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Review Article

Aging and Pharmacology

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Abstract

Aging is a natural physiological process which is progressing at different rates in some people. With increasing age, many changes occur in organs and organ systems, which leads to a progressive weakening and damage to their function, so in old age certain chronic diseases occur more frequently, and thus the functional disability of the elderly. Old age is a time when life acquires new spiritual dimensions and benefits that were not present at a younger age. Opportunities for development and opportunities for reorientation work activities are opening up. Active healthy aging involves adapting to new circumstances, cognitions, and constant learning and discovering the benefits of aging and old age. Thanks to the increase in the general standard of living and the improvement of health care and as a consequence of the reduction of natural increase, in developed countries there has been an increase in life expectancy, and thus a higher share of older people in the total population. The number of inhabitants over the age of 65 is constantly and rapidly growing, primarily in economically developed countries, and this tendency is also present in developing countries.

Keywords: Age; Aging; Pharmacology; Health

Introduction

Aging is a physiologic process, and the term healthy aging does not imply an absence of limitations, but rather an adaptation to the changes associated with the aging process that is acceptable to the individual [1]. Successful or healthy aging appears to include three factors: (1) low probability of disease and disability, (2) higher cognitive and physical functioning, and (3) an active engagement with life. Healthcare providers can promote healthy aging by assisting the older adult in developing competence in directing and managing future roles, thereby maintaining autonomy and a sense of self-worth.

While there are common physiologic changes associated with aging, the geriatric population is a highly heterogeneous group with varying degrees of chronic disease, and physical and cognitive disability within individuals. A number of chronic conditions commonly affect this population. The overall health status and well-being of older adults is highly complex and results from many interacting processes, including risk factor exposure (tobacco, alcohol, drugs, diet, sedentary lifestyle), biological agerelated changes, and the development and consequences of functional impairments. Many of the conditions previously considered "normal aging" are now known to be modifiable or even preventable with appropriate disease prevention and health promotion strategies.

Aging, from maturity to senescence, results in an apparent depletion of physiologic reserves that has been termed homeostenosis [2]. This term suggests a narrowing of homeostatic reserve mechanisms. Homeostenosis leads to the increased vulnerability to disease that occurs with aging. Primary aging changes, upon which we focus here, are those that occur as a result of the passage of time and are independent of disease state, although there may be overlap between disease and these changes. The age changes may be accelerated or slowed by lifestyle but are usually evident by the fourth or fifth decade and are gradual and inexorable. Overall, primary aging changes result in little change

in function when the older individual (or animal) is assessed in the unstressed state, but these age changes become readily evident when the older individual is stressed or moved away from homeostasis. Because disease produces such stresses, the impact, presentation, and natural history of diseases are modified with age because the substrate, perhaps more than the disease pathophysiology, has been modified.

With aging, the capacity of older persons to bring themselves back to homeostasis after a challenge becomes smaller. All challenges to homeostasis are movements off the baseline,and larger challenges require greater physiologic reserves to return to homeostasis. Aging itself brings the individual closer to the precipice or threshold by the loss of physiologic reserves. The "precipice" may be defined, for example, as death or ill enough to have a cardiac arrest or for hospital admission. The precipice may also be the appearance of common and protean symptoms, such as confusion, weight loss, sleep disorder, or weakness.

Changes

Aging is generally considered as a progressive and irreversible set of structural and functional changes, due both to the genetic background of the individual and the oxidative damage and modifications of intracellular signaling mechanisms [3]. Although the anatomical and physiological alterations associated to aging (e.g. sarcopenia, cognitive and sensorial decline, functional loss in cardiovascular system…) are not a disease, they reduce the functional reserve of the organism, ultimately leading to pathological alterations and death.

Improvements of nutrition, hygiene and public health, and medical diagnosis and treatments have dramatically extended life expectancy in the last decades. However, the rate of human aging is to the moment an elusive target in biomedical interventions. The achievement of a slowing of human age is not necessarily linked to an increase of morbid, unhealthy population, but is likely to postpone the onset of age-related pathologies. Pharmacological intervention to decelerate aging and age-related diseases is highly attractive because it would target all the population during many years. If successful, antiaging therapy will be more efficient in reducing mortality than to fight separately each age-related disease. Research on anti-aging interventions has evolved along the main theories of aging.

Aging produces both pharmacokinetic and pharmacodynamic changes [4]. Muscle mass progressively decreases with aging along with an increase in body fat content resulting in decreased total body water. This reduces the volume of distribution of water-soluble drugs while increasing the volume of distribution of lipid-soluble drugs. Renal function decreases with age resulting in the decline of the kidney's ability to excrete drugs. Liver mass and blood flow decreases with age, thus, the rate of biotransformation of drugs also decline. Distribution and elimination are also affected by protein binding.

Process

The aging process begins in the third and fourth decade of life but then progresses quickly throughout the sixth decade [5]. However, fine lines and wrinkles can begin to appear on the skin as early as the second decade of life. Certain factors such as the amount of sun exposure and other lifestyle habits such as smoking, hydration, stress, environmental exposures, chemical exposures, and other factors initiate and accelerate aged appearance. Static lines are visible at rest or without facial muscle motion, and contribute to the appearance of aging. These lines are a source of distress for many aesthetic patients and are a frequent cause for aesthetic consultation.

Many patients also complain of fine, crêpey skin under the eyes. The thinness of the skin in the suborbital area lends itself to fine lines, even when the remainder of the facial skin may have few, if any wrinkles. Non-ablative carbon dioxide laser resurfacing treatments have been successful in treating fine lines in the thin skin of the upper and lower eyelids. In addition to laser treatments, lower eyelid skin has been shown to respond favorably to topical tretinoin.

Deeper wrinkles and folds are the result of one or more of the following: (1) sun exposure with subsequent collagen breakdown, (2) gravity in association with volume loss from aging or weight loss, (3) facial muscle contraction, (4) genetic influence, (5) bone changes. Some of these causes can be prevented or controlled, while some are the result of a natural process or genetic tendencies. Facial changes become more apparent between 35 and 50 years of age. This age group is the largest portion of the population who seeks aesthetic enhancement.

Static lines, increased skin laxity, discoloration, changes in bone structure, and softening of tissues that support the face all intensify the appearance of aging. Prevention of damage from ultraviolet (UV) radiation from sun exposure is an important aspect in the prevention of pre-mature aging. Protection from the UV rays of the sun can be achieved by using physical block, such as clothing, or chemical block from sunscreens. This is an important strategy recommended for young and old alike.

Antioxidants

Given the large evidence linking oxidative stress with aging, the use of antioxidants has been a repeated approach in anti-aging research for decades [3]. Even if aging itself is not due to oxidative damage, this approach could extend average life by reducing the mortality of a number of pathological conditions associated to oxidation.

The most frequently assayed antioxidants are present in vegetables and fruits, not only vitamins E (tocopherols), A (carotenes) and C, but also flavonoids (from tea and Ginkgo biloba), phenolic compounds (e.g. resveratrol in grapes), catechins and others. A number of artificial antioxidants have also been assayed (deprenyl, NDGA, PBN, thioproline,…). It must be noted that efficiency not only depends on their oxidant scavenging activity, but also in humans bioavailability factors (absorption, lifetime,…) so that animal studies are a requisite even for initial evaluation of the potential utility of an antioxidant.

CR

Caloric restriction (CR) is the most robust non-genetic nutritional experimental intervention for slowing aging, and maintaining health and vitality in organisms ranging from budding yeast (Sacharomyces cerevisiae) to humans [3]. It is defined as a reduction of total macronutrient intake without causing malnutrition, with food intake reduced by 30-40% compared to ad libitum levels. Experiments involving CR in rodents in 1935 provided the first promise for modulation of lifespan. Since then CR has been repeatedly proved to be effective in extending average and maximum lifespan and delaying the onset of age-associated pathologies in diverse species. It was not until the 1990s that CR became widely viewed as a scientific model that could provide insights into the underlying mechanisms of aging and lifespan extension. The fact that CR significantly increased the average and maximum lifespan in many simpler eukaryotes, including the common model organisms used in aging research, Drosophila melanogaster, Caenorhabditis elegans and Saccharomyces cerevisiae pointed out that CR represents an evolutionarily conserved mechanism for modulating longevity and opened the possibility of using genetic tools in these models that helped to unveil intracellular pathways related to pro-longevity.

CR induces transcriptional alterations that are indicative of metabolic reprogramming, a change in how energy is generated and how fuel is utilized. A key metabolic change during CR is a shift from fat storage to fat utilization impacting stress signaling pathways and ROS production. Immediately following food intake there was a period of endogenous fatty acid synthesis that was then followed by a period of prolonged fatty acid oxidation, which induces large changes in the respiratory quotient (RQ). In addition, during CR there is an increase in the AMP/ATP ratio which leads to the activation of the AMP-activated protein kinase (AMPK) that promotes fat oxidation increasing the transport of fatty acids into the mitochondrion. In fact, marked phosphorylation of AMPK has been found after long term CR. Because fatty acid substrates enter the electron transport chain predominantly via complex II rather than complex I, the main ROS generator is bypassed when the metabolism is switched predominantly to fatty acid oxidation. This might represent a mechanism minimizing oxidative stress under CR.

Minerals

Calcium and phosphate, the major mineral constituents of bone, are also two of the most important minerals for general cellular function [6]. Accordingly, the body has evolved complex mechanisms to carefully maintain calcium and phosphate homeostasis. Approximately 98% of the 1–2 kg of calcium and 85% of the 1 kg of phosphorus in the human adult are found in bone, the principal reservoir for these minerals. This reservoir is dynamic, with constant remodeling of bone and ready exchange of bone mineral with that in the extracellular fluid. Bone also serves as the principal structural support for the body and provides the space for hematopoiesis. This relationship is more than fortuitous, as elements of the bone marrow affect skeletal processes just as skeletal elements affect hematopoietic processes. During aging and in nutritional diseases such as anorexia nervosa and obesity, fat accumulates in the marrow, suggesting a dynamic interaction

between marrow fat and bone. Furthermore, bone has been implicated as an endocrine tissue with release of osteocalcin, which in its uncarboxylated form stimulates insulin secretion and testicular function. Abnormalities in bone mineral homeostasis can lead to a wide variety of cellular dysfunctions (eg, tetany, coma, muscle weakness), disturbances in structural support of the body (eg, osteoporosis with fractures), and loss of hematopoietic capacity (eg, infantile osteopetrosis).

Diabetes

Diabetes is a group of metabolic disorders characterized by inefficient utilization of blood glucose in the body due to the body's inability to produce any or enough insulin [7]. The three most commonly recognized forms of diabetes are: (i) Type 1 Diabetes Mellitus (T1DM) or Insulin Dependent Diabetes Mellitus (IDDM); (ii) Type 2 Diabetes Mellitus (T2DM) or NonInsulin Dependent Diabetes Mellitus (NIDDM); and (iii) Gestational Diabetes. Approximately, 90% of all diabetes cases worldwide are T2DM followed by 5-10% of T1DM cases. Gestational diabetes is typically seen in females during pregnancy.

With the steady rise in diabetes over the past decade, it is projected that by 2050 the prevalence of diabetes will increase from 14% to between 21% and 33% of the adult population [8]. This rise is expected to be at least partially due to the increasing size of high-risk minority populations and the aging of the population. The burden of diabetes is rapidly growing and placing a significant impact on the health-care system as well as the quality of life for these individuals.

Pharmacists in a variety of practice settings can be an integral part of managing patients with diabetes or identifying those patients at a high risk of developing diabetes. Pharmacists are exposed to rigorous curriculums that prepare them not only to be medication experts but also to effectively manage patients with chronic disease states, such as diabetes. With the increasing number of patients affected by diabetes and amount of education and attention needed to properly manage these patients, combined with shortage of primary care providers, patients may not be receiving adequate diabetes education or management. Pharmacists are well positioned and qualified to help fill this gap in care experienced by many patients. Having a pharmacist as part of the diabetes care team allows the practitioner to see more patients with acute problems while still having the large number of patients with chronic conditions managed.

Hypertension

A specific cause of hypertension can be established in only 10 - 15% of patients [9]. Patients in whom no specific cause of hypertension can be found are said to have essential or primary hypertension. Patients with a specific etiology are said to have secondary hypertension. It is important to consider specific causes in each case, however, because some of them are amenable to definitive surgical treatment: renal artery constriction, coarctation of the aorta, pheochromocytoma, Cushing's disease, and primary aldosteronism.

In most cases, elevated blood pressure is associated with an overall increase in resistance to flow of blood through arterioles, whereas cardiac output is usually normal. Meticulous investigation of autonomic nervous system function, baroreceptor reflexes, the renin-angiotensin-aldosterone system, and the kidney has failed to identify a single abnormality as the cause of increased peripheral vascular resistance in essential hypertension. It appears, therefore, that elevated blood pressure is usually caused by a combination of several (multifactorial) abnormalities. Epidemiologic evidence points to genetic factors, psychological stress, and environmental and dietary factors (increased salt and decreased potassium or calcium intake) as contributing to the development of hypertension. Increase in blood pressure with aging does not occur in populations with low daily sodium intake. Patients with labile hypertension appear more likely than normal controls to have blood pressure elevations after salt loading.

Glaucoma

The demographic change in aging societies entails that the prevalence of neurodegenerative diseases increases [10]. Degenerative eye diseases impede independence and life quality of patients and lead to accidents and high nursing costs. Therefore, a good visual function is crucial for aging humans. Globally, glaucoma is the most frequent cause for blindness. Many cases remain undiagnosed. Glaucoma prevalence increases with age and amounts to about 3.5% in 40 - 80-year-old people. Therefore, glaucoma treatment has high priority.

Glaucoma is characterized by a disbalance of aqueous humor production and absorption (outflow in the anterior chamber).

The major risk factor for glaucoma development is increased IOP (Intraocular pressure). Accordingly, to reduce IOP is the most important aim of pharmacological intervention. Myopia, low cornea thickness, poorly controlled hypertension, other eye diseases, a positive family history, and DM (Diabetes mellitus) favor glaucoma development.

In the rare narrow-angle glaucoma, Schlemm's canal is constricted and humor outflow is reduced. No apparent pathological changes appear in the very common open-angle glaucoma, but nonetheless, humor outflow is reduced in relation to humor production. As consequence of the disbalance, the IOP, usually ranging between 10 and 21 mm Hg, is increased. It is determined by tonometry. A long-lasting IOP increase leads to damage of the optic disc and excavation. This is diagnosed by fundoscopy, kinking of blood vessels being a hallmark. Initially, patients do not have symptoms. When time goes by, increasing peripheral scotomas develop, ultimately affecting central vision. Scotomas are diagnosed by perimetry. In many cases, glaucoma develops in spite of an IOP within the normal range. Nonetheless, IOP is crucial for therapy because an effective pressure reduction delays disease progression even with apparently "normal" values. An important cause for glaucoma pathogenesis is systemic or local long-term therapy with GCR (Glucocorticoid receptor) agonists which inhibit humor outflow.

Alcoholism

Alcohol is a psychoactive (mind-altering) chemical that, like heroin and tranquilizers, depresses the CNS (central nervous system) [11]. It is an efficient tranquilizer with the ability to reduce short-term anxiety. However, alcohol first affects the part of the brain that controls inhibitions: Drinkers talk more, exude self-confidence, and may get foolish or even rowdy; there is a general loss of self-restraint.

Alcohol is a complex substance that affects a number of neurotransmitter and receptor systems in the brain: endorphin, dopamine, serotonin, and glutamine. When alcoholics imbibe, their brains release elevated levels of endorphins, triggering rewarding sensations that entice the person to drink more. However, at low doses, alcohol acts as a stimulant, and initially, the user of alcohol often experiences it as an energizer with euphoric effects. As with most other psychoactive substances, this is the result of alcohol stimulating the dopaminergic reward pathway in the brain.

Regular use of moderate daily amounts of alcohol can produce psychological dependence, the lack of alcohol resulting in anxiety and mild panic attacks. Prolonged or chronic drinking produces both psychological and physical dependence. The stronger depressant effect lasts about two hours, while a weaker stimulation of the CNS lasts about six times as long. As the time since the last drink increases, the longer-lasting stimulating effect becomes dominant, and the drinker becomes agitated-the "morning-after hangover". This is the start of the drinker's withdrawal syndrome. Because of alcohol's primary depressant effect, calm can be temporarily restored by more drinking. For the alcoholic the morning drink has a calming effect that is part of a vicious cycle of continued alcohol use.

At age 65, the body's ability to respond to alcohol is quite different from that at age 45. Thus, older adults can get into trouble after drinking an amount of alcohol that would not be considered immoderate at a younger age. As people age, they lose muscle, bone, and lean body mass and acquire a greater percentage of body fat. As a result, there is a decrease in body water, in which alcohol is soluble, replaced by fat, in which alcohol is not soluble. Aging also results in a decline in a stomach enzyme that breaks down alcohol before it reaches the bloodstream. As a result, there is greater burden on the liver, where most alcohol metabolism takes place. Advancing age also causes a decline in the blood flow through the liver, so alcohol is eliminated more slowly from the blood. Thus, blood alcohol levels in older people are 30–40 percent higher than those in younger people.

Alcoholism is a complex relapsing disorder of heterogeneous etiology, affecting people internationally [12]. Alcohol dependence is a cumulative response of inability to stop drinking, craving and developing the symptoms of physical dependence and tolerance. In past few decades, mounting evidence has suggested that alcoholism or alcohol addiction is a host of major psychological, social, financial and health problems. According to World Health Organization, alcoholism is responsible for 4% of global disease burden and is the third major preventable risk factor for premature

death and disability in developed nations. Although, the exclusive biological mechanisms underlying the development of alcoholism are still uncertain, the major risk factors contributing towards the development of alcoholism are age (adolescents are at higher risk of developing alcoholism), gender (men are more prone to develop alcoholism as compared to women due to depression), personality (experience seeking), and psychiatric or behavioral disorders. The prevalence, age of onset, clinical symptoms and outcome of alcoholism differs from individual to individual and varies according to ethnicity. In addition to this, lower social status and low education have also been found to be associated with alcoholism in cross sectional and longitudinal studies.

Genetic factors have been found to play a critical role in the etiology of alcoholism. Researchers have suggested that 50-60% of alcohol dependence is determined by genetics. Based on results of adoption, twin, and family studies it is now clear that the vulnerability to alcoholism is determined by genetic factors as well as by environmental factors. However, it is difficult to determine the individual determinant of alcoholism. The candidate gene approach has revealed a number of biomarkers, which are responsible for alcoholism. Certain variants of alcohol dehydrogenase and aldehyde dehydrogenase genes (genes encoding for alcohol metabolizing enzymes) have been found to alter the metabolism of alcohol in a dramatic way. In addition to this, polymorphisms in neurotransmitter genes (target receptor genes) such as gamma amino butyric acid and opioid receptor genes have also been reported to be associated with marked risk of alcohol dependence. Current treatment approaches to alcoholism are moderately effective with perhaps as many as half of the patients receiving treatment due to abstinent or significantly reducing episodes of binge drinking.

Conclusion

Older people represent a very specific and vulnerable age group whose share is progressively increasing, which significantly affects the health, economic, social, educational and economic structure of the entire population. Gerontology is a scientific discipline which studies aging in the broadest sense, ie its clinical, biological, economic, social and psychological aspects. This results in a comprehensive, holistic approach to health care for the elderly, which ensures the improvement of all forms of health care for the elderly. Knowledge about aging is constantly increasing and changing, which is why gerontology as a scientific discipline occupies an increasingly important place in the developed countries of the world. Older people are the biggest consumers of drugs and consume twice as many prescription drugs as the general population. Due to the peculiarities of this age group, which are a consequence of aging, there is a change in the function of individual organs and the organism as a whole. Changes can be manifested throughout the course of the drug, from ingestion to excretion. It is therefore important that the elderly take the medication in the exact prescribed dose and in the prescribed manner. Older people should not take medication "on their own" without consulting a doctor, and especially not to change their dose. The amount of a drug in an elderly person may be less than the amount that a younger person will receive for the same disease. The two most important organs involved in the decomposition and excretion of the drug - the liver and the kidney - work weakened and the dose should be adjusted to their function. Older people are also more sensitive to the effects of some medications, especially those for sleep and sedation, and to pain medications. Because of that, side effects to the drug are also more common in older people.

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