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Ageing and Its Different Perspectives

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ABSTRACT

Ageing is universal but complex biological process characterized by impairment of various functions and decreased ability to respond stress whose manifestations are familiar and unambiguous. The population of world is ageing rapidly. With the rapid increase in the population of people 60 years of age and older, considerable research is being focused on how to prevent or delay ageing and age-related disabilities. Although, there are many theories to explain the ageing phenomenon, there is no inclusive explanation of ageing by any one theory and why the ageing process can vary so much in speed and quality from individual to individual. Various theories of ageing have been proposed like mitochondrial ageing theory, glycation theory of ageing, free radical induced damage, etc. In this review, we attempt to sight how major theories are revolving around free radical induced damage and they are indeed interrelated, along with some traditional remedies to give reader general sketch of ageing process.

KEYWORDS - Ageing, Oxidative Stress, Glycation, Traditional Medicine.

INTRODUCTION

Ageing is universal but complex biological process with proverbial and unambiguous manifestations characterized by impairment of various functions and decreased ability to respond stress. It is also accompanied by syndrome of changes and has been a concern of every society. Scientific language that describes human ageing also vacillate, it struggles to differentiate ageing from disease, healthy ageing from unhealthy ageing, and optional ageing from obligatory ageing and whether growing old is pathological or physiological (1). According to WHO in 2000, there were 600 million people aged 60 and over; there will be 1.2 billion by 2025 and 2 billion by 2050. In the developed world, the very old (age 80+) is the fastest growing population group (2). The proportion of the population made up of elderly persons in the United States is projected to increase from 13 to 20 percent of the population in 2000 to 2030 (3). Consequently, age-related diseases will increase greatly over the coming decades and will have a great impact on the quality of life of the elderly as well as economy of country. When events go awry, molecular processes take place that, over time, can lead to neurodegenerative disease (4). An accepted definition of ageing and a detailed understanding of the biological mechanisms underpinning ageing are elusive. Ageing has been defined as the progressive loss of function accompanied by decreasing fertility and increasing mortality and disability (5).

THEORIES OF AGEING

Various theories have been put forward to explain the phenomenon of ageing; however, no single theory has yet accounted for all phenotypes, though many have attempted to explain at least some of the major and most frequent ageing phenomenon. Theories of ageing have been grouped as molecular, cellular and systemic theories. Molecular theories propose that the genes, by interacting with the environmental factors, govern the lifespan of any species. Ageing may result from changes in DNA template activity, which regulates the formation of the final cellular products. The molecular theories include codon restriction, somatic mutation, error theory, and gene regulation theory. They also include antagonistic pleiotropy, dysdifferentiation and soma disposal hypothesis. Cellular theories, on the other hand, relate to changes that occur in structural and functional elements of cells with the passage of time. These theories include wear and tear, age pigments, free radicals, cross-linking and membrane alterations. Systemic theories include the endocrine and neuro-endocrine and immunological systems. These theories view that the overall performance of an animal is closely related to the efficacy of a variety of control mechanisms that regulate the interaction between different organs and tissues. The effectiveness of homeostatic adjustments declines with age and leads to consequent failure of adaptive mechanisms, ageing and death. The details of these theories have been reviewed extensively in various studies. Also there are plethora of reports regarding several factors that are associated with ageing and longevity. Among all these theories some leading are considered here with their possible interdependence.

Mitochondrial damage theory and oxidative stress

Mitochondria, tiny cellular bodies or organelles, are among the most complex structures within the cell that contain a small loop of DNA. The mitochondrial theory of ageing remains to date one of the most popular theories of ageing. One major model of ageing is replicative senescence, where the irreversible loss of division potential of somatic cells occurs after a more or less constant number of cell divisions (6). A number of proteins essential to energy production come

from mitochondrial DNA and damage to this DNA can cripple the ability of the mitochondrion to produce energy (7). At the same time, there are several studies reporting strong correlation between mitochondrial DNA mutation and ageing (8-10). Mitochondria from the cells of older individuals tend to be less efficient than those from the cells of younger people (11). The finding lends support to the mitochondrial theory of ageing, which says those damaged mitochondria increase with age and are responsible for the physical changes of ageing.

The oxidative stress hypothesis is one of the prevailing theories of ageing (12, 13). This theory states that free radicals produced during cellular respiration damage lipids, proteins, and DNA thereby accelerating the ageing process and increasing disease risk. Scientists have studied the connection among mitochondria, oxidative stress and ageing in fruit flies by housing the flies in an environment of 100% oxygen. The elevated oxygen levels cause the mitochondrial membranes to crimp in swirled patterns, which in turn decrease the life span of the insects from two months to about a week. The injury caused by free radicals initiates a self-perpetuating cycle in which oxidative damage impairs mitochondrial function, which results in the generation of even greater amounts of oxygen-free radicals (14). Among the byproducts of mitochondrial energy production are reactive oxygen species. Oxygen-free radicals, unless they are quickly neutralized by antioxidants, can cause considerable damage to the membranes of mitochondria and to mitochondrial DNA.

***Ageing*, *AGE (Advanced Glycation End Products)* and oxidative stress**

Now a days, considerable research is being focused on Advanced Glycation End products (AGEs), which are composed of various glucose or carbohydrate adducts, are thought to be responsible for age related conditions and complications. AGEs are heterogeneous class of compound resultant of non-enzymatic protein glycation. Several study reports close association between AGEs and ageing. AGEs arise from the non-enzymatic addition of reducing sugars to the side chain of lysine and/or arginine residues of the protein (15). The receptor for advanced glycation end products (RAGE), a member of the immunoglobulin super family whose gene is located in the vicinity of the MHC complex in humans. Various studies suggested that binding of ligands to RAGE results in rapid and sustained cellular activation and gene transcription. Its involvement in inflammation has been suggested by many findings. First, RAGE is unregulated in all inflammatory lesions studied, including rheumatoid arthritis, inflammatory kidney disease, arteriosclerosis, inflammatory bowel disease, and others (16).

The generation of AGEs is an inevitable process in vivo and their accumulation in different tissues has been implicated in the process of ageing and also in the pathogenesis of several pathological conditions, including diabetes, atherosclerosis, Alzheimer's disease and renal failure. AGE modification can lead to tissue damage through alterations of tissue protein structure and function, and stimulates cellular responses mediated by a specific receptor (RAGE) (17).

Chronic hyperglycemia and oxidative stress in diabetes result in the formation and accumulation of AGEs. AGEs have a wide range of chemical, cellular, and tissue effects that contribute to the development of micro vascular complications. The effect of AGEs appears to be synergistic with other pathogenic pathways in diabetes including oxidative stress, hypertension, and activation of the renin-angiotensin system. The therapies that inhibit the formation of AGEs or remove established AGE modifications will form an important component part of future therapy in patients with diabetes, acting in concert with conventional approaches to prevent diabetic renal injury (18, 19). Thus oxidative stress also has synergistic role in ageing through AGE formation.

AGE and free radicals

The AGEs produces fifty fold more free radicals than non glycated proteins (20). These free radicals are superoxide radical generated by protein bound Amadori products in the presence of transition metal ions such as iron. AGEs are produced very frequently in various pathological conditions (21). However, the underlining mechanism of ageing remains largely unknown. D-galactose a reducing sugar reacts with free amino groups of proteins, to form in soluble aggregates of AGE (22). The role of AGE in ageing was set by different parameters in different model. C57 mice injected daily with D-galactose, D-galactose modified AGE-lysine (AGE-lysine), L-glucose, L-lysine for 8 weeks had a significant increase in serum AGE levels, memory latency time and error rate, and skin hydroxyproline content. These mice also had a significant decrease in motor activity, lymphocyte mitogenesis, interleukin-2 (IL-2) production, and superoxide dismutase (SOD) enzyme activity. Whereas those treated with the AGE formation inhibitor, aminoguanidine showed no significant changes in these parameters. Aminoguanidine also helps to prevent ageing associated changes like aortic stiffening as well as cardiac hypertrophy (23). These data indicate that D-galactose and L-glucose form AGEs in vivo and that elevated AGEs may accelerate the ageing process. The fact that both D-galactose and AGE treated mice resemble aged mice suggests that advanced glycation, at least partially, accounts for the mechanism of this ageing model (24).

As the age progress the amount of AGE levels enhanced in cartilage tissue as compared to young once. This result in increase collagen damage and enhance release of proteoglycans. The attempt to repair the matrix damage was impaired. Proteoglycan synthesis and retention were decreased at enhanced AGE levels (25). One of the mean through which advanced glycation end products modulates cellular function is through binding to specific cell surface receptor molecules and activate intracellular signal transduction mechanism which evoke formation of free radicals (26). During ageing there is increased production of ROS, hence increased lipid peroxidation (27). Superoxide anion, hydrogen peroxide and the hydroxyl radical are the major reactive oxygen species (ROS), which function in concert to induce LPO of cell membrane lipids. The natural cellular antioxidant enzymes include SOD, which scavenges the superoxide ion by speeding up its dismutation, CAT, a haeme enzyme that removes hydrogen peroxide and GPX (28),

a selenium-containing enzyme, which scavenges hydrogen peroxide and other peroxides. The ROS scavenging activity of SOD (29) is effective only when it is followed by the actions of CAT and GPX, because the dismutase activity of SOD generates hydrogen peroxide from the superoxide ion, which is more toxic than oxygen-derived free radicals and requires to be scavenged further by CAT and GPX (30). Apart from its own toxicity, hydrogen peroxide, in the presence of iron, leads to the generation of toxic hydroxyl ions (31). Thus glycation theory also revolves around free radical theory in some aspects through above explained mechanism.

Telomerase theory

The telomere-based model of cell ageing is most enduring hypotheses in cell biology. Telomeres are repetitive DNA sequences at the ends of linear chromosomes. Telomerase, a cellular reverse transcriptase, helps maintain telomere length in human stem cells, reproductive cells and cancer cells by adding TTAGGG repeats onto the telomeres. This model, suggesting that the gradual loss of telomere sequences during the proliferation of cultured human somatic cells imposes a barrier on cellular replicative potential, has been strongly supported by recent genetic and biochemical studies (32-34). The obligatory loss of telomeric DNA with each cell division serves as a mitotic clock and marks the rate of growth and repair processes in the cell. Although much more work is required, existing studies support the notion that telomere shortening is not only a clock of cellular division, but also marks relative growth rate, as well as contributing to common degenerative processes of ageing through its impact on cellular senescence. Accelerated telomere shortening appears be related to 'lifestyle diseases' that accompany certain concomitant metabolic factors such as obesity, hypernutrition and lack of exercise. The use of telomere length provides a new dimension to the study of metabolic and cardiovascular diseases with special reference to atherosclerosis (35). Recent research suggests that the relationship between telomere length and cell/ organism longevity is strong. Worms/birds with longer telomeres have been shown to have long lifespan (36).

DNA-repair defects can cause phenotypic changes that resemble premature ageing, and senescent cells that show DNA damage accumulate in the elderly (37).

Hormones and ageing

There are various obvious reports connecting hormones and ageing. The content of the neurosteroids, dehydroepiandrosterone (DHEA) in the brain decreases with ageing. Also the oxidative energy metabolism is known to decrease with ageing (38). In one study, neither DHEA nor low-dose testosterone replacement in elderly people has physiologically relevant beneficial effects on body composition, physical performance, insulin sensitivity, or quality of life (39). DHEA treatment stimulated mitochondrial dehydrogenases activities in both the groups. Results of our studies suggest that judicious use of DHEA treatment can improve oxidative energy metabolism parameters in brain mitochondria from young adult as well as old rats (40). Association studies have linked all of these age-related changes in hormone levels to some of the phenotypic changes of ageing, increased fat mass with visceral adiposity, reduced bone mineral density (BMD) and an increased risk of fracture, sarcopenia and frailty, a decreased quality of life, cognitive impairment, and an increased risk of cardiovascular disease (41). However, association is not causation is demonstrated by different studies (42).

The search for eternal youth will continue, but the reversal of age-related decreases in the secretion of DHEA and testosterone through "physiologic" replacement regimen offers no answer and should not be attempted. In light of an evidence base for the efficacy of DHEA in patients with adrenal insufficiency, DHEA should no longer be accepted as a food supplement and should instead be treated as a regulated drug. Appropriate regulation would dispel much of the quackery associated with this elusive hormone (43). It remains to be determined whether growth hormone secretagogues that consistently increase endogenous production of growth hormone are beneficial in the elderly. Anti-ageing therapy with growth hormone has not yet been proved effective according to objective outcome criteria (44). Once its detailed regulatory mechanisms are established, it could be an important tool to prevent diseases of old age and to promote healthy (quality) ageing in humans in near future (45).

Other factors

There are also several factors other than various theories, which can be crucial for ageing. It is known widely that healthy life styles, diet, exercise can increase longevity thus can be helpful for healthy ageing. Findings in older physically capable men indicate that regular walking is associated with a lower overall mortality rate. Encouraging elderly people to walk may benefit their health (46). In postindustrial societies, overeating, inactivity, and obesity have emerged as new challenges in public health. Considerable effort is now being devoted to determining the pathophysiological consequences of overeating. Several lines of evidence suggest that caloric intake influences the rate of ageing and the onset of associated diseases in animals and, possibly, humans. Excessive calorie intake can cause diabetes and hyperinsulinemia, whereas dysregulation of the insulin pathway has been shown to induce cellular senescence in vitro. Calorie restriction or a reduction of insulin signals extends the lifespan of various species and decreases biomarkers of cellular senescence in vivo. Caloric restriction in animal models delays many age-related pathological conditions. The observation that laboratory rats not only live longer but also have fewer age-associated diseases when their food intake is restricted dates back to the 1930s. Numerous subsequent studies have found that when the *ad libitum* food intake of mice and rats was reduced by 30 to 60 percent, the average life span and the maximal life span (the mean survival of the longest-lived decile) increased by similar amounts. In contrast, rats with nearly unrestricted caloric intake (92 percent of the average unrestricted intake) that were kept lean with exercise and weighed about 40 percent less than sedentary control rats with the same caloric intake had an increase in the average life span but not in the maximal life span. In all these studies, the life-extending

benefits of caloric restriction depended on the prevention of malnutrition and a reduction in overall caloric intake rather than any particular nutrient (47, 48). Ageing rats have characteristically increased body weight, fat mass and a specific body fat distribution. This report will focus on the potential cause-effect relationship between increased fat mass and accelerated ageing. In humans, increased fat mass (obesity), and in particular increases in abdominal obesity as a result of deposition of visceral fat, are associated with the metabolic syndrome of ageing. This syndrome is associated with hyperinsulinaemia, dyslipidaemia, type 2 diabetes mellitus, atherosclerosis, hypercoagulability and hypertension. Study suggests that decrease in fat mass and its beneficial repercussions observed in ageing animal models may apply also to human ageing and its related pathology (49).

Caloric restriction (CR) extends maximum longevity and slows ageing in mice, rats, and numerous non-mammalian taxa. The apparent generality of the longevity-increasing effects of CR has prompted speculation that similar results could be obtained in humans (50). Recent study claims a hypothesis-neutral model describing the relationship between diet and longevity. Applying this general model to the special case of human longevity and diet indicates that the benefits of caloric restriction in humans would be quantitatively small (51). Various studies also have been carried out in order to study effect of diet and longevity. Number of compounds found helpful in delaying onset of ageing symptoms. Lutein and zeaxanthine often occur together in green leafy vegetables, and are also found in such foods as corn, egg yolk, orange peppers, kiwi, and various kinds of squash. Dietary lutein and zeaxanthine are the two carotenoids most clearly associated with a decreased risk of age-associated macular degeneration, the leading cause of blindness among adults (52).

TRADITIONAL SYSTEM OF MEDICINE AND AGEING

Ayurveda, literally the "science of life and longevity" in ancient Sanskrit, is the one of the oldest healing system, based on lifestyle, diet and herbs. Ayurvedic texts contained complete sections on anti-ageing. Ayurveda contains several such plants have been dealt with ageing (53). *Susruta*, ancient Indian physician defies Rasayana as a measure, which prolongs and provides positive health, improves mental faculties and provides resistance and immunity against diseases. *Charaka Samhita,* a great ancient classic treatise of Ayurveda states that the means of obtaining optimum nourishment to the *Dhatus* are called Rasayanas (54). Rasayana plants are said to possess properties such as anti ageing, re-establish youth, strengthen life, brain power and prevent diseases all of which imply that they increase the resistance of the body against any onslaught. Traditionally, Rasayana drugs are used against a plethora of seemingly diverse disorders (55-57).

Traditional remedies and free radical induced damage

Ayurveda not only incorporates detoxification, antioxidant, *Vajikarana* (virilification) therapies, immunomodulation, Rasayana and adaptogens as well, but focuses on development of a specific lifestyle plan including individual dietary and exercise guidelines as well. Many of the traditional drugs are still proving useful beyond doubt and in future also, traditional knowledge will contribute pivotal role in ageing research. Plants with antioxidant activity are in high demand because of their anti-ageing effects (58). The use of herbal tonics as a part of a daily health regimen is found everywhere in traditional medicine (59). The Ayurvedic system contains several powerful antioxidant herbs as well as Rasayana drugs available to prevent degenerative diseases. For example, Amalaki (*Emblica officinalis*), or Indian Gooseberry is prized for its concentrations of naturally occurring vitamin C. This herb has been taken for centuries as chief ingredient in *Chyavanprash*, fortified with other balancing herbs as an antioxidant to prevent the occurrence of free radical chain reactions. In the Ayurvedic textbooks, rejuvenation has been termed as Rasayana. According to the definition of Ayurveda, Rasayana is one, which destroys the old age and disease. Rejuvenating agents are taken so that you become healthy and give your services for others. It is taken so that you can explore the spiritual aspect of life and help the society, the sick, the hungry, the poor and the disabled. The Rasayana or rejuvenation therapy aims at keeping the enzymes in the tissue cells in their normal functioning condition. This prevents the process of ageing and makes the individual free from any disease even during an advanced age.

Guduchi (*Tinospora cordifolia*), Gokshur (*Tribulus terestris*) are another Rasayana drugs. The Rasayana are the rejuvenative tonics that keep cells young and helped reverse age related damage. The objective is that all functions of the body are kept toned and working at optimum effectiveness. Ancient Ayurvedic physicians had developed certain dietary and therapeutic measures to arrest/delay ageing and rejuvenating whole functional dynamics of the body system. This revitalization and rejuvenation is known as the 'Rasayan chikitsa' (rejuvenation therapy). Adaptogenic herbs have the ability to work as a biological response modifier to environmental and psychological stress. Adaptogens in herbs like Ashwagandha support adrenal function by supporting the endocrine system (60). Rege et al. have studied adaptogenic potential of whole, aqueous and standardized extracts of selected plants *Tinospora cordifolia, Asparagus racemosus, Emblica officinalis, Withania somnifera, Piper longum* and *Terminalia chebula.* These plants are found to offer protection against these stressors, as judged by using markers of stress responses and objective parameters for stress manifestations (61). Indian system of medicine Ayurveda also have plethora of drugs, which are recommended for prevention of ageing. Antioxidant effect of active principles of *Withania somnifera* may explain, at least in part, the reported anti-stress, immunomodulatory, cognition-facilitating, anti-inflammatory and anti-ageing effects produced by them in experimental animals, and in clinical situations (62). 'Medhya rasayana', is known to act on the nervous system and is claimed to improve mental ability.

The Medhya rasayana contains mainly the extracts from plants like *Centella asiatica*, *Acorus calamus*, *Nordostrychnus jatamansi*, *Bacopa monnieri*, etc (63). Antioxidant effect of

active principles of W. somnifera may explain, at least in part, the reported antistress, immunomodulatory, cognition-facilitating, anti-inflammatory and anti-aging effects produced by them in experimental animals, and in clinical situations (64). *Chlorophytum tuberosum* Baker commonly referred as 'Musli' has been widely used as a potent 'Rasayana' drug in Ayurveda as a rejuvenator and tonic (65).

Traditional Chinese system and anti-ageing plants

Traditional Chinese system of medicine, one of the oldest living systems, put forward various anti-ageing drugs, in which Ginseng, astragalus and many other plants are important. Chinese systems of medicine also have various drugs and from reported studies there is strong correlation between antioxidant, nootropic and anti-ageing activities shown by different plants. Although plants with antioxidant potential are much greater in number, some of them are used as anti-ageing in these traditional systems of medicine. There are many studies of above mentioned plants acts as free radical scavenger.

Cheng Y et al overviewed the discovery of new biological activities induced by ginsenoside Rg1 and Rb1 and discussed possible mechanisms of action. Both compounds could increase neural plasticity in efficacy and structure; especially Rg1, as one small molecular drug with important neuron protective factors, can increase proliferation and differentiation of neural progenitor cells in dentate gyrus of hippocampus of normal adult mice and global ischemia model in gerbils. This finding has great value for treatment of Alzheimer's disease and other neurodegenerative disorders which is characterized by neurons loss (66). Total lactones of ginkgo possess effect on anti-ageing via attenuating lipid peroxidation and NO and apoptosis of cerebral cells (67). Ginsenoside Rg1 was found to selectively enhance the deteriorated immune function in aged animals, ameliorate age-related alterations in both behavior and motor response, promote hippocampal neuronal function of aged rats, and provide partial protection against the excitotoxic effect of glutamate. All of these provide several aspects of explanation to elucidate Rg1's anti-ageing and nootropic mechanisms (68). Enhanced maze performance and reduced oxidative stress was observed by combined extracts of *Zingiber officinale* and *Ginkgo biloba* in the aged rat and might also facilitate spatial learning in aged animals (69). *Phragmizes communis* polysaccharide could obviously increase the activity of CAT, SOD and GSH-PX in blood, lower the levels of LPO in plasma and the thick liquid made of grinding the tissues of brain and liver, and markedly resist the atrophy of the thymus, spleen and brain tissues of ageing mice (70). Astragalus (AST) has an anti-ageing effect on D-galactose induced senescent mice and has the effect of delaying senility of the middle aged mice, which was related to its improvement of brain function and immunomodulatory effects. AST was found to ameliorate age related alternations in both motor response and memory, enhance the deteriorated cellular immunity in D-galactose treated mice and the pre-aged (17 month old) mice (71). The active oxygen scavenging activity of 70 traditional herbal medicines used in China and Japan as nourishing tonics was evaluated by electron spin resonance (ESR) technique, in order to evaluate their effectiveness for anti-ageing and to search for new active-oxygen scavengers from natural resources. Most of the 70 herbal medicines showed scavenging activity with various intensities. These active-oxygen scavengers may contribute, to different extents, to their anti-ageing action (72). Chen K et al. reports studies on 386 traditional effective anti-ageing medications, the effects of which on cell generation, survival time, immunomodulation, improvement of visceral and metabolic functions, and anti-infection, and their trace element contents were further summarized and analyzed. This suggests that the investigations of traditional anti-ageing Materia Medica in China are now well under way and some effective drugs and compound prescriptions have been explored, such as Ginseng, Radix Astragali seu Hedysari, Radix Angelicae Sinensis, Herba Epimedii, Cordyceps, Ganoderma Lucidum seu Japonicum, Radix Polygoni Multiflori, Radix Acanthopanacis Senticosi, Rhizoma Polygonati, Fructus Lycii, and Poria. However, all of these preliminary results remain to be further investigated (73). In a nutshell, traditional systems can act as complementary medicine with a viable system of health maintenance for ageing research. In future, also it has potential to provide many leads for ageing research.

OVERVIEW AND CONCLUSION

Most theories of ageing have strong correlation with oxidative stress and revolve around free radical induced damage which may be mediated through by one or another mechanism. Mitochondrial damage and glycation induced consequences are associated with free radicals. With the advent of newer concepts, the scope of subject has widened in recent two decades. In this situation, traditional knowledge can play key role with number of plants giving protection against free radicals. This also necessitates further research in this field to corroborate traditional claims with modern techniques. Healthy ageing and maximum longevity may depend on the genetic make-up of an organism, with the proviso of strict control by nature and nurture. As there is no current magic-bullet that retards or reverses ageing, at present search for magic bullet for ageing seems big challenge in front of mankind.

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