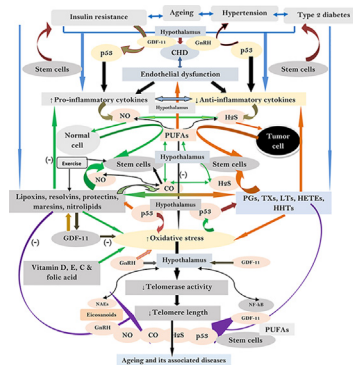Review

Ageing: Is there a role for arachidonic acid and other bioactive lipids? A review

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GRAPHICAL ABSTRACT

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ABSTRACT

Ageing is inevitable. Recent studies suggest that it could be delayed. Low-grade systemic inflammation is seen in type 2 diabetes mellitus, hypertension and endothelial dysfunction that are common with increasing age. In all these conditions, an alteration in arachidonic acid (AA) metabolism is seen in the form of increased formation of pro-inflammatory eicosanoids and decreased production of anti-inflammatory lipoxins, resolvins, protectins and maresins and decreased activity of desaturases. Calorie restriction, exercise and parabiosis delay age-related changes that could be related to enhanced proliferation of stem cells, decrease in inflammation and transfer of GDF-11 (growth differentiation factor-11) and other related molecules from the young to the old, increase in the formation of lipoxin A4, resolvins, protectins and maresins, hydrogen sulfide (H_2S) and nitric oxide (NO); inhibition of ageing-related hypothalamic or brain IKK-β and NF-kB activation, decreased gonadotropin-releasing hormone (GnRH) release resulting in increased neurogenesis and consequent decelerated ageing. This suggests that hypothalamus participates in ageing process. N-acylethanolamines (NAEs) and lipid-derived signalling molecules can be tuned favorably under dietary restriction to extend lifespan and/or prevent advanced age associated diseases in an mTOR dependent pathway manner. Sulfur amino acid (SAA) restriction increased hydrogen sulfide (H_2S) production and protected tissues from hypoxia and tissue damage. Anti-inflammatory metabolites formed from AA such as LXA4, resolvins, protectins and maresins enhance production of NO, CO, H_2S; suppress NF-kB expression and alter mTOR expression and thus, may aid in delaying ageing process. Dietary restriction and exercise enhance AA metabolism to form LXA4, resolvins, protectins and maresins that have anti-inflammatory actions. AA and their metabolites also influence stem cell biology, enhance neurogenesis to improve memory and augment autophagy to prolong life span. Thus, AA and other PUFAs and their anti-inflammatory metabolites inhibit inflammation, augment stem cell proliferation, restore to normal lipid-derived signaling molecules and NO and H_2S production, enhance autophagy and prolong life span.

Introduction

It is estimated that ~100,000 people die each day of age-related causes. Ageing seems to be inevitable and irreversible. Ageing is characterized by reduced ability to respond to both endogenous and exogenous stress, homeostatic imbalance and increased risk and incidence of various disease(s), changes that may ultimately result in death. But, recent studies are expanding our horizon of ageing and molecular mechanisms involved in it. Based on this new knowledge it is leading to the belief that like all other diseases, ageing also could be considered as a disease that can be either prevented or postponed and potentially treatable.

There is reasonable evidence to suggest that ageing is a low-grade systemic inflammatory condition [1–3] as evidenced by increased inflammatory cytokine production. This is supported by the observation that chronic, progressive low-grade inflammation induced by knockout of the nfkb1 subunit of the transcription factor NF-κB induces premature ageing in mice. These mice have reduced regeneration in liver and gut that may explain reduced or defective healing seen with advanced age. Furthermore, nfkb1(−/−) fibroblasts exhibited aggravated cell senescence that could be related to enhanced activity of NF-κB and COX-2 and ROS generation. It was reported that there is a major role for the NF-kB target COX-2 in instigating oxidative stress, which in turn contributes to induction and maintenance of telomere dysfunction by increasing oxidative stress at least partially through COX-2 activation [4]. Blocking this oxidative stress by anti-inflammatory or anti-oxidant treatment rescued tissue regeneration potential, suggesting that systemic chronic inflammation accelerates ageing via ROS-mediated exacerbation of telomere dysfunction and cell senescence in the absence of genetic or environmental factor [4]. These evidences suggest that methods designed to suppress inflammation, enhance telomere lengthening and enhance regenerative capacity could form a reasonable approach to the problem of ageing.

Telomere and ageing

Ageing is, at least partly, due to a genetic program and cellular senescence can be ascribed to the shortening of telomeres with each cell cycle. When telomeres become too short the cells die [5–7]. Hence, the length of telomeres is considered as the "molecular clock," of ageing process and it implies that maintaining or enhancing telomere length could prevent cell death and thus, may prevent ageing process itself.

Calorie restriction is one of the best-known interventions (~consuming calories 30–50% less than an *ad libitum* animal would consume, yet maintaining proper nutrient intake) to increase lifespan up to 50% though the increase in lifespan is effective only if the caloric restriction is started early in life. It is likely that calorie reduction mediates its action by reducing cellular growth and, therefore, the lengthening of the time between cell divisions.

Calorie restriction has anti-inflammatory actions as evidenced by the observation that it suppresses lipopolysaccharide (LPS)-induced release of pro-inflammatory cytokines (especially that of IL-6), blocks LPS-induced fever, and shifts hypothalamic signaling pathways to an anti-inflammatory bias. Furthermore, calorie restriction attenuated LPS-stimulated microglial activation in the hypothalamic arcuate nucleus (ARC) by upregulating the synthesis of neuropeptide Y (NPY), an orexigenic neuropeptide, that is upregulated which has anti-inflammatory properties [8–10].

Calorie restriction enhances the activity of delta-6-desaturase and delta-5-desaturase enzymes that are essential for the metabolism of dietary essential fatty acids: linoleic acid (LA, 18:2, n-6) and alpha-linolenic acid (ALA, 18:3n-3), leading to increase in the formation of their long-chain metabolites: gamma-linolenic acid (GLA, 18:3n-6), dihomo-GLA (DGLA, 20:3n-6) and arachidonic acid (AA, 20:4n-6) and eicosapentaenoic acid (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3), the precursors of several pro- and anti-inflammatory metabolites [11–15]. In contrast to this, consumption of high fat diet inhibits the activity of desaturases resulting in decreased levels of AA, EPA and DHA [16]. Since, dietary restriction (in the form of calorie restriction) enhances the availability of AA, EPA and DHA whereas high fat diet decreases their (AA, EPA and DHA) availability and calorie restriction has anti-inflammatory actions [8–10] as opposed to high fat diet ability to induce inflammation [17–19], this implies that increased concentrations of AA, EPA and DHA induced by dietary restriction leads to an increase in the synthesis of anti-inflammatory lipoxins, resolvins, protectins and maresins whereas high fat diet-induced decrease in the levels of AA, EPA and DHA somehow enhances formation of pro-inflammatory eicosanoids resulting in pro-inflammatory status. This is supported by the observation that high fat diet enhances the formation of pro-inflammatory eicosanoids such as leukotoxins {epoxyoctadecenoic acids (EpOMEs)} and prostaglandin E2 (PGE2) [20,21]. Thus, high fat diet-induced pro-inflammatory state enhances production of reactive oxygen species (ROS) that can produce telomere dysfunction and cell senescence [4], in addition to its capacity to induce obesity, type 2 diabetes mellitus, hypertension, hyperlipidemia and other features of metabolic syndrome [22,23]. In this context, it is noteworthy that telomere length is decreased in diabetes mellitus, hypertension, and correlates with the degree of endothelial dysfunction [24–40]. Thus, all age-related diseases and ageing are interrelated and indicates that some common approaches are possible in their prevention and management.

In this context, it is noteworthy that AA and other PUFAs and their metabolites play a significant role in the pathobiology of diabetes mellitus, hypertension, endothelial function, in the generation and action of nitric oxide (NO), carbon monoxide (CO) and hydrogen sulfide (H_2S). In addition, either directly or indirectly AA and other PUFAs and their metabolites seem to influence telomere length. It is noteworthy that various PUFAs and their metabolites have significant influence on inflammation and immune response and may also alter telomere length. Since endothelial dysfunction, diabetes mellitus and hypertension are low-grade systemic inflammatory conditions and are associated with significant changes in immune system, it is reasonable to suggest that a close interaction(s) exists among PUFAs and their metabolites (especially AA and its pro- and anti-inflammatory metabolites), NO, CO, H_2S, telomere length and ageing process. In this context, it is important that a brief review on the metabolism of AA is discussed.

AA metabolism

Essential fatty acids (EFAs) namely: *cis*-linoleic acid (18:2n-6) and α-linolenic acid (ALA, 18:3n-3), are also designated as polyunsaturated fatty acids (PUFAs) since they contain two or more double bonds. Although there are at least four independent families of PUFAs, only LA and ALA have significant physiological actions that are relevant to the present discussion. EFAS are essential for life and their deficiency may lead to skin abnormalities, dehydration, immunosuppression and ultimately lead to death. EFAs deficiency is rare since they are very widely distributed in human diet.

Both LA and ALA are acted upon by the enzymes: Δ^6 and Δ^5 desaturases to form their respective long-chain metabolites. Thus, LA is converted to gamma-linolenic acid (GLA, 18:3), dihomo-GLA (DGLA, 20:3) and AA (20:4); whereas ALA is converted to form eicosapentaenoic acid (EPA, 20:5) and docosahexaenoic acid (DHA, 22:6). It is noteworthy that many of the actions of LA and ALA can be brought about by GLA, DGLA, AA, EPA and DHA and hence, these long-chain metabolites of EFAS are also called as "functional EFAs". The importance of DGLA, AA, and EPA lies in the fact that they form precursors to 1 series prostaglandins (PGs) (derived from DGLA); 2 series of PGs, thromboxanes (TXs) and the 4 series of leukotrienes (LTs) (from AA) and 3 series of PGs, TXs and the 5 series of LTs (from EPA) respectively. PGs, TXs and LTs are generally pro-inflammatory in nature, though PGs and LTs derived from EPA are much less potent in their pro-inflammatory actions. It is important to note that AA also forms precursor to lipoxin A4 (LXA4), EPA gives rise to resolvins, and DHA (docosahexaenoic acid, 22:6, n-3 is derived from EPA) forms precursor to resolvins, protectins and maresins, which are all potent anti-inflammatory compounds [11,12,23,41–43]. For all practical purposes, LA, GLA, DGLA, AA, ALA, EPA, and DHA are all PUFAs, but only LA and ALA are EFAs. The fact that both pro-inflammatory (PGs, TXs, and LTs) and anti-inflammatory (LXA4, resolvins, protectins and maresins) are derived from the same precursors, it is likely that the balance between these products may determine the outcome of the inflammatory process in several diseases (see Fig. 1 for metabolism of EFAs). Thus, it is reasonable to propose that atherosclerosis, asthma, inflammatory bowel disease, rheumatoid arthritis, lupus, sepsis, cancer, depression, schizophrenia and other inflammatory conditions are due to an imbalance between the pro-inflammatory and anti-inflammatory molecules derived from DGLA, AA, EPA and DHA. Since ageing is also considered as an inflammatory condition, it is likely that there could occur an imbalance between PGs, LTs and TXs on one hand and LXA4, resolvins, protectins and maresins on the other. It is noteworthy that nitrolipids formed due to interaction between NO and various PUFAs (such as nitrolinoleate formed due to the nitration of linoleate by NO) stimulate smooth muscle relaxation, prevent platelet aggregation, and neutrophil pro-inflammatory functions [44–48]. Thus, it is not only PUFAs and their metabolites but also compounds that are formed as a result of interaction between PUFAs and NO are biologically active and have a significant role in various physiological and pathological processes.

Since LA and ALA (and also oleic acid: OA, a n-9 fatty acid) are acted upon by the same desaturases and elongases, there is bound to be a competition among these fatty acids for these enzymes. It is opined that desaturases and elongases prefer ω-3 to ω-6 and ω -6 over ω-9 (ω-3 > ω-6 > ω-9). It is well documented that presence of significant amounts of 20:3 ω-9 in the plasma and tissues is an indication of deficiency of ω-3 and ω-6 fatty acids. Since Δ^6 and Δ^5 desaturases are the rate limiting steps in the metabolism of LA and ALA, in conditions wherein the plasma and tissue levels of GLA, AA, EPA and DHA ae low, one need to consider reduced activity of these enzymes as a factor responsible for their low levels.

Phospholipase A2 (PLA2), a membrane bound enzyme, is needed for the release of DGLA, AA, EPA and DHA from cell membrane lipid pool for the formation of various PGs, LTs, TXs, LXA4, resolvins, protectins and maresins. Several hormones and growth factors act via G-protein coupled receptors (GPCRs) to activate PLA2. DGLA, AA, EPA and DHA are acted upon by cyclo-oxygenases, lipoxygenases and cytochrome P450 enzymes to form their respective metabolites. NO, CO and reactive oxygen species (ROS) have modulatory influence on the activity of P450 enzymes. Similar to PGs, LTs, TXs, LXA4, resolvins, protectins and maresins, products formed from DGLA, AA, EPA and DHA by the action of cytochrome P450 also function as second messengers to regulate vascular, renal and cardiac function. Of all the PUFAs, metabolism of AA seems to be complex and important (though that of EPA and DHA are no less complex) in view of their ability to give rise to variety of metabolites that have diametrically opposite actions (see Fig. 2 for metabolism of AA). For instance, LTs of 4 series are pro-inflammatory in nature while LXA4 has potent anti-inflammatory action, though all these metabolites are derived from AA. Thus, the balance between pro-inflammatory and anti-inflammatory products formed from AA are crucial to maintain homeostasis and prevent inappropriate inflammation. In view of this, it is reasonable to propose that inflammation may be initiated and perpetuated not simply because pro-inflammatory metabolites are synthesized and released but also because anti-inflammatory metabolites that suppress inflammation and induce resolution of inflammation from AA (and also from EPA and DHA) are not elaborated in adequate amounts. Thus, low-grade systemic inflammatory conditions such as obesity, type 2 diabetes mellitus, hypertension, coronary heart disease, non-alcoholic fatty liver disease (NAFLD), Alzheimer's disease, depression, schizophrenia, and ageing could be ascribed to decreased formation of anti-inflammatory bioactive lipids such as LXA4, resolvins, protectins and maresins that, in turn, could be due to decreased formation of AA, EPA and DHA from EFAs due to decreased activity of desaturases. In this context, it is interesting to note that in majority of these conditions, the activities of desaturases are altered, plasma and tissue content AA is low compared to that of EPA and DHA, plasma pro-inflammatory PGs and LTs are increased and anti-inflammatory LXA4, resolvins, and protectins are decreased [15,23,42,43,49–66] implying that the metabolism of EFAs are defective and of all, AA seems to be more crucial role in these diseases. It is important to note that in addition to alterations in the metabolism of AA, there could occur changes in the metabolism of EPA and DHA and their products. Thus, alterations in the metabolism of EFAs and AA, EPA and DHA in these diseases may lie in the activities of desaturases, elongases, PLA2, COX, LOX and P450 enzymes. Sometimes the defect may lie in the co-factors that are critical for the activities of desaturases.

Factors that modulate the activities of desaturases and elongases

It is known that the activities of desaturases and elongases are influenced by various dietary and other factors. For instance, the activities of desaturases and elongases are suppressed by saturated fats, cholesterol, trans-fatty acids, alcohol, adrenaline, and gluco-
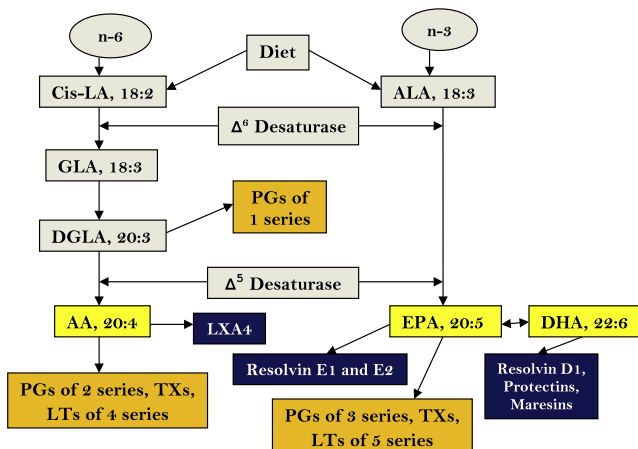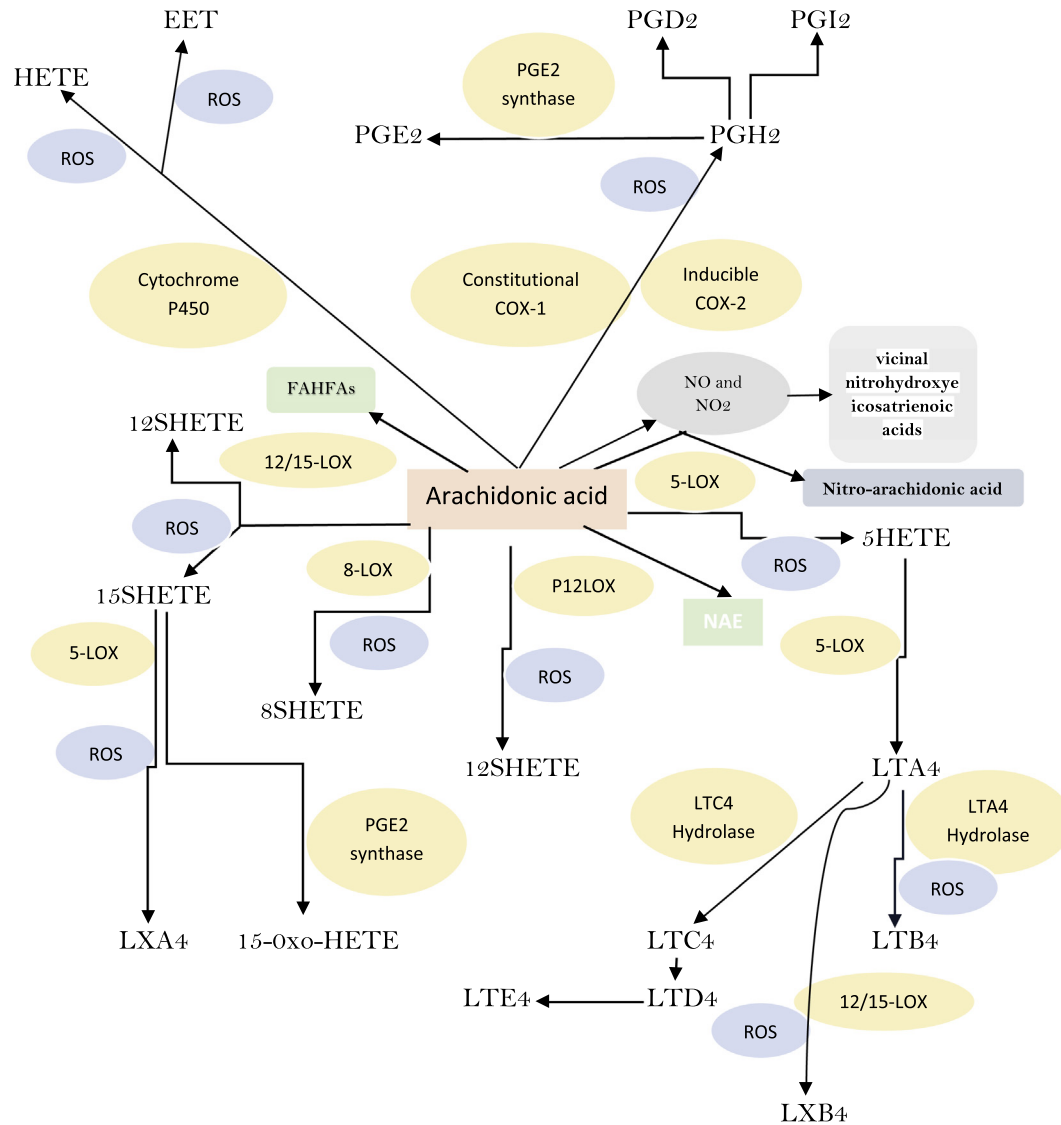

Fig. 1. Scheme showing metabolism of essential fatty acids, their role in inflammation and cytoprotection of endothelial cells.

Fig. 2. Scheme showing metabolism of arachidonic acid. AA can react with NO and NO2 and form vicinal nitrohydroxyeicosatrienoic acids that have vasodilator actions [68]. Even EPA and DHA may give rise to similar metabolites that are formed from AA. Fatty acid hydroxy fatty acids (FAHFAs) are newly discovered and are also called as lipokines. They can be formed from all PUFAs. So far lipokines derived from DHA, LA, palmitic acid and stearic acid have been described. But are likely to be formed form other PUFAs as well. They are present in the plasma, adipose tissue and human breast milk. Some of the DHA derived FAHFAs include: 9- and 13-hydroxyoctadecadienoic acid (HLA) or 14-hydroxydocosahexaenoic acid (HDHA), termed 9-DHAHLA, 13-DHAHLA, and 14-DHAHDHA. FAHFAs have the potential to improve blood sugar, protect against diabetes, and reduce inflammation. PAHSA, the combination of palmitic acid and hydroxy stearic acid, was abundantly found in the fat of diabetes-resistant mice and was significantly reduced in humans with early stages of diabetes. When fed to obese diabetic mice, 9-PAHSA was reported to contribute to glucose-insulin homeostasis and to elicit anti-inflammatory effects. FAHFAs do exist at low levels within certain foods, but are mainly synthesized in the body. FHAFAs may also form from AA. Patients with type 2 diabetes have low plasma levels of FHAFAs, AA and LXA4, which have anti-inflammatory actions. This may imply that decreased formation of AA in the elderly may render them to develop low-grade systemic inflammation, partly, due to decreased formation of FHAFAs and LXA4 from AA. N-acylethanolamine (NAE) is a type of fatty acid amide formed when one of several types of acyl group is linked to the nitrogen atom of ethanolamine. These amides can be formed from a fatty acid and ethanolamine with the release of a molecule of water. NAE can be formed due to the action of phospholipase D that cleave the phospholipid unit from N-acylphosphatidylethanolamines. Examples of N-acylethanolamines include: (i) Anandamide (N-arachidonoylethanolamine; NAE 20:4) or arachidonlyethanolamine (AEA) is the amide of arachidonic acid (20:4 ω-6) and ethanolamine. It is the ligand of both cannabinoid receptors and vanilloid receptor that attenuates pain sensation. (ii) N-Palmitoylethanolamine is the amide of palmitic acid (16:0) and ethanolamine. It has anti-inflammatory activity and also attenuates pain sensation. N-Oleoylethanolamine is the amide of oleic acid (18:1) and ethanolamine. It has anorexic effects and enables fat breakdown by stimulating PPAR-alpha. (iii) N-Stearoylethanolamine is the amide of stearic acid (18:0) and ethanolamine. It has pro-apoptotic activity. It operates independently of the known cannabinoid and vanilloid receptors targeted by anandamide. (iv) N-Docosahexaenoylethanolamine is the amide of docosahexaenoic acid (22:6) and ethanolamine. It has anti-proliferative effects on prostate cancer cell lines and promotes synaptogenesis. Thus, NAEs may be formed from PUFAs that have important biological functions.

corticoids [12,41,67]. On the other hand, pyridoxine, zinc, nicotinic acid, and magnesium are much needed co-factors for the normal Δ^6 desaturase activity. Insulin activates Δ^6 desaturase, indicating that when insulin levels are low or insulin resistance is present it results in decreased activity of Δ^6 desaturase. This could be one of the reasons as to why diabetics have decrease in plasma and tissue levels of GLA, DGLA, AA, EPA and DHA. The activity of Δ^6 desat-

urase falls with age. Δ^6 desaturase activity is inhibited by oncogenic viruses and radiation, which may explain as to why cancer cells have low PUFA content and tumor cells are resistant to the action of radiation and anti-cancer drugs since PUFAs have tumoricidal action. Total fasting, protein deficiency, and a glucose-rich diet reduce, whereas fat-free diet and partial caloric restriction enhance Δ^6 desaturase activity. Furthermore, Δ^6 and Δ^5 desat-

urases are regulated by sterol regulatory element binding protein-1 (SREBP-1) and peroxisome proliferator-activated receptor-α (PPAR-α) [69].

Pufas and telomere

It was reported that increase in plasma DHA + EPA levels were associated with longer telomere, while patients with coronary artery disease have decreased plasma levels of EPA and DHA and shorter telomere [70]. EPA/DHA may prevent reduction in the telomere length, possibly, due to increased formation of their anti-inflammatory metabolites: lipoxins, resolvins, protectins and maresins and decrease in lipid peroxidation [71].

It is interesting to note that a close association has been observed between various vitamins and minerals and telomere length [72–76]. For instance, it was reported that (i) higher serum vitamin D concentrations are associated with longer leukocyte telomere length in women; (ii) multivitamin use has been linked to longer telomere length; (iii) age-dependent telomere shortening can be slowed by increased intake of vitamin C that increases intracellular vitamin C content that, in turn, suppresses oxidative stress; (iv) age-dependent telomere-shortening can be repressed by phosphorylated alpha-tocopherol; and (v) telomere length in peripheral blood mononuclear cells was found to be directly related to the folate status. These evidences suggest that oxidative stress is a factor that regulates telomere length. It is noteworthy that both vitamin C and folic acid are needed for EFA metabolism and enhance the production of anti-inflammatory PGE1 and NO synthesis and have the ability to modulate the activities of desaturases [77–80]. Furthermore, elevated plasma homocysteine, a risk factor for vascular diseases due to homocysteine-mediated oxidative stress and inflammation, has been associated with decrease in leukocyte telomere length [81]. Folic acid is known to reduce homocysteine levels.

Oxidative stress increases with age and is present in diabetes mellitus, hypertension, coronary heart disease and atherosclerosis that may explain as to why telomere length is short in these conditions. Thus, there is a close association among oxidative stress, various age-related diseases, ageing, and telomere. Furthermore, endothelial dysfunction is a dominant feature of hypertension, diabetes mellitus, coronary heart disease, ageing and atherosclerosis, while endothelial function and endothelial cell integrity reflects in its ability to secrete adequate amounts of NO [82,83].

For instance, it was noted that hyperglycemia causes stress-induced premature senescence and replicative senescence of endothelial cells and decreased their telomerase activity. On the other hand, insulin preserved telomere length and delayed endothelial senescence even in the presence of hyperglycemia. Insulin is known to reduce reactive oxygen species generation and increase endothelial NO synthesis. Physiological concentrations of insulin can reverse hyperglycemia-induced inflammatory events. Streptozotocin-induced diabetic animals have increased number of senescent cells in the aortic endothelium compared to age-matched control and insulin-treated animals [82], indicating that insulin has anti-inflammatory actions, suppresses free radical generation and inhibits lipid peroxidation and thus, regulates endothelial senescence [83–85]. On the other hand, hyperglycemia shortens telomere length by inducing oxidative stress and reducing NO generation. These results are noteworthy since NO quenches superoxide anion in addition to its anti-inflammatory actions [84–93]. In addition, insulin has been shown to inhibit IL-6 and TNF-α synthesis and thus, brings about its anti-inflammatory action [89–93]. Pioglitazone not only enhanced insulin sensitivity but also enhanced NO generation, and increased telomerase activity [83].

Ageing, PG system, hyperglycemia, oxidative stress, and telomere length

In this context, it is noteworthy that mean basal production of both PGE2 and PGF2α were reported to be higher in streptozotocin-induced diabetic animals with little or no change in TXB2 compared to normal control [94]. This increase in PG production seems to have been promoted by hyperglycemia, though PGs themselves are known to induce peripheral insulin resistance [95]. In addition, it was reported that an imbalance in PGI2 and TXA2 generation from AA occurs in diabetes mellitus that has been attributed to increase in susceptibility to cardiovascular disease [96].

In another study aimed at studying the effect of PGs on central nervous system regulation of blood sugar homeostasis, it was noted that microinjection of PGD2, PGE1, PGE2, and PGF2α into the third cerebral ventricle of anesthetized rats produced hyperglycemia (P GF2α > PGD2 > PGE1 > PGE2) and hyperthermia (PGE2 > PGF2α > P GE1 > PGD2) suggesting that there is a link between hyperglycemia and hyperthermia. In addition, PGF2α caused an increase in the hepatic venous plasma glucose level. Subsequent studies revealed that hyperglycemia induced by injection of PGF2α into the ventricle is as a result of an increase in epinephrine secretion from the adrenal medulla, muscarinic receptors of cholinoceptive neurons and, in part, by H1 receptors in the central nervous system. [97,98]). These studies suggest that PG system plays a role in the development of hyperglycemia both by peripheral (by inducing inflammation and insulin resistance) and by central actions. Since ageing is a systemic inflammatory condition, it is likely that there could occur an increase in PGF2α levels in the peripheral circulation and central nervous system and thus, may cause age-associated hyperglycemia. This PG-induced hyperglycemia can cause endothelial dysfunction by reducing NO release. On the other hand, hyperglycemia upregulates COX-2 expression leading to an increase in TXA2 formation and a reduction in PGI2 and NO release as a result of hyperglycemia induced oxidative stress. Thus, there is a close interaction among COX-2-PG system, hyperglycemia-induced oxidative stress and NO release [99]. This hyperglycemia-induced oxidative stress can decrease telomere length (see Fig. 3).

It is noteworthy that in aged animals, the production of PGE2 decreases by 60% compared with the young. Yet the ratio of the production rate of PGE2 to that of PGF2α is maintained constant. In contrast to this, the incorporation of AA into phospholipids is increased as a mirror image of PG synthesis [100]. On the other hand, other studies reported that PGE2 excretion is increased significantly with increasing age and an even more pronounced increase of PGF2α was reported with age was noted [101]. This decrease in PGE2 with ageing seems to be associated with increased sensitivity in all tissues in subjects above the age of 70, suggesting that decreased levels of PGE2 is compensated by increased sensitivity to its action [102]. Furthermore, acute hyperglycemia that may occur in type 2 diabetes was found to increase plasma concentrations of 8-epi-PGF2α isoprostane concentrations indicating free radical-mediated oxidative stress [103].

In a study designed to determine changes in the expression of COX-1, COX-2, eNOS, and prostanoid synthases in the endothelium and of prostanoid receptors in vascular smooth muscle during ageing and hypertension, it was observed that ageing caused overexpression of eNOS, COX-1, COX-2, thromboxane synthase, hematopoietic-type prostaglandin D synthase, membrane prostaglandin E synthase-2, and prostaglandin F synthase in endothelial cells and COX-1 and prostaglandin E(2) (EP)(4) receptors in SMC. Hypertension augmented the expression of COX-1, prostacyclin synthase, thromboxane synthase, and hematopoietic-type prosta-
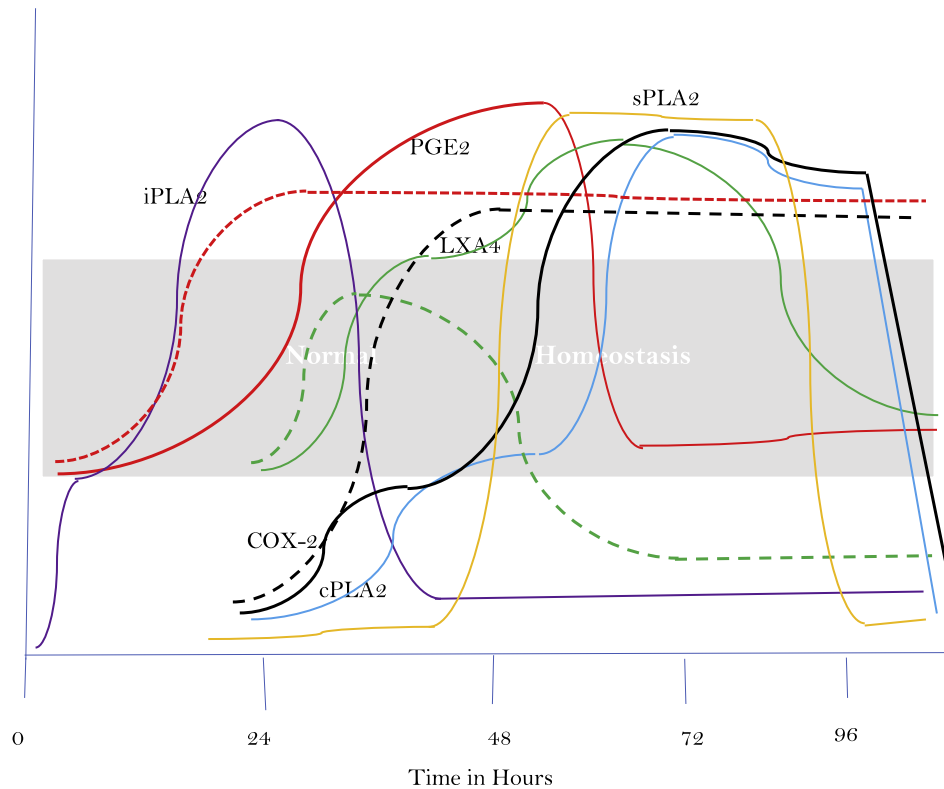
Fig. 3. Scheme showing possible relationship among PGE2, LXA4, and various PLA2 enzymes as seen in inflammation and inflammation resolution process. ————PGE2; ————LXA4; ————iPLA2; ————sPLA2; ————cPLA2; ————COX-2. All these concentrations and activities of enzymes as expected to behave during normal inflammatory process. - - - - -PGE2 when inflammation persists; — — — COX-2 when inflammation persists. — — — LXA4 when resolution of inflammation is defective.

Although possible changes in the activities of various PLA2 are not shown during persistance of inflammation or defective resolution of inflammation, they are expected to behave in tune with the concentrations of PGE2 and LXA4. It also need to be noted that despite the fact that LXA4, resolvins, protectins and maresins have anti-inflammatory actions, there could be subtle differences in their major and minor actions with some amount of overlap in their anti-inflammatory actions. Though the role of nitrolipids is not shown, it is expected to behave similar to LXA4. It is evident from the figure that there are two waves of release of AA (and other PUFAs), one in the early period of inflammation (within the first 24 h due the activation of iPLA2) that leads to the formation of PGE2 and other pro-inflammatory molecules. Once the concentrations of PGE2 reach the optimum level (say by the end of 24–48 h), a second wave of AA release occurs (due to the activation of sPLA2) that leads to the formation of LXA4 that initiates resolution of inflammation. The activation of cPLA2 occurs around 48–72 h in all probability to accelerate or continue the resolution of inflammation process. The activation of iPLA2 and formation of PGE2 are closely associated with the activation of COX-2. In this process of inflammation and resolution of inflammation there is a critical role for PGDH enzyme (see text for details). With regard to the actions of LXA4, resolvins, protectins and maresins, it is to be noted here that though all these are anti-inflammatory molecules they may have slightly but critically important differences in their actions to resolve the inflammation. For instance, LXA4 is needed to induce anti-inflammatory events (to suppress inflammation and this is not equal to resolution of inflammation. During the process of suppressing inflammation, LXA4 may inhibit leukocyte infiltration); while resolvins are needed for resolution of inflammation (such as removing the debris of wound, phagocytosis of dead leukocytes, etc.,); protectins protect normal cells/tissues from further damage; and maresins may act on stem cells for the repair process to proceed and restore homeostasis. Despite these different actions assigned to different molecules (LXA4, resolvins, protectins and maresins), all these bioactive lipids have all the enumerated actions except that the degree to which each action is brought about may be variable and it may vary from cell/tissues that are in the need of their action. It is also depicted in the figure how this sequence of orderly activation and deactivation of PLA2, COX-2 and formation of PGE2 and LXA4 are likely to get deranged in the face of failure of resolution of inflammation process. It is likely that in patients with hypertension, diabetes mellitus and ageing there is low-grade systemic inflammation as a result of sustained activation of COX2 and formation of PGE2 and failure of formation of adequate amounts of LXA4 and other anti-inflammatory compounds and corresponding activation of PLA2 at the most appropriate time. It is noteworthy that failure of the inflammation resolution process may lead to the onset of ageing associated osteoporosis, sarcopenia and when this inflammatory process is severe it can lead to sepsis and septic shock.

glandin D synthase in endothelial cells and prostaglandin D(2) (DP), EP(3), and EP(4) receptors in SMC. The expression of thromboxane synthase was increased in the cells of ageing or hypertensive rats. These results suggest that with ageing there is a tendency to form excess of vasoconstrictor prostanoids and also in hypertension. This may explain as to why hypertension incidence is more common with ageing [104]. These results imply that the observed decrease in PGE2 and other prostanoids and increase in the sensitivity to their action reported in some previous studies [102] may be a compensatory effort to restore homeostasis. But, on the whole, there seems to be a tendency to enhance the production of pro-inflammatory prostanoids that is tune with the fact that ageing is a low-grade systemic inflammatory condition.

In support of this concept, it is reassuring to know that there is a significant increase in plasma IL-6 and TNF-r1 with age, whereas

IL-1ra, IL-10, and CRP did not significantly increase with age with non-Hispanic whites had significantly higher levels of IL-1ra than Mexican Americans, whereas non-Hispanic blacks had significantly higher levels of IL-6 and CRP than Mexican Americans as well as non-Hispanic whites with CRP levels in non-Hispanic blacks were not significant after adjusting for body mass index (BMI). These results demonstrate that pro-inflammatory cytokine levels are influenced by both age and ethnicity [105,106].

This pro-inflammatory status seems to be due to release of mitochondrial components, including mitochondrial DNA (mtDNA) into extracellular space. The mtDNA when released extracellularly can act as "damage-associated molecular pattern" (DAMP) agents and cause inflammation. In a study performed in 831 Caucasian subjects including 429 siblings aged 90–104 years, it was observed that mtDNA plasma levels increased gradually

after the fifth decade of life. Subjects who had the highest mtDNA, showed enhanced plasma levels of TNF-α, IL-6, RANTES, and IL-1ra. Furthermore, *in vitro* stimulation of monocytes with mtDNA concentrations similar to the highest levels observed *in vivo* resulted in an increased production of TNF-α, suggesting that mtDNA enhances the production of proinflammatory cytokines [107]. This pro-inflammatory status may ultimately result in telomere shortening.

Although, in general, PGEs are considered as pro-inflammatory in nature, it need to be emphasized that it may also serve as a trigger of anti-inflammatory responses. It is known that there are two waves of release of AA and other PUFAs: one at the onset of inflammation that causes the synthesis and release of PGE2 and a second at resolution for the synthesis of anti-inflammatory PGD2, 15deoxyΔ$^{12-14}$PGJ$_2$, and lipoxins, resolvins, protectins and maresins that are essential for the suppression and resolution of inflammation. Thus, COX-2 enzyme has both harmful and useful actions by virtue of its ability to give rise to pro-inflammatory and anti-inflammatory PGs and LXs. Hence, it is likely that once the production of PGE2 reaches a peak, it automatically triggers (or as a feed-back regulatory event) production of LXA4 and other anti-inflammatory bioactive lipids (this include resolvins, protectins and maresins) that initiates resolution of inflammation. It has been shown that continued production of PGE2 is necessary (by blocking PGDH: 15-hydroxyprostaglandin dehydrogenase that inactivates PGE2) to enhance tissue regeneration especially of the liver after partial hepatectomy, prevents or ablates inflammatory bowel disease and increases hematopoiesis [108,109]. These results can be interpreted to mean that under certain circumstances PGE2 behaves as a pro-inflammatory molecule; and under certain other situations it may actually be beneficial. It remains to be seen whether these paradoxical actions of PGE2 are due to PGE2 itself or due to the presence of other bioactive molecules such as LXA4. It is likely that local concentrations of PGE2; degree of raise and fall in the levels of PGE2; duration of increase in PGE2 levels; and perhaps tissue(s) wherein this increase in PGE2 is sustained are all important in determining the final outcome of the actions of PGE2 reported. It is possible that with increasing age, homeostasis of PGE2 synthesis and degradation as per the needs of the local tissues is lost or defective that results in continued inflammation and tissue damage (see Fig. 3). Similar to the defects in PGE2 synthesis and action, a concomitant dysfunction of LXA4/resolvins/protectins/maresins may also occur with increasing age. It is likely that the trigger for synthesis of LXA4/resolvins/protectins/maresins is initiated only when PGE2 concentrations reach a certain peak level (see Fig. 3). This feedback regulation between PGE2 and LXA4, both of which are derived from AA, is partly dependent on the type of phospholipase that is activated to induce the release of AA from the cell membrane lipid pool. For example, there seem to occur a sequential activation of various phospholipases during inflammation from its onset till resolution. During initial stages of inflammation (first 24 h till 72 h), type VI iPLA2 protein expression is increased, while in the next 48–72 h type IIa and V sPLA2 expressions are increased, whereas the expression of type IV cPLA2 expression is gradually increased during resolution phase of inflammation and peaking at 72 h. Increase in type IV cPLA2 expression coincides with enhanced expression of COX-2. Thus, different types of PLA2 have very specific roles in the inflammatory process. This dramatic yet sequential activation of various PLA2s and COX-2 is meant to control PGE2/LTB4 and LXA4 (possibly, resolvins/protectins/maresins) production aimed at triggering adequate inflammation that is essential yet to control inappropriate inflammation and at the same time trigger inflammation resolution process to restore tissue homeostasis as shown in Fig. 3 [42,43,110–112].

Calorie restriction, exercise, PI3K/Akt/mTOR pathway, GnRH, and hypothalamic inflammation in ageing

Since inflammation seems to have a significant role in ageing, strategies employed to reduce inflammation may be important to prevent and postpone ageing process. In order to delay ageing, stem cells are needed to replace worn out cells/tissues by new cells/tissues. Calorie restriction (that has anti-inflammatory actions and enhances the activity of desaturases) is known to delay ageing and the effects of calorie restriction on stem-cell function is regulated by mTOR [113]. Ageing retardation and lifespan extension can be related to ageing-related hypothalamic or brain IKK-β and NF-kB activation, implying a role for microglia–neuron immune crosstalk that inhibited gonadotropin-releasing hormone (GnRH) release. GnRH treatment leads to an increase in ageing-impaired neurogenesis and decelerated ageing. This suggests that hypothalamus plays a significant role in ageing via immune–neuroendocrine integration [114]. N-acylethanolamines (NAEs), lipid-derived signaling molecules, are reduced by dietary restriction and NAE deficiency extends lifespan in an mTOR dependent manner [115]. Thus, a close interaction occurs among PI3K/Akt/mTOR pathway, GnRH and neuron-immune crosstalk. Preservation of intestinal stem cells by calorie restriction is due to reduced mTOR signaling (specifically mTORC1). Parabiosis enhanced neurogenesis observed in older animal has been attributed to a reduction of the pro-inflammatory chemokine CCL11. In general, under normal physiological conditions interleukin-4 (IL-4) inhibits CCL11 and thus, encourages neurogenesis and enhances memory formation and learning ability. With advancing age, CCL11 levels are increased (an indication of increase in inflammation) leading to reduced neurogenesis and consequently decreases memory [116,117]. Parabiosis experiment revealed that GDF11 (growth differentiation factor 11), also known as bone morphogenetic protein 11 (BMP-11) and a myostatin-homologous protein that belongs to the transforming growth factor β superfamily, enhanced growth of new blood vessels, olfactory neurons in the mouse brain and improved muscle and brain function possibly, by its action on stem cells [118]. It is noteworthy that PUFAs and their metabolites regulate the survival, proliferation and differentiation of stem cells [119–121], modulate immune response [122] and PI3K/Akt/mTOR system [123–125] and inflammation. The ability of exercise to improve muscle tone, suppress inflammation and enhance neurogenesis and memory can be related to its capacity to augment production of BDNF (brain-derived neurotrophic factor) [126] and LXA4 [127], and ageing is associated with profound decrease in circulating LXA4 levels [128]. LXA4 is not only an anti-inflammatory molecule but also has anti-diabetic action [129,130]. Thus, the close interaction(s) that exists among microglia–neuron immune crosstalk, PI3K/Akt/mTOR pathway, cytokines, chemokines, GDF-11, BDNF and fatty acid-eicosanoid and LXA4 system is relevant to ageing and its associated diseases (see Fig. 4). Our recent studies revealed that BDNF can augment the production of LXA4 and vice versa (LXA4 enhances the production of BDNF) (unpublished data). It remains to be seen whether GDF-11 can augment the synthesis and action of LXA4 to account for its anti-ageing action.

H$_2$S, NO, and PUFAs may interact to bring about their beneficial actions

In this context, there could be a role for certain biologically active gases in the pathobiology of ageing. NO in addition to being a potent vasodilator and neurotransmitter, it also interacts with other biologically active gases such as carbon monoxide (CO) and hydrogen sulfide (H$_2$S). NO and H$_2$S interact with each other to ring
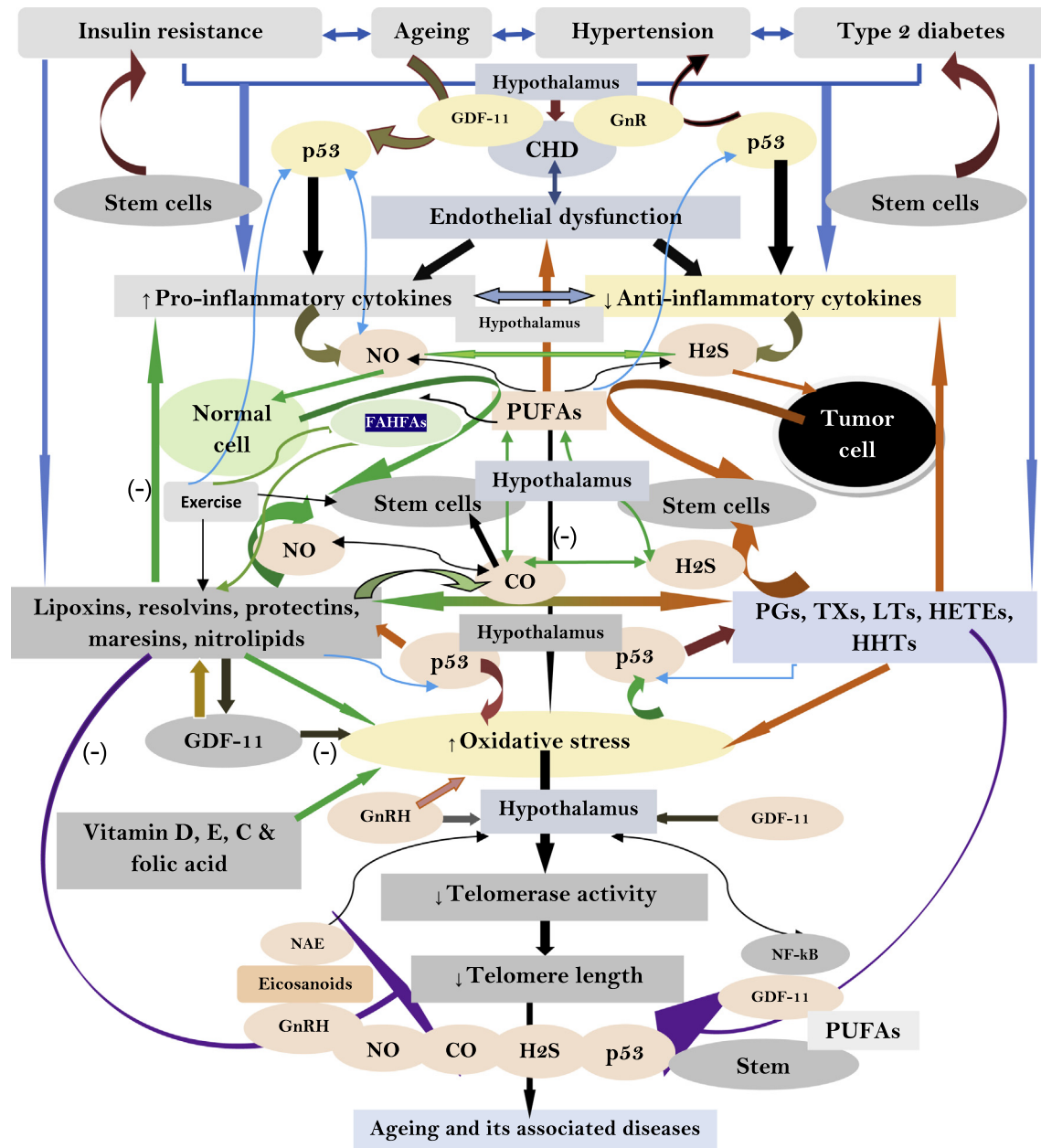
Fig. 4. Scheme showing relationship among ageing and its associated diseases and their relationship to hypothalamus, oxidative stress, PUFAs, lipoxins, resolvins, protectins, maresins, eicosanoids, CO, NO, H_2S and telomere length. High calorie diet stimulates ROS generation that may overwhelm antioxidant system protection in adipose and other tissues; augment the synthesis of pro-inflammatory cytokines, inhibit the formation of anti-inflammatory cytokines that ultimately results in low-grade systemic inflammation, enhance DNA damage and ageing. These events may lead to ageing of endothelial cells and telomere shortening, and alteration in p53 expression. These events cause endothelial dysfunction and insulin resistance leading to the development of hypertension, type 2 diabetes mellitus, atherosclerosis and ageing. High calorie diet and insulin resistance suppress Δ^6 and Δ^5 desaturases activity resulting in reduced formation of PUFAs, the precursors of lipoxins, resolvins, protectins and maresins. Decreased lipoxins, resolvins, protectins and maresins impair resolution of inflammation, DNA damage, telomere shortening, p53 dysfunction, and stem cell function leading to the onset and progression of ageing and age-associated diseases. These events may also decrease CO, NO and H_2S production. PUFAs and their metabolites influence stem cell biology and thus, affect ageing process and ageing-associated diseases including Alzheimer's disease (for further details see text). PUFAs can give rise to FAHFAs that have anti-inflammatory properties and may enhance NO, CO and H_2S production, and mediate exercise-induced anti-inflammatory actions. PUFAs form precursors to anti-inflammatory lipoxins, resolvins, protectins and maresins that suppress production of pro-inflammatory IL-6, TNF-α and prostanoids. It is not yet known but possible that FAHFAs may suppress tumor cell growth, inhibit inflammatory events that occur in hypothalamus due to high fat diet. Though the role of p53 in ageing and diseases is not discussed in detail here, it may be noted that p53 is the guardian of the genome. PUFAs and their metabolites, cytokines, NO, CO, H_2S, ROS, GDF-11, GnRH and NAE may modulate the action of p53. For instance, exercise reduces the incidence of cancer, possibly, by augmenting the production of IL-6 and TNF-α that are cytotoxic to tumor cells either by their direct action and/or enhancing the production of ROS that are tumoricidal. In addition, exercise may enhance the expression and action of p53 that leads to apoptosis of cancer cells. PUFAs have tumoricidal action and may bring about this action by augmenting free radical generation and formation of excess lipid peroxides selectively in tumor cells and augmenting the expression and action of p53.

about their beneficial actions [131]. This synergistic interaction between NO and H_2S can be extended to carbon monoxide (CO), another gaseous molecule of significant physiological action [132]. NO, CO, and H_2S are endogenously produced and mediate

their actions by acting on the cyclic guanosine monophosphate (cGMP) pathway. It was also reported that synergistic interactions between NO and CO/cGMP occurs, while H_2S inhibits NO-induced cGMP but not CO-induced cGMP, suggesting that all three gaseous

molecules have interactive roles in modulating cGMP signaling (133). CO and H_2S, which are produced by several tissues including the gastrointestinal tract are known to regulate smooth muscle membrane potential and tone, modulate function of enteric nerves (including vagus), and regulate the immune system. NO, H_2S, and CO interact with each and inhibit and/or potentiate the levels and activity of each other to produce optimal physiological actions. However, their half-lives are different; CO is more stable and hence, may have effects distal to the site of production, whereas NO and H_2S are short lived and so may be able act only close to their sites of production. PUFAs enhance the production of H_2S, CO and NO. CO has been shown to enhance the resolution of inflammation by augmenting the production of LXA4, resolvins and protectins, whereas LXA4/resolvins/protectins/maresins were found to enhance the activity of heme-oxygenase and CO synthesis [133]. Thus, there is a close association among CO, NO, H_2S and bioactive lipids (LXA4/resolvins/protectins/maresins) that accounts for their anti-inflammatory actions. This suggests that age associated decrease in LXA4/resolvin/protectins/maresins may result in deficient production of CO/NO/H_2S and thus, facilitate the development age-associated diseases such as cardiovascular and cerebrovascular diseases, diabetes mellitus, etc.

AA and other PUFAs and their metabolites in ageing

Previously, we showed that plasma phospholipid content of AA is decreased in those with type 2 DM, hypertension and coronary heart disease that are known to be common with ageing [62,134,135]. AA is the precursor to potent anti-inflammatory metabolite LXA4) that can prevent atherosclerosis, platelet aggregation and a vasodilator. It is also known that with age plasma levels of LXA4 decrease [128] that explains the high incidence of type 2 DM, hypertension and coronary heart disease with advancing age.

In this context, it is relevant to note that glitazones enhance generation of LXA4 [136]. It is known that LXA4 enhances production of NO and exercise enhances both NO and LXA4 synthesis [127] and thus, prevent atherosclerosis [137].

Based on these evidences, I propose that AA and other PUFAs deficiency, alterations in the activities of 5/12/15 lipoxygenase enzymes and phospholipases (which are needed for the release of AA and other PUFAs from the cell membrane lipid pool and their metabolism) leads to decrease in the formation of anti-inflammatory lipoxins, resolvins, protectins and maresins that results in defective resolution of inflammation and consequent tissue/organ damage. Hence, it is likely that deficiency of various PUFAs, and dysfunction of 5/12/15 lipoxygenases and phospholipases that occurs during ageing results in decreased formation of lipoxins, resolvins protectins and maresins and in hypertension, type 2 diabetes mellitus, atherosclerosis, cancer, Alzheimer's disease and ageing itself (see Fig. 4).

Lipoxins, resolvins, protectins and maresins enhance the formation of NO, H_2S and CO; suppress the activity of MPO (myeloperoxidase) and generation of free radicals and thus, serve as genome protectors. For instance, we reported that radiation and chemical-induced chromosomal damage is prevented by PUFAs [138–142] may be attributed to lipoxins, resolvins protectins and maresins. This implies that PUFAs and lipoxins, resolvins, protectins and maresins prevent shortening of telomere and thus, reverse some of the manifestations of ageing.

Stems cells are needed to replace the worn cells and tissues. PUFAs and their products modulate stem cell biology [119–121] by regulating proliferation and differentiation of embryonic stem cells in addition to their modulatory influence on inflammation.

Aging is a low-grade systemic inflammatory condition

Ageing is a low-grade systemic inflammatory condition [143]. There is a direct relationship between ageing and the incidence of insulin resistance, obesity, hypertension, type 2 diabetes mellitus and cancer. In age-related diseases such as endothelial dysfunction, atherosclerosis, diabetes mellitus, hypertension, coronary heart disease and cancer, there could occur a deficiency of various PUFAs and their anti-inflammatory products such as lipoxins, resolvins, protectins and maresins and NO. This implies that telomere shortening seen in all these conditions and ageing could be due to decreased formation of NO, lipoxins, resolvins, protectins, maresins and other anti-inflammatory products. In addition, ageing is associated with increased formation of pro-inflammatory cytokines that could be due to absence of negative feed-back control exerted by lipoxins, resolvins, protectins, maresins and other similar anti-inflammatory compounds.

Calorie restriction and exercise that prolong life span and reverse or halt some of the changes associated with ageing could be related to increased formation of lipoxins, resolvins, protectins, maresins, NO and suppression of synthesis of pro-inflammatory cytokines, free radicals and maintenance of telomere length. Calorie restriction enhances the activity of Δ^6 and Δ^5 desaturases, enzymes that are essential for the conversion of dietary linoleic and alpha-linolenic acids to their long chain metabolites: AA, EPA and DHA, the precursors of lipoxins, resolvins, protectins and maresins. Furthermore, PUFAs, lipoxins, resolvins, protectins and maresins also augment formation of NO [144–147] and possibly, H_2S and CO.

Recent studies showed that dietary restriction without malnutrition increased expression of the transsulfuration pathway (TSP) enzyme cystathionine g-lyase (CGL), leading to an increase in the formation of H_2S. Inhibition of H_2S production blocked dietary restriction-mediated beneficial actions [148].

Conclusions and future implications

Ageing is certainly a complex process regulated by genes and environment. Ageing is a low-grade systemic inflammatory condition in which plasma and tissue levels of pro-inflammatory cytokines increase and anti-inflammatory cytokines and lipid molecules are low; GDF-11 levels, NO, H_2S, CO synthesis decrease and stem cell dysfunction occurs eventually resulting in increasing the incidence of obesity, hypertension, type 2 diabetes mellitus, atherosclerosis, CHD and cancer. Hence, measures designed to augment anti-inflammatory events in the form of Mediterranean diet, exercise and perhaps, anti-inflammatory drugs, infusion of GDF-11 and lipid-derived signaling molecules may retard the ageing and its associated diseases. One method of enhancing the formation of anti-inflammatory lipids: LXA4, resolvins, protectins and maresins is to administer AA/EPA/DHA in combination with aspirin (11). The beneficial action of AA and LXA4 in the prevention of one of the age-related diseases namely type 2 DM is evident from our recent studies that showed that these two (AA and LXA4) can prevent chemical (alloxan and streptozotocin) and high-fat diet-induced type 2 DM [129,130]. In addition, it was reported that AA supplementation enhances plasma AA content without increasing the formation of pro-inflammatory eicosanoids and, in fact, enhances LXA4 formation and lowers plasma LDL-cholesterol levels [149–152], events that can contribute to suppression of unwanted inflammation and enhance health. This is supported by the observation that systemic disruption of the Δ^5 desaturase gene led to a significant reduction in the plasma and hepatic levels of AA with a reciprocal increase in its precursor DGLA, resulting in a profound increase in 1-series PGs and a concomitant decrease in 2-series-

derived PGs. This disruption of AA formation led to a profound perturbed intestinal crypt proliferation, immune cell homeostasis, and a heightened sensitivity to acute inflammatory challenge. In addition, null mice failed to thrive, dying off by 12 weeks of age, while dietary supplementation of AA restored the longevity of null mice to normal [153]. It is interesting to note that the lack of AA-derived 2 series of PGs (especially PGE2) resulted in reduction in intestinal crypt proliferation and their inability (Δ^5 desaturase deficient mice) to tolerate an acute intestinal inflammatory challenge. Similar results have been reported in microsomal PGE synthase Null mice and consequent COX-2 deficiency [153], suggesting that PGE2 has a cytoprotective action and is essential for the integrity of the epithelial intestinal wall. It appears that PGE2 loss or deficiency may promote polymicrobial sepsis. Thus, as discussed above PGE2 is not always pro-inflammatory and its actions depend on the local concentration, degree of elevation and duration of exposure of tissues. These results emphasize the importance of AA for normal homeostasis and life span.

Direct support to the proposal that AA could have a role in ageing and longevity comes from the studies performed in the model organism *Caenorhabditis elegans*. It was reported that fasting induced the expression of a lipase in C. elegans, which, in turn, led to an enrichment of n-6 PUFAs especially that of DGLA and AA and increased their resistance to starvation and extended their life span in conditions of food abundance. Supplementation of *C. elegans* or human epithelial cells with these n-6 PUFAs activated autophagy, a mechanism that promotes starvation survival and slows ageing. Furthermore, inactivation of *C. elegans* autophagy components reversed the increase in life span conferred by supplementation of n-6 PUFAs. Thus, one mechanism by which n-6 PUFAs prolong life span could be by augmenting autophagy process [154].

Ageing in bone and muscle, osteoporosis and sarcopenia, are two important aspects of ageing in which the role of pro-inflammatory cytokines and eicosanoids remains controversial. Excessive bone resorption and failure to replace lost bone due to defects in bone formation leading to an imbalance between the osteoclasts and osteoblasts (osteoclasts > osteoblasts) mainly due to estrogen deficiency plays a critical role in the development of osteoporosis. While calcium and vitamin D deficiencies and secondary hyperparathyroidism also contribute to its pathogenesis, interaction of systemic hormones, local cytokines, growth factors, eicosanoids and transcription factors are important players in osteoporosis [155]. Immobilization causes osteoporosis as a result of increase in PGE production [156]. In contrast, exercise prevents osteoporosis and sarcopenia. It was shown that IL-6, TNF-α and PGE2 are involved in post-menopausal osteoporosis and osteoporosis seen in patients with rheumatoid arthritis [157,158] suggesting a critical role for inflammation and that estrogen has anti-inflammatory actions [159]. In a study aimed at the effect of ageing on normal one repair, it was observed that ageing was associated with a decreased rate of chondrogenesis, decreased bone formation, reduced callus vascularization, delayed remodeling, and altered expression of genes involved in repair and remodeling. COX-2 expression was reduced by 75% and 65% in fractures from aged mice compared with young mice on days 5 and 7, respectively. Local administration of an EP4 (PGE receptor4) agonist to the fracture repair site in aged mice enhanced the rate of chondrogenesis and bone formation to levels observed in young mice, suggesting that the expression of COX-2 during the early inflammatory phase of repair is critical for subsequent chondrogenesis, bone formation, and remodeling [160]. These results coupled with the observation that activation of EP4 can rescue impaired bone fracture healing in COX-2(−/−) mice suggest that COX-2/ EP4 agonists reduce fracture healing associated with ageing and COX-2, the inducible regulator of PGE2 synthesis, is critical for normal bone repair [161]. It is noteworthy that low intensity, low frequency, single pulse electromagnetic fields significantly suppressed the trabecular bone loss and restored the trabecular bone structure in bilateral ovariectomized rats by attenuating ovariectomy associated increase in serum PGE2 concentrations [162]. PGE2-induced differentiation of bone marrow cells into osteoclasts could be inhibited b JAK1/2 (Janus kinase) inhibitor by reducing PGE2-induced up-regulation of RANKL and IL-6 and IL-11 secretion by osteoblasts [163]. These results [154–163] once again emphasize the importance of initial inflammation triggered by PGE2 for subsequent beneficial actions: initial optimal inflammation triggered by PGE2 is beneficial in enhancing bone formation and bone repair whereas continued low-grade inflammation due to continued enhanced levels of PGE2 induces osteoporosis. Similar results were obtained with regard to the effects of PGE2 on muscle mass and strength improvement [164,165]. These results are in tune with the concept that initial inflammation triggered by exercise is responsible for its beneficial actions (see Fig. 3). Furthermore, exercise-induced generation of BDNF, LXA4, NO seem to have a potential role in the prevention of ageing associated osteoporosis and sarcopenia [166–169]. Thus, some of the interventions that could be employed to prevent or postpone ageing include: calorie restriction, exercise, administration of L-arginine, the precursor of NO or NO donors; AA with aspirin to augment LXA4 formation, and BDNF analogues. In order to ascertain the role of various bioactive lipids (especially PUFAs) and their metabolites in the pathophysiology of ageing, it is important to measure their plasma and tissue concentrations at various stages of ageing and several pathological processes (such as diabetes, hypertension, metabolic syndrome, osteoporosis, lupus, and various stages of life) for which sensitive and reliable methods need to be employed as described recently [170,171]. Based on the preceding discussion, it is certainly tempting to recommend periodic transfusion of young blood (akin to parabiosis) and/or GDF-11 to prevent ageing, though more evidence is needed for its implementation.

Conflict of interest

The author has declared no conflict of interest.

Compliance with Ethics Requirements

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

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