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Review

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

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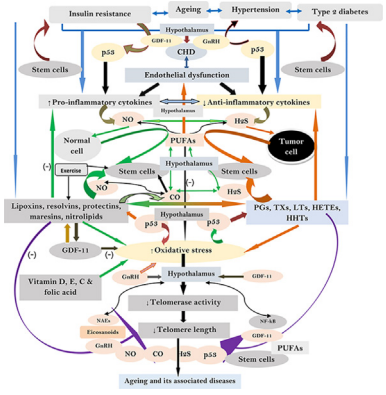
GRAPHICAL ABSTRACT



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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

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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

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