dilating substance from arachidonate. *Prostaglandins* 12: 337–353, 1976. doi:10.1016/0090-6980(76)90015-0.
106. **Lauterbach B, Barbosa-Sicard E, Wang MH, Honeck H, Kargel E, Theuer J, Schwartzman ML, Haller H, Luft FC, Gollasch M, Schunck WH.** Cytochrome P450-dependent eicosapentaenoic acid metabolites are novel BK channel activators. *Hypertension* 39: 609–613, 2002.
107. **Lee AR, Pechenino AS, Dong H, Hammock BD, Knowlton AA.** Aging, estrogen loss and epoxyeicosatrienoic acids (EETs). *PLoS One* 8: e70719, 2013. doi:10.1371/journal.pone.0070719.
108. **Lee TH, Menica-Huerta JM, Shih C, Corey EJ, Lewis RA, Austen KF.** Characterization and biologic properties of 5,12-dihydroxy derivatives of eicosapentaenoic acid, including leukotriene B5 and the double lipoxygenase product. *J Biol Chem* 259: 2383–2389, 1984.
109. **Lemaitre RN, Rice K, Marciante K, Bis JC, Lumley TS, Wiggins KL, Smith NL, Heckbert SR, Psaty BM.** Variation in eicosanoid genes, non-fatal myocardial infarction and ischemic stroke. *Atherosclerosis* 204: e58–e63, 2009. doi:10.1016/j.atherosclerosis.2008.10.011.
110. **Leng S, Winter T, Aukema HM.** Dietary linoleic acid and sex effects on oxylipin profiles in rat kidney, liver and serum differ from their effects on polyunsaturated fatty acids. *J Lipid Res* 58:1702–1712, 2017. doi:10.1194/jlr.M078097.
111. **Li X, Hong S, Li P-L, Zhang Y.** Docosahexanoic acid-induced coronary arterial dilation: actions of 17*S*-hydroxy docosahexanoic acid on K^+ channel activity. *J Pharmacol Exp Ther* 336: 891–899, 2011. doi:10.1124/jpet.110.176461.
112. **Liu SZ, Jemiolo B, Lavin KM, Lester BE, Trappe SW, Trappe TA.** Prostaglandin E2/cyclooxygenase pathway in human skeletal muscle: influence of muscle fiber type and age. *J Appl Physiol* 120: 546–551, 2016. doi:10.1152/japplphysiol.00396.2015.
113. **Lundström SL, Yang J, Källberg HJ, Thunberg S, Gafvelin G, Haeggström JZ, Grönneberg R, Grunewald J, van Hage M, Hammock BD, Eklund A, Wheelock AM, Wheelock CE.** Allergic asthmatics show divergent lipid mediator profiles from healthy controls both at baseline and following birch pollen provocation. *PLoS One* 7: e33780, 2012. doi:10.1371/journal.pone.0033780.
114. **Ma YH, Gebremedhin D, Schwartzman ML, Falck JR, Clark JE, Masters BS, Harder DR, Roman RJ.** 20-Hydroxyeicosatetraenoic acid is an endogenous vasoconstrictor of canine renal arcuate arteries. *Circ Res* 72: 126–136, 1993. doi:10.1161/01.RES.72.1.126.

115. **Manev H, Uz T, Sugaya K, Qu T.** Putative role of neuronal 5-lipoxygenase in an aging brain. *FASEB J* 14: 1464–1469, 2000. doi:10.1096/fj.14.10.1464.
116. **Marmol F, Puig-Parellada P, Sanchez J, Trullas R.** Influence of aging on thromboxane A2 and prostacyclin levels in rat hippocampal brain slices. *Neurobiol Aging* 20: 695–697, 1999. doi:10.1016/S0197-4580(99)00069-X.
117. **Marx N, Bourcier T, Sukhova GK, Libby P, Plutzky J.** PPARgamma activation in human endothelial cells increases plasminogen activator inhibitor type-1 expression: PPARgamma as a potential mediator in vascular disease. *Arterioscler Thromb Vasc Biol* 19: 546–551, 1999. doi:10.1161/01.ATV.19.3.546.
118. **Matz RL, de Sotomayor MA, Schott C, Stoclet JC, Andriantsitohaina R.** Vascular bed heterogeneity in age-related endothelial dysfunction with respect to NO and eicosanoids. *Br J Pharmacol* 131: 303–311, 2000. doi:10.1038/sj.bjp.0703568.
119. **McLaughlin VV, Genthner DE, Panella MM, Rich S.** Reduction in pulmonary vascular resistance with long-term epoprostenol (prostacyclin) therapy in primary pulmonary hypertension. *N Engl J Med* 338: 273–277, 1998. doi:10.1056/NEJM199801293380501.
120. **Mendez M, LaPointe MC.** PGE2-induced hypertrophy of cardiac myocytes involves EP4 receptor-dependent activation of p42/44 MAPK and EGFR transactivation. *Am J Physiol Heart Circ Physiol* 288: H2111–H2117, 2005. doi:10.1152/ajpheart.00838.2004.
121. **Meydani SN, Shapiro AC, Meydani M, Blumberg JB.** Lung eicosanoid synthesis is affected by age, dietary fat and vitamin E. *J Nutr* 122: 1627–1633, 1992.
122. **Mickleborough TD, Lindley MR, Ionescu AA, Fly AD.** Protective effect of fish oil supplementation on exercise-induced bronchoconstriction in asthma. *Chest* 129: 39–49, 2006. doi:10.1378/chest.129.1.39.
123. **Miller AM, van Bekkum DW, Kobb SM, McCrohan MB, Knaan-Shanzer S.** Dietary fish oil supplementation alters LTB4:LTB5 ratios but does not affect the expression of acute graft versus host disease in mice. *Prostaglandins Leukot Essent Fatty Acids* 49: 561–568, 1993. doi:10.1016/0952-3278(93)90161-O.
124. **Moller K, Ostermann AI, Rund K, Thoms S, Blume C, Stahl F, Hahn A, Schebb NH, Schuchardt JP.** Influence of weight reduction on blood levels of C-reactive protein, tumor necrosis factor-α, interleukin-6, and oxylipins in obese subjects. *Prostaglandins Leukot Essent Fatty Acids* 106: 39–49, 2016. doi:10.1016/j.plefa.2015.12.001.
125. **Moran JH, Weise R, Schnellmann RG, Freeman JP, Grant DF.** Cytotoxicity of linoleic acid diols to renal proximal tubular cells. *Toxicol Appl Pharmacol* 146: 53–59, 1997. doi:10.1006/taap.1997.8197.
126. **Morita I, Murota S.** Effect of aging on the prostaglandin-synthesizing system in rat liver. *Prostaglandins Med* 4: 45–52, 1980. doi:10.1016/0161-4630(80)90062-2.
127. **Mukherjee D, Nissen SE, Topol EJ.** Risk of cardiovascular events associated with selective COX-2 inhibitors. *JAMA* 286: 954–959, 2001. doi:10.1001/jama.286.8.954.
128. **Musiek ES, Yin H, Milne GL, Morrow JD.** Recent advances in the biochemistry and clinical relevance of the isoprostane pathway. *Lipids* 40: 987–994, 2005. doi:10.1007/s11745-005-1460-7.
129. **Nakajima M, Hashimoto M, Wang F, Yamanaga K, Nakamura N, Uchida T, Yamanouchi K.** Aging decreases the production of PGI_2 in rat aortic endothelial cells. *Exp Gerontol* 32: 685–693, 1997. doi:10.1016/S0531-5565(97)00089-2.
130. **Nakamura A, Nagaya N, Obata H, Sakai K, Sakai Y, Yoshikawa M, Hamada K, Matsumoto K, Kimura H.** Oral administration of a novel long-acting prostacyclin agonist with thromboxane synthase inhibitory activity for pulmonary arterial hypertension. *Circ J* 77: 2127–2133, 2013. doi:10.1253/circj.CJ-13-0107.
131. **Nakao J, Ito H, Koshihara Y, Murota S.** Age-related increase in the migration of aortic smooth muscle cells induced by 12-L-hydroxy-5,8,10,14-eicosatetranoic acid. *Atherosclerosis* 51: 179–187, 1984. doi:10.1016/0021-9150(84)90166-7.
132. **Neckář J, Kopkan L, Husková Z, Kolář F, Papoušek F, Kramer HJ, Hwang SH, Hammock BD, Imig JD, Malý J, Netuka I, Ošťádal B, Červenka L.** Inhibition of soluble epoxide hydrolase by *cis*-4-[4-(3-adamantan-1-ylureido)cyclohexyl-oxy]benzoic acid exhibits antihypertensive and cardioprotective actions in transgenic rats with angiotensin II-dependent hypertension. *Clin Sci (Lond)* 122: 513–525, 2012. doi:10.1042/CS20110622.
133. **Needleman P, Raz A, Minkes MS, Ferrendelli JA, Sprecher H.** Triene prostaglandins: prostacyclin and thromboxane biosynthesis and unique biological properties. *Proc Natl Acad Sci USA* 76: 944–948, 1979. doi:10.1073/pnas.76.2.944.
134. **Nelson DR, Zeldin DC, Hoffman SM, Maltais LJ, Wain HM, Nebert DW.** Comparison of cytochrome P450 (CYP) genes from the mouse and human genomes, including nomenclature recommendations for genes, pseudogenes and alternative-splice variants. *Pharmacogenetics* 14: 1–18, 2004. doi:10.1097/00008571-200401000-00001.
135. **Node K, Huo Y, Ruan X, Yang B, Spiecker M, Ley K, Zeldin DC, Liao JK.** Anti-inflammatory properties of cytochrome P450 epoxygenase-derived eicosanoids. *Science* 285: 1276–1279, 1999.
136. **Novella S, Dantas AP, Segarra G, Novensa L, Heras M, Hermenegildo C, Medina P.** Aging enhances contraction to thromboxane A_2 in aorta from female senescence-accelerated mice. *Age (Dordr)* 35: 117–128, 2013. doi:10.1007/s11357-011-9337-y.
137. **Oh SF, Pillai PS, Recchiuti A, Yang R, Serhan CN.** Pro-resolving actions and stereoselective biosynthesis of 18S E-series resolvins in human leukocytes and murine inflammation. *J Clin Invest* 121: 569–581, 2011. doi:10.1172/JCI42545.
138. **Oliw EH, Sprecher HW.** Metabolism of polyunsaturated (*n*-3) fatty acids by monkey seminal vesicles: isolation and biosynthesis of omega-3 epoxides. *Biochim Biophys Acta* 1086: 287–294, 1991. doi:10.1016/0005-2760(91)90172-E.
139. **Oltman CL, Weintraub NL, VanRollins M, Dellsperger KC.** Epoxyeicosatrienoic acids and dihydroxyeicosatrienoic acids are potent vasodilators in the canine coronary microcirculation. *Circ Res* 83: 932–939, 1998. doi:10.1161/01.RES.83.9.932.
140. **Omata K, Abraham NG, Escalante B, Schwartzman ML.** Age-related changes in renal cytochrome P-450 arachidonic acid metabolism in spontaneously hypertensive rats. *Am J Physiol* 262: F8–F16, 1992.
141. **Ozawa T, Sugiyama S, Hayakawa M, Satake T, Taki F, Iwata M, Taki K.** Existence of leukotoxin 9,10-epoxy-12-octadecenoate in lung lavages from rats breathing pure oxygen and from patients with the adult respiratory distress syndrome. *Am Rev Respir Dis* 137: 535–540, 1988. doi:10.1164/ajrccm/137.3.535.
142. **Pace-Asciak CR.** Pathophysiology of the hepoxilins. *Biochim Biophys Acta* 1851: 383–396, 2015. doi:10.1016/j.bbalip.2014.09.007.
143. **Parkening TA, LaGrone LF, Brouhard BH.** Concentrations of prostaglandins in plasma, seminal vesicles, and ovaries of aging C57BL/6NNia mice. *Exp Gerontol* 20: 291–294, 1985. doi:10.1016/0531-5565(85)90055-5.
144. **Patrono C.** Cardiovascular effects of nonsteroidal anti-inflammatory drugs. *Curr Cardiol Rep* 18: 25, 2016. doi:10.1007/s11886-016-0702-4.
145. **Patwardhan AM, Akopian AN, Ruparel NB, Diogenes A, Weintraub ST, Uhlson C, Murphy RC, Hargreaves KM.** Heat generates oxidized linoleic acid metabolites that activate TRPV1 and produce pain in rodents. *J Clin Invest* 120: 1617–1626, 2010. doi:10.1172/JCI41678.
146. **Petrich K, Ludwig P, Kühn H, Schewe T.** The suppression of 5-lipoxygenation of arachidonic acid in human polymorphonuclear leucocytes by the 15-lipoxygenase product (15*S*)-hydroxy-(5*Z*,8*Z*,11*Z*,13*E*)-eicosatetraenoic acid: structure-activity relationship and mechanism of action. *Biochem J* 314: 911–916, 1996. doi:10.1042/bj3140911.
147. **Powell WS, Gravel S, Gravelle F.** Formation of a 5-oxo metabolite of 5,8,11,14,17-eicosapentaenoic acid and its effects on human neutrophils and eosinophils. *J Lipid Res* 36: 2590–2598, 1995.
148. **Psychogios N, Hau DD, Peng J, Guo AC, Mandal R, Bouatra S, Sinelnikov I, Krishnamurthy R, Eisner R, Gautam B, Young N, Xia J, Knox C, Dong E, Huang P, Hollander Z, Pedersen TL, Smith SR, Bamforth F, Greiner R, McManus B, Newman JW, Goodfriend T, Wishart DS.** The human serum metabolome. *PLoS One* 6: e16957, 2011. doi:10.1371/journal.pone.0016957.
149. **Qu T, Uz T, Manev H.** Inflammatory 5-LOX mRNA and protein are increased in brain of aging rats. *Neurobiol Aging* 21: 647–652, 2000. doi:10.1016/S0197-4580(00)00167-6.
150. **Ramsden CE, Ringel A, Majchrzak-Hong SF, Yang J, Blanchard H, Zamora D, Loewke JD, Rapoport SI, Hibbeln JR, Davis JM, Hammock BD, Taha AY.** Dietary linoleic acid-induced alterations in pro-and anti-nociceptive lipid autacoids: implications for idiopathic pain syndromes? *Mol Pain* 12: 1744806916636386, 2016. doi:10.1177/1744806916636386.
151. **Randriamboavonjy V, Busse R, Fleming I.** 20-HETE-induced contraction of small coronary arteries depends on the activation of Rho-kinase. *Hypertension* 41: 801–806, 2003. doi:10.1161/01.HYP.0000047240.33861.6B.

152. **Rangel-Huerta OD, Gil A.** Omega 3 fatty acids in cardiovascular disease risk factors: an updated systematic review of randomised clinical trials. *Clin Nutr.* In press. doi:10.1016/j.clnu.2017.05.015.
153. **Reed KA, Tucker DE, Aloulou A, Adler D, Ghomashchi F, Gelb MH, Leslie CC, Oates JA, Boutaud O.** Functional characterization of mutations in inherited human cPLA$_2$ deficiency. *Biochemistry* 50: 1731–1738, 2011. doi:10.1021/bi101877n.
154. **Ridker PM, Cook NR, Lee IM, Gordon D, Gaziano JM, Manson JE, Hennekens CH, Buring JE.** A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med* 352: 1293–1304, 2005. doi:10.1056/NEJMoa050613.
155. **Rizos EC, Elisaf MS.** Does supplementation with omega-3 PUFAs add to the prevention of cardiovascular disease? *Curr Cardiol Rep* 19: 47, 2017. doi:10.1007/s11886-017-0856-8.
156. **Rodriguez-Leyva D, Weighell W, Edel AL, LaVallee R, Dibrov E, Pinneker R, Maddaford TG, Ramjiawan B, Aliani M, Guzman R, Pierce GN.** Potent antihypertensive action of dietary flaxseed in hypertensive patients. *Hypertension* 62: 1081–1089, 2013. doi:10.1161/HYPERTENSIONAHA.113.02094.
157. **Roman RJ.** *P*-450 metabolites of arachidonic acid in the control of cardiovascular function. *Physiol Rev* 82: 131–185, 2002. doi:10.1152/physrev.00021.2001.
158. **Ryan VH, Primiani CT, Rao JS, Ahn K, Rapoport SI, Blanchard H.** Coordination of gene expression of arachidonic and docosahexaenoic acid cascade enzymes during human brain development and aging. *PLoS One* 9: e100858, 2014. doi:10.1371/journal.pone.0100858.
159. **Samuelsson B.** Leukotrienes: a new class of mediators of immediate hypersensitivity reactions and inflammation. *Adv Prostaglandin Thromboxane Leukot Res* 11: 1–13, 1983.
160. **Samuelsson B, Dahlén SE, Lindgren JA, Rouzer CA, Serhan CN.** Leukotrienes and lipoxins: structures, biosynthesis, and biological effects. *Science* 237: 1171–1176, 1987. doi:10.1126/science.2820055.
161. **Sato M, Yokoyama U, Fujita T, Okumura S, Ishikawa Y.** The roles of cytochrome p450 in ischemic heart disease. *Curr Drug Metab* 12: 526–532, 2011. doi:10.2174/138920011795713715.
162. **Schebb NH, Ostermann AI, Yang J, Hammock BD, Hahn A, Schuchardt, JP.** Comparison of the effects of long-chain omega-3 fatty acid supplementation on plasma levels of free and esterified oxylipins. *Prostaglandins Other Lipid Mediat* 113–115: 21–29, 2014. doi:10.1016/j.prostaglandins.2014.05.002.
163. **Schuchardt JP, Schmidt S, Kressel G, Dong H, Willenberg I, Hammock BD, Hahn A, Schebb NH.** Comparison of free serum oxylipin concentrations in hyper- vs. normolipidemic men. *Prostaglandins Leukot Essent Fatty Acids* 89: 19–29, 2013. doi:10.1016/j.plefa.2013.04.001.
164. **Schuchardt JP, Schmidt S, Kressel G, Willenberg I, Hammock BD, Hahn A, Schebb NH.** Modulation of blood oxylipin levels by long-chain omega-3 fatty acid supplementation in hyper- and normolipidemic men. *Prostaglandins Leukot Essent Fatty Acids* 90: 27–37, 2014. doi:10.1016/j.plefa.2013.12.008.
165. **Schuchardt JP, Schneider I, Willenberg I, Yang J, Hammock BD, Hahn A, Schebb NH.** Increase of EPA-derived hydroxy, epoxy and dihydroxy fatty acid levels in human plasma after a single dose of long-chain omega-3 PUFA. *Prostaglandins Other Lipid Mediat* 109–111: 23–31, 2014. doi:10.1016/j.prostaglandins.2014.03.001.
166. **Sekiya F, Takagi J, Sasaki K, Kawajiri K, Kobayashi Y, Sato F, Saito Y.** Feedback regulation of platelet function by 12*S*-hydroxyeicosatetraenoic acid: inhibition of arachidonic acid liberation from phospholipids. *Biochim Biophys Acta* 1044: 165–168, 1990. doi:10.1016/0005-2760(90)90232-M.
167. **Sekiya F, Takagi J, Usui T, Kawajiri K, Kobayashi Y, Sato F, Saito Y.** 12*S*-hydroxyeicosatetraenoic acid plays a central role in the regulation of platelet activation. *Biochem Biophys Res Commun* 179: 345–351, 1991. doi:10.1016/0006-291X(91)91376-N.
168. **Serhan CN, Dalli J, Colas RA, Winkler JW, Chiang N.** Protectins and maresins: new pro-resolving families of mediators in acute inflammation and resolution bioactive metabolome. *Biochim Biophys Acta* 1851: 397–413, 2015. doi:10.1016/j.bbalip.2014.08.006.
169. **Serhan CN, Krishnamoorthy S, Recchiuti A, Chiang N.** Novel anti-inflammatory-pro-resolving mediators and their receptors. *Curr Top Med Chem* 11: 629–647, 2011. doi:10.2174/1568026611109060629.
170. **Serhan CN, Petasis NA.** Resolvins and protectins in inflammation resolution. *Chem Rev* 111: 5922–5943, 2011. doi:10.1021/cr100396c.
171. **Setty BN, Werner MH, Hannun YA, Stuart MJ.** 15-Hydroxyeicosatetraenoic acid-mediated potentiation of thrombin-induced platelet functions occurs via enhanced production of phosphoinositide-derived second messengers−*sn*-1,2-diacylglycerol and inositol-1,4,5-trisphosphate. *Blood* 80: 2765–2773, 1992.
172. **Seubert J, Yang B, Bradbury JA, Graves J, Degraff LM, Gabel S, Gooch R, Foley J, Newman J, Mao L, Rockman HA, Hammock BD, Murphy E, Zeldin DC.** Enhanced postischemic functional recovery in CYP2J2 transgenic hearts involves mitochondrial ATP-sensitive K^+ channels and p42/p44 MAPK pathway. *Circ Res* 95: 506–514, 2004. doi:10.1161/01.RES.0000139436.89654.c8.
173. **Shahabi P, Siest G, Meyer UA, Visvikis-Siest S.** Human cytochrome P450 epoxygenases: variability in expression and role in inflammation-related disorders. *Pharmacol Ther* 144: 134–161, 2014. doi:10.1016/j.pharmthera.2014.05.011.
174. **Shearer GC, Newman JW.** Impact of circulating esterified eicosanoids and other oxylipins on endothelial function. *Curr Atheroscler Rep* 11: 403–410, 2009. doi:10.1007/s11883-009-0061-3.
175. **Shureiqi I, Wojno KJ, Poore JA, Reddy RG, Moussalli MJ, Spindler SA, Greenson JK, Normolle D, Hasan AA, Lawrence TS, Brenner DE.** Decreased 13*S*-hydroxyoctadecadienoic acid levels and 15-lipoxygenase-1 expression in human colon cancers. *Carcinogenesis* 20: 1985–1995, 1999. doi:10.1093/carcin/20.10.1985.
176. **Silva BC, de Miranda AS, Rodrigues FG, Silveira AL, Resende GH, Moraes MF, de Oliveira AC, Parreiras PM, Barcelos LS, Teixeira MM, Machado FS, Teixeira AL, Rachid MA.** The 5-lipoxygenase (5-LOX) inhibitor zileuton reduces inflammation and infarct size with improvement in neurological outcome following cerebral ischemia. *Curr Neurovasc Res* 12: 398–403, 2015. doi:10.2174/1567202612666150812150606.
177. **Siscovick DS, Barringer TA, Fretts AM, Wu JH, Lichtenstein AH, Costello RB, Kris-Etherton PM, Jacobson TA, Engler MB, Alger HM, Appel LJ, Mozaffarian D; American Heart Association Nutrition Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Epidemiology and Prevention; Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; and Council on Clinical Cardiology.** Omega-3 polyunsaturated fatty acid (fish oil) supplementation and the prevention of clinical cardiovascular disease: a Science Advisory from the American Heart Association. *Circulation* 135: e867–e884, 2017. doi:10.1161/CIR.0000000000000482.
178. **Sisemore MF, Zheng J, Yang JC, Thompson DA, Plopper CG, Cortopassi GA, Hammock BD.** Cellular characterization of leukotoxin diol-induced mitochondrial dysfunction. *Arch Biochem Biophys* 392: 32–37, 2001. doi:10.1006/abbi.2001.2434.
179. **Smith RJ, Justen JM, Nidy EG, Sam LM, Bleasdale JE.** Transmembrane signaling in human polymorphonuclear neutrophils: 15(*S*)-hydroxy-(5*Z*,8*Z*,11*Z*,13*E*)-eicosatetraenoic acid modulates receptor agonist-triggered cell activation. *Proc Natl Acad Sci USA* 90: 7270–7274, 1993. doi:10.1073/pnas.90.15.7270.
180. **Smith WL, Urade Y, Jakobsson PJ.** Enzymes of the cyclooxygenase pathways of prostanoid biosynthesis. *Chem Rev* 111: 5821–5865, 2011. doi:10.1021/cr2002992.
181. **Spector AA, Fang X, Snyder GD, Weintraub NL.** Epoxyeicosatrienoic acids (EETs): metabolism and biochemical function. *Prog Lipid Res* 43: 55–90, 2004. doi:10.1016/S0163-7827(03)00049-3.
182. **Spector AA, Kim HY.** Cytochrome P450 epoxygenase pathway of polyunsaturated fatty acid metabolism. *Biochim Biophys Acta* 1851: 356–365, 2015. doi:10.1016/j.bbalip.2014.07.020.
183. **Spite M, Serhan CN.** Novel lipid mediators promote resolution of acute inflammation: impact of aspirin and statins. *Circ Res* 107: 1170–1184, 2010. doi:10.1161/CIRCRESAHA.110.223883.

183a. **Steering Committee of the Physicians' Health Study Research Group.** Preliminary report: findings from the aspirin component of the ongoing physicians' health study. *N Engl J Med* 318: 262–264, 1988.

184. **Strassburg K, Esser D, Vreeken RJ, Hankemeier T, Müller M, van Duynhoven J, van Golde J, van Dijk SJ, Afman LA, Jacobs DM.** Postprandial fatty acid specific changes in circulating oxylipins in lean and obese men after high-fat challenge tests. *Mol Nutr Food Res* 58: 591–600, 2014. doi:10.1002/mnfr.201300321.
185. **Sultana C, Shen Y, Rattan V, Kalra VK.** Lipoxygenase metabolites induced expression of adhesion molecules and transendothelial migration of monocyte-like HL-60 cells is linked to protein kinase C activation. *J Cell Physiol* 167: 477–487, 1996. doi:10.1002/(SICI)1097-4652(199606)167:3<477::AID-JCP12>3.0.CO;2-1.

186. **Sun C, Simon SI, Foster GA, Radecke CE, Hwang HV, Zhang X, Hammock BD, Chiamvimonvat N, Knowlton AA.** 11,12-Epoxyecosatrienoic acids mitigate endothelial dysfunction associated with estrogen loss and aging: Role of membrane depolarization. *J Mol Cell Cardiol* 94: 180–188, 2016. doi:10.1016/j.yjmcc.2016.03.019.
187. **Tada M, Kuzuya T, Inoue M, Kodama K, Mishima M, Yamada M, Inui M, Abe H.** Elevation of thromboxane B2 levels in patients with classic and variant angina Pectoris. *Circulation* 64: 1107–1115, 1981. doi:10.1161/01.CIR.64.6.1107.
188. **Taha AY, Blanchard HC, Cheon Y, Ramadan E, Chen M, Chang L, Rapoport SI.** Dietary linoleic acid lowering reduces lipopolysaccharide-induced increase in brain arachidonic acid metabolism. *Mol Neurobiol* 54: 4303–4315, 2017. doi:10.1007/s12035-016-9968-1.
189. **Takenaga M, Hirai A, Terano T, Tamura Y, Kitagawa H, Yoshida S.** Comparison of the in vitro effect of eicosapentaenoic acid (EPA)-derived lipoxygenase metabolites on human platelet function with those of arachidonic acid. *Thromb Res* 41: 373–384, 1986. doi:10.1016/0049-3848(86)90248-3.
190. **Takata S, Papayianni A, Matsubara M, Jimenez W, Pronovost PH, Brady HR.** 15-Hydroxyeicosatetraenoic acid inhibits neutrophil migration across cytokine-activated endothelium. *Am J Pathol* 145: 541–549, 1994.
191. **Theken KN, Schuck RN, Edin ML, Tran B, Ellis K, Bass A, Lih FB, Tomer KB, Poloyac SM, Wu MC, Hinderliter AL, Zeldin DC, Stouffer GA, Lee CR.** Evaluation of cytochrome P450-derived eicosanoids in humans with stable atherosclerotic cardiovascular disease. *Atherosclerosis* 222: 530–536, 2012. doi:10.1016/j.atherosclerosis.2012.03.022.
192. **Tloti MA, Moon DG, Weston LK, Kaplan JE.** Effect of 13-hydroxyoctadeca-9,11-dienoic acid (13-HODE) on thrombin induced platelet adherence to endothelial cells in vitro. *Thromb Res* 62: 305–317, 1991. doi:10.1016/0049-3848(91)90151-L.
193. **Tohgi H, Konno S, Tamura K, Kimura B, Kawano K.** Effects of low-to-high doses of aspirin on platelet aggregability and metabolites of thromboxane A_2 and prostacyclin. *Stroke* 23: 1400–1403, 1992. doi:10.1161/01.STR.23.10.1400.
194. **Ueno R, Osama H, Urade Y, Hayaishi O.** Changes of enzymes involved in prostaglandin metabolism and prostaglandin binding proteins in rat brain during development and aging. *J Neurochem* 45: 483–489, 1985. doi:10.1111/j.1471-4159.1985.tb04014.x.
195. **Ungvari Z, Kaley G, de Cabo R, Sonntag WE, Csiszar A.** Mechanisms of vascular aging: new perspectives. *J Gerontol A Biol Sci Med Sci* 65: 1028–1041, 2010. doi:10.1093/gerona/glq113.
196. **United States Food and Drug Administration.** *Resources for Information on Approved Drugs*; https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ [6 July 2017].
197. **Uz T, Pesold C, Longone P, Manev H.** Aging-associated up-regulation of neuronal 5-lipoxygenase expression: putative role in neuronal vulnerability. *FASEB J* 12: 439–449, 1998.
198. **Valone FH, Franklin M, Sun FF, Goetzl EJ.** Alveolar macrophage lipoxygenase products of arachidonic acid: isolation and recognition as the predominant constituents of the neutrophil chemotactic activity elaborated by alveolar macrophages. *Cell Immunol* 54: 390–401, 1980. doi:10.1016/0008-8749(80)90219-1.
199. **Van Diemen JJ, Fuijkschot WW, Wessels TJ, Veen G, Smulders YM, Thijs A.** Evening intake of aspirin is associated with a more stable 24-h platelet inhibition compared to morning intake: a study in chronic aspirin users. *Platelets* 27: 1–6, 2015. doi:10.3109/09537104.2015.1107536.
200. **VanRollins M.** Epoxygenase metabolites of docosahexaenoic and eicosapentaenoic acids inhibit platelet aggregation at concentrations below those affecting thromboxane synthesis. *J Pharmacol Exp Ther* 274: 798–804, 1995.
201. **VanRollins M, Baker RC, Sprecher HW, Murphy RC.** Oxidation of docosahexaenoic acid by rat liver microsomes. *J Biol Chem* 259: 5776–5783, 1984.
202. **VanRollins M, Murphy RC.** Autooxidation of docosahexaenoic acid: analysis of ten isomers of hydroxydocosahexaenoate. *J Lipid Res* 25: 507–517, 1984.
203. **Varga Z, Sabzwari SRA, Vargova V.** Cardiovascular eisk of nonsteroidal anti-inflammatory drugs: an under-recognized public health issue. *Cureus* 9: e1144, 2017. 0.7759/cureus.1144.
204. **Vericel E, Croset M, Sedivy P, Courpron P, Dechavanne M, Lagarde M.** Platelets and aging. I−Aggregation, arachidonate metabolism and antioxidant status. *Thromb Res* 49: 331–342, 1988. doi:10.1016/0049-3848(88)90313-1.
205. **Viswanathan S, Hammock BD, Newman JW, Meerarani P, Toborek M, Hennig B.** Involvement of CYP 2C9 in mediating the proinflammatory effects of linoleic acid in vascular endothelial cells. *J Am Coll Nutr* 22: 502–510, 2003. doi:10.1080/07315724.2003.10719328.
206. **Wada M, DeLong CJ, Hong YH, Rieke CJ, Song I, Sidhu RS, Yuan C, Warnock M, Schmaier AH, Yokoyama C, Smyth EM, Wilson SJ, FitzGerald GA, Garavito RM, Sui X, Regan JW, Smith WL.** Enzymes and receptors of prostaglandin pathways with arachidonic acid-derived versus eicosapentaenoic acid-derived substrates and products. *J Biol Chem* 282: 22254–22266, 2007. doi:10.1074/jbc.M703169200.
207. **Wakefield AP, Ogborn MR, Ibrahim N, Aukema HM.** A dietary conjugated linoleic acid treatment that slows renal disease progression alters renal cyclooxygenase-2-derived prostanoids in the Han: SPRD-cy rat. *J Nutr Biochem* 23: 908–914, 2012. doi:10.1016/j.jnutbio.2011.04.016.
208. **Wang X, Ni L, Yang L, Duan Q, Chen C, Edin ML, Zeldin DC, Wang DW.** CYP2J2-derived epoxyeicosatrienoic acids suppress endoplasmic reticulum stress in heart failure. *Mol Pharmacol* 85: 105–115, 2014. doi:10.1124/mol.113.087122.
209. **Wang Z, Gorski JC, Hamman MA, Huang SM, Lesko LJ, Hall SD.** The effects of St John's wort (*Hypericum perforatum*) on human cytochrome P450 activity. *Clin Pharmacol Ther* 70: 317–326, 2001. doi:10.1016/S0009-9236(01)17221-8.
210. **Westphal C, Konkel A, Schunck WH.** CYP-eicosanoids−a new link between omega-3 fatty acids and cardiac disease? *Prostaglandins Other Lipid Mediat* 96: 99–108, 2011. doi:10.1016/j.prostaglandins.2011.09.001.
211. **Westphal C, Konkel A, Schunck WH.** Cytochrome P450 enzymes in the bioactivation of polyunsaturated fatty acids and their role in cardiovascular disease. *Adv Exp Med Biol* 851: 151–187, 2015. doi:10.1007/978-3-319-16009-2_6.
212. **Whitaker MO, Wyche A, Fitzpatrick F, Sprecher H, Needleman P.** Triene prostaglandins: prostaglandin D_3 and icosapentaenoic acid as potential antithrombotic substances. *Proc Natl Acad Sci USA* 76: 5919–5923, 1979. doi:10.1073/pnas.76.11.5919.
213. **White PJ, St-Pierre P, Charbonneau A, Mitchell PL, St-Amand E, Marcotte B, Marette A.** Protectin DX alleviates insulin resistance by activating a myokine-liver glucoregulatory axis. *Nat Med* 20: 664–669, 2014. doi:10.1038/nm.3549.
214. **Wong SL, Leung FP, Lau CW, Au CL, Yung LM, Yao X, Chen ZY, Vanhoutte PM, Gollasch M, Huang Y.** Cyclooxygenase-2-derived prostaglandin F_{2alpha} mediates endothelium-dependent contractions in the aortae of hamsters with increased impact during aging. *Circ Res* 104: 228–235, 2009. doi:10.1161/CIRCRESAHA.108.179770.
215. **Wu S, Chen W, Murphy E, Gabel S, Tomer KB, Foley J, Steenbergen C, Falck JR, Moomaw CR, Zeldin DC.** Molecular cloning, expression, and functional significance of a cytochrome P450 highly expressed in rat heart myocytes. *J Biol Chem* 272: 12551–12559, 1997. doi:10.1074/jbc.272.19.12551.
216. **Yang C, Yang J, Xu X, Yan S, Pan S, Pan X, Zhang C, Leung GP.** Vasodilatory effect of 14,15-epoxyeicosatrienoic acid on mesenteric arteries in hypertensive and aged rats. *Prostaglandins Other Lipid Mediat* 112: 1–8, 2014. doi:10.1016/j.prostaglandins.2014.05.001.
217. **Ye D, Zhang D, Oltman C, Dellsperger K, Lee HC, VanRollins M.** Cytochrome *P*-450 epoxygenase metabolites of docosahexaenoate potently dilate coronary arterioles by activating large-conductance calcium-activated potassium channels. *J Pharmacol Exp Ther* 303: 768–776, 2002. doi:10.1124/jpet.303.2.768.
218. **Zein CO, Lopez R, Fu X, Kirwan JP, Yerian LM, McCullough AJ, Hazen SL, Feldstein AE.** Pentoxifylline decreases oxidized lipid products in nonalcoholic steatohepatitis: new evidence on the potential therapeutic mechanism. *Hepatology* 56: 1291–1299, 2012. doi:10.1002/hep.25778.
219. **Zhang W, Nagao M, Takatori T, Iwadate K, Itakura Y, Yamada Y, Iwase H, Oono T.** Immunohistochemical dynamics of leukotoxin (9,10-epoxy-12-octadecenoic acid) in lungs of rats. *Int J Legal Med* 107: 174–178, 1995. doi:10.1007/BF01428400.
220. **Zhang J, Yang J, Chang X, Zhang C, Zhou H, Liu M.** Ozagrel for acute ischemic stroke: a meta-analysis of data from randomized controlled trials. *Neurol Res* 34: 346–353, 2012. doi:10.1179/1743132812Y.0000000022.

221. **Zhang W, Yang AL, Liao J, Li H, Dong H, Chung YT, Bai H, Matkowskyj KA, Hammock BD, Yang GY.** Soluble epoxide hydrolase gene deficiency or inhibition attenuates chronic active inflammatory bowel disease in IL-10(−/−) mice. *Dig Dis Sci* 57: 2580–2591, 2012. doi:10.1007/s10620-012-2217-1.
222. **Zheng J, Plopper CG, Lakritz J, Storms DH, Hammock BD.** Leukotoxin-diol: a putative toxic mediator involved in acute respiratory distress syndrome. *Am J Respir Cell Mol Biol* 25: 434–438, 2001. doi:10.1165/ajrcmb.25.4.4104.
223. **Ziboh VA, Miller CC, Cho Y.** Significance of lipoxygenase-derived monohydroxy fatty acids in cutaneous biology. *Prostaglandins Other Lipid Mediat* 63: 3–13, 2000. doi:10.1016/S0090-6980(00)00093-9.
224. **Zijlstra FJ, Vincent JE, Mol WM, Hoogsteden HC, Van Hal PT, Jongejan RC.** Eicosanoid levels in bronchoalveolar lavage fluid of young female smokers and non-smokers. *Eur J Clin Invest* 22: 301–306, 1992. doi:10.1111/j.1365-2362.1992.tb01466.x.
225. **Zulyniak MA, Roke K, Gerling C, Logan SL, Spriet LL, Mutch DM.** Fish oil regulates bloody fatty acid composition and oxylipin levels in healthy humans: a comparison of young and older men. *Mol Nutr Food Res* 60: 631–641, 2016. doi:10.1002/mnfr.201500830.