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Review Article

DIETARY POLYAMINES FOR MODULATION OF AGING PROCESS IN THE GERIATRIC POPULATION

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ABSTRACT

Polyamines (putrescine, spermidine and spermine) are ubiquitous low molecular weight amines that are positively charged under physiological conditions. Homeostatic control of intracellular polyamines level is achieved by regulating the synthesis, catabolism and transport of these molecules. Polyamines are involved in the regulation of a diverse range of vital cellular processes in both eukaryotic and prokaryotic cells, including cell proliferation, signal transduction and membrane stabilization. Putrescine, spermine and spermidine universally occurring in plant organs are involved in a wide array of processes, ranging from triggering organogenesis to protecting against stress. These plant polyamines provide the basis of dietary supplementation to maintain health. Although intake of dietary polyamines has been known for years as an important factor of health and disease, there are not too many literature reporting the exact polyamine food contents. The latest findings on the action of polyamines on the aging and disease processes suggest that polyamines, especially spermidine, are proven to be beneficial for modulating the aging process in the normal geriatric population. Up to this point, most of the modifications recognized to be beneficial to aging via dietary modification may be actually helpful against age-related diseases.

Keywords: Polyamines, Dietary polyamines, Aging

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INTRODUCTION

Polyamines, in all living eukaryotic and prokaryotic cells, are biogenic amines which are basic in nature, having physiologically important roles in cell growth and differentiation via their modulations of DNA, RNA and protein synthesis (1,2). Polyamines are involved in the regulation of a diverse range of vital cellular processes in both eukaryotic and prokaryotic cells, including cell proliferation, signal transduction, and membrane stabilization [3]. These amine molecules are also involved in the regulation of gene expression and translation [3], and control programmed cell death in some organisms [4]. The diamine putrescine and the triamine spermidine have been found to accumulate in nearly all organisms and are the most abundant polyamines in prokaryotic cells, such as bacteria, while the tetraamine spermine is mainly found in eukaryotic cells. In the human being, body polyamine pools have sourced the diet, synthesized in the cell, and through microbial synthesis in the intestine [5,6]. The action of cytoplasmic arginase yields ornithine, which can be converted into putrescine via the action of ornithine decarboxylase (ODC), the highly regulated and rate-limiting enzyme in the polyamine biosynthesis [1, 2]. Other regulated enzymes convert putrescine to spermidine and spermine by the addition of aminopropyl groups. The groups can also be removed by being first acetylated and then oxidized by specific enzymes [7], allowing for interconversion and degradation of the different polyamine pools. As much as the uptake of polyamines is important, the efflux of polyamines is also tightly regulated to maintain specific polyamine contents within the cells [1, 2, 7, 8].

In recent years there have been considerable interests in investigating the role of ingested polyamines from plant-based foods on human health. In a recent study comparing several vegetable crops cultivated using organic or conventional procedures, A group of investigators recently reported that organic vegetables contained higher concentrations of polyamines than those produced by conventional cultivation, and suggested that this could be due to plants cultivated organically being subjected to stress from pests and/or diseases [9]. It is important that factors regulating polyamine metabolism in plants be thoroughly studied in order to understand the role of polyamines of plant origin on human health, After all, these ubiquitous molecules involve in an array of specific roles that are essential to cell growth and proliferation. Polyamines may be considered especially important in the young [10]. However, it is well established that the capacity for polyamine synthesis decreases with age [11]. It is therefore postulated that a decrease in polyamines contents could contribute to the acceleration of aging process in human beings.

Nutritional polyamines from different dietary sources

As have been suggested previously, polyamines exert a number of physiological functions in plants. Overall, these molecules are associated with plant growth, differentiation, and development. Polyamines have been found to play important roles in the process of embryogenesis, root and shoot formation, floral initiation and fruit development [12]. In many years there have been burgeoning interests in studying the roles for polyamines in protecting plants against environmental stressors [13]. In this regards, cellular polyamines have been known to fluctuate significantly in both compositions and concentrations responding to specific kinds of environments and their conditions [8, 13, 14]. Amid the fact that they clearly play important roles in protecting plant cells from unfriendly environmental conditions, their precise action remains largely unknown. However, stress-driven fluctuations in polyamine metabolism may lead to the fluctuating levels of bioavailable polyamines in plant-based foods.

Putrescine contents are commonly found to be the highest among polyamines in nature, and this fact correlated well with the average total polyamine daily intake by adult subjects. A recent study conducted in the United Kingdom found that the average polyamine intake of adult subjects was 388 µmol, represented by 220 µmol of putrescine, 99 µmol of spermidine and 69 µmol of spermine [15]. Some of the tested foods contain a considerably higher average of putrescine level (above 40 mg/kg), namely mandarins, oranges, grapefruit juice, orange juice, and other processed foods ketchup, frozen green peas, sauerkraut, and soy fermented products [16]. Spermidine contents in plant foods are commonly higher than spermine levels. Some food items like soyben, legumes, the fruitpear, the vegetables cauliflower and broccoli belong to categories with the highest spermidine level, usually above 30 mg/kg) [16]. In this regards, legumes, also have the highest spermine level.

There are reports on polyamine content of green vegetables to be high in spermidine [15]. Red meat and poultry have been found to be high in the spermine content, whereby some other vegetables, fish, and certain fruits were high in putrescine [15]. Other studies suggest that peas, corn and potatoes are particularly good sources for putrescine and spermidine [16]. Other vegetables such as peas are also rich in spermine compared with the other foods of plant origin tested. The fruit oranges provide high levels of putrescine, while pears provide high putrescine and spermidine levels [11]. Another report Japanese suggests soybean, green pepper, wheat germ, rice bran, pumpkin, fermented natto, pistachio nut, orange, mango, and green tea leaf contain high polyamine contents from the corresponding plant sources [17]. Another group researchers also investigated the polyamine levels of Asian foods [18]. The highest putrescine concentrations were found in soybeans, citrus fruits maize, and peas, while spermidine was found in high amounts in soybeans, other beans, and vegetables. Soybeans and other beans were also rich in spermine [18].

Wide variations of polyamine contents within the individual foods are common. For example, food originated from meat, fish and meat products tend to be high in concentrations of putrescine and spermine, but low in concentrations of spermidine, which are in contrast to plant-derived foods, which tend to be high in concentrations of putrescine and spermidine [16]. Fermentation of food enhances the polyamine content of some products, just an example, the putrescine contents of sauerkraut and cooked cabbage was reported to be 146 mg/kg and 5.6 mg/kg, respectively [16]. The polyamine contents in cheese are reportedly high, particularly in mature cheddar, but are relatively low in yoghurt [19]. It is interesting to note that cooking appears to have little effect on the composition and concentration of polyamines in most foods tested (e. g. carrot and potato), but does influence content in others [19]. For example, mean putrescine content decreases slightly in broccoli after cooking, but spermidine decreases quite considerably [19]. A decrease in polyamine content tends to occur as fruits and vegetables ripen [16, 20] indicating that ripeness and length of time from harvesting to consumption may also influence the polyamine content of plant-derived foods [10].

Dietary polyamine supplementation

Long-term supplementation of diets with polyamines or polyamine-rich foods has been shown to increase polyamine concentrations in the blood in animal models and humans. For example, mice fed experimental chow containing high concentrations of polyamines for 26 w had significantly higher concentrations of blood spermine and spermidine than mice fed chow containing low or normal concentrations of polyamines [21]. The investigators noted that there were considerable blood spermine and spermidine variability between mice, which was exaggerated in mice fed the high polyamine diet [21]. These findings are supported with human data [10.14]. Healthy human male volunteers were asked to either exclude soybean products and fermented foods from their diet or include 50-100 g of natto, a fermented soybean product, in their diet for 2 mo [22]. Following long-term daily consumption of natto, blood spermine concentrations significantly increased, but concentrations remained unchanged in those from the control (no natto) group. The blood spermidine concentrations did not change for either group. Interestingly, although not statistically significant (p=0.06), age had a positive correlation (r=0.62) with changes in blood spermine concentration [22]. The findings from this study demonstrate that long-term intake of a polyamine-rich diet can increase polyamine blood concentrations, and the effect of dietary polyamines might be greater in older people.

Polyamines and human aging

By the year of 2050, total world population with the age of 80 y and older will more than 3 times, nearing 400 million people [23]. As the world population gets older, the total burden of disease and disability globally would rise. It has been estimated that from year 50 of human life, advancing age is correlated with an exponential rise in burden originated from a number of different chronic diseases [24]. The most reliable and effective methods to decrease disease burden and impose cost control measures is to postpone this progression by extending healthy life span, i.e. the time a person lives in a free of disease and disability condition [24]. A key to extending health span is addressing the problem of aging itself, potentially by means of dietary modification in the elderly.

As have been implicated in a number of studies, aging is a multifaceted biological process, possibly advanced by many intervening parameters which pose many consequences at every level within the organism [25, 26]. It has been implicated that factors which lead to the aging process are numerous, which among others, include chronic inflammation, cellular and molecular stress, cell survival and death, dysregulation of lipid metabolism, as well as the phenomenon of autophagy [26]. These factors are known interact with each other in a complex process as yet to be deciphered. All interventions against aging ought to impact many different factors affecting aging and its sequelae [24]. Dietary restriction could be one of such interventions having its wide-ranging effects [10]. In this regard, diets containing polyamines, especially spermidine, hold a promise as an aging process modulator [27].

There is a consensus among the literature that polyamine concentrations within the body decrease with age, although this may be tissue specific [28]. The effect that this has on health is still being understood; however, enhancing polyamine intake appears to have a positive effect on health as aging progress. However, it has only been recently that the effect of polyamine spermidine on aging has been recognized. A group of investigators recently reported that spermidine levels in humans with the ages between sixty and eighty years old were lower than in those with age below fifty years old, but people older than ninety have levels similar to people below fifty [29]. These results suggest that maintaining a certain level of spermidine in the body may, in fact, contribute to longevity [27]. Several investigators have also shown that polyamine concentrations could be elevated in both model organisms and humans by dietary polyamine supplementation [27, 30]. Some foods and drinks known to contain high polyamine levels are orange, green tea, mushroom, rice bran, green pepper, broccoli, and soybean.

The effect of age on polyamine concentrations in tissues was also examined by Nishimura *et al.* [17]. Overall, the concentration of polyamines (spermidine and spermine) decreased with increasing age (0-9 mo) in all tissues examined from rats [31]. However, the decrease in spermidine was most marked during the first month of life, decreasing relatively slowly after one month, and the concentrations of spermine increased slightly during the first month in the liver, thymus, spleen and kidneys, and remained unchanged or decreased slightly after one month, and from birth in other tissues. Similar trends were observed in aging mice (3 to 26 w), with a significant decrease of spermidine in the thymus, spleen, ovary, liver, stomach, lung, kidney, heart and muscle, as well as skin from the ear and abdomen [17]. In contrast, however, the polyamine concentrations in the pancreas, brain and uterus were maintained in the aging mice. It was suggested that stimulation of protein synthesis and modulation of the ion channels are the most important functions of polyamines, and these functions are necessary activities in these organs/tissues. Therefore mechanisms exist in these tissues to maintain polyamine concentrations through aging [17]. Furthermore, these investigators recommended that since the decrease in spermidine was most marked, either foods containing putrescine, spermidine and spermine or foods particularly rich in spermidine should be consumed [17]. As indicated above, green vegetables, corn, peas, beans, and potatoes are particularly rich sources of spermidine, possibly suggesting that a predominantly plant-based diet would provide the polyamines of most benefit as humans' age.

The dietary intake of polyamines has been cautioned in the past because the increased requirement for polyamines by rapidly dividing cells and tissues, such as tumor cells, has been well recognized [1, 2, 8]. Notwithstanding the requirement for polyamines in tumorigenic tissue, evidence suggests that enhanced endogenous polyamine concentrations promote health during aging via a number of mechanisms. Enhancement of lifespan in human

cells was recently demonstrated using the long-term culture of peripheral blood mononuclear cells (PBMCs), treated with or without exogenous spermidine in the culture medium, and measuring cell survival by flow cytometry [32]. After 12 d, only 15% of the control cells had survived, whereas 50% of spermidine (20 nM)-treated cells survived [32]. Staining indicated that enhanced cell survival by spermidine was not as a result of inhibition of apoptosis, but rather an inhibition of necrosis. According to the investigators, necrosis culminates in the leakage of intracellular compounds resulting in local inflammation, a suspected cause of 'inflammaging [32].' Following on from this, the effect of exogenous spermidine on oxidative stress was examined, given that, in the free radical theory, aging is attributed to the accumulation of oxidative stress. Indeed, mice fed spermidine (3 mM added to drinking water) for 200 d had an increase in free thiol groups compared with control mice, suggesting a lower degree of oxidative stress and protein damage [32]. Furthermore, autophagy, the major lysosomal degradation pathway for recycling damaged and potentially harmful cellular material, is thought to be essential for healthy aging and longevity. Given that polyamines appear to increase lifespan, their involvements in preventing or delaying the onset of the major underlying pathologies that contribute to aging are also of worthy consideration.

Molecular mechanism by which Spermidine may act as an anti-aging molecule

Polyamines exert their physiological effects by regulating signaling pathways at the cellular level via the second messenger system [27]. Spermidine has been shown to be able to trigger a general hypoacetylation, which will likely induce changes in gene expression [32]. Administration of spermidine altered the phosphorylation condition of many protein kinases [33] and activated several protein phosphatases [34] in human colonic carcinoma HCT116 cells. Spermidine is potentially able to regulate many signaling pathways. Spermidine imposes its anti-aging effects via a pathway which involves the process of autophagy [27, 28, 32]. Likewise, spermidine may target some pathways which lead to the process of autophagy [27,32]. However, it is inferred that the spermidine modulation may not involve SIRT1, the mTOR pathway as well as AMPK [27]. It has been known that SIRT1 does not play a role for autophagy induction by spermidine. In addition, spermidine does not modify the state of mTOR, AMPK and their substrate proteins phosphorylations [32]. Autophagy can also be regulated by several other pathways. It has been previously known that autophagy genes are targets for the Foxo protein [34]. Foxo protein is the downstream effector of the insulin-like signaling pathway, which is involved in the regulation of aging and lifespan. In addition, spermidine can decrease the phosphorylation rate of PKB/Akt protein in HCT116 cells [35] and of Akt protein in BV2 microglial cells activated by lipopolysaccharides [36]. A possible candidate pathway by which spermidine exerts its anti-aging effects is the MAPK, also known to be involved in autophagy [37]. Autophagy is a catabolic process in the cytoplasm which protects the cell against harmful and stressful conditions [38]. The cellular components that are damaged are directed by autophagy into the lysosomes [39}. These are where cellular component degradation occurs and where component recycling takes place to be re-utilized as alternative protein synthesis and cellular repair building blocks [39]. Aging is a process in which cellular repair mechanisms fail to work over time. Aging leads to the accumulation of molecular and cellular damage and loss of function of many cellular components. Capacity for molecular degradation via autophagy also decreases with age, and this in itself may constitute cellular burdens which speed up the aging process [38]. Several studies in mouse animal model have shown that mutations at single genes could prolong lifespan in an evolutionarily conserved fashion, and these provide evidence that the course of the aging process can be reversed [39, 40].

In addition to the regulation of autophagy, it is known that polyamines modulate the MAPK pathway [41]. It is known that CK2, a ubiquitous protein kinase, phosphorylates directly raf protein as well as KSR (a protein kinase suppressor of ras that can act as raf activator). Studies have shown that polyamines directly modulate the phosphorylation of raf by CK2. Spermine acts as an inhibitor, while putrescine, spermidine or spermine can act as raf activator [41]. CK2 could also serve as a cellular polyamine sensor, which then relays the information to the MAPK pathway. In addition, spermidine has been shown to alter the phosphorylation status of some MAPKs in HTC116 cells [42] and MAPKs phosphorylation can be reduced by polyamine spermidine in BV2 microglial cells activated by LPS [36]. In green tomato fruits exposed to spermidine at high temperature, the polyamine has been shown to upregulate MAPK family genes [43], suggesting roles for polyamines to modulate the MAPK pathway. Lastly, the expression of MAPKs-targets transcription factors have been shown to be altered by depletion polyamines and then re-administration of spermidine in NIH3T3 mouse fibroblast cells [44].

CONCLUSION

We have discussed in this review, the different aspects of polyamine metabolism and a possible role for dietary polyamines as anti-aging molecules. Polyamines putrescine, spermidine, and spermine accumulate in cells where they exert a number of physiological functions. Polyamines' roles in human cellular growth, proliferation, and differentiation have been of great interest to many investigators. Because of their ubiquity in human tissue and involvement in a wide range of vital cellular processes, the importance of polyamines to the maintenance of human health during the aging process is started to be recognized. The evidence discussed in this paper indicates that polyamines have the potentials on good health maintenance in the geriatric population, and the total body polyamine pool may be influenced by dietary modification. Plant-derived foods tend to be a rich source of putrescine and spermidine; however, research is lacking an examination of the form in which polyamines are present in plant-derived foods (free, conjugated or bound) and whether this influences the bioavailability and bioactivity of polyamines in humans. Nevertheless, plant-derived foods represent an important source of dietary polyamines. There is good evidence to suggest that polyamines may assist with healthy aging. Until then, more research is to be conducted before recommendations on optimal and safe polyamine intake can be made. Specific epidemiological studies must be carried out across the different geriatric populations using different food and food items known to contain high polyamine levels.

CONFLICT OF INTERESTS

Declared none

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