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POLYAMINES - FACTORS OF AGING AND LONGEVITY REGULATION. MINI-REVIEW.

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Abstract

Polyamines (spermidine and spermine) are unique positively charged molecules that have pleiotropic genetic, biochemical, and physiological activity in all animal and human tissues. Currently, the study of the role of polyamines in aging and longevity processes is becoming particularly important. The purpose of this mini-review was to assess the role of spermidine and spermine in the aging process. To achieve this goal, the following tasks were identified: to determine the relationship between polyamine levels and life expectancy in vertebrates; to assess the metabolic characteristics of polyamines in birds that are associated with their longevity; to evaluate the dynamics of changes in polyamine metabolism in age-related pathologies; and to present the latest literature data on the molecular mechanisms of endogenous spermine's effects. This raises the question: can polyamines be considered a predictor of aging and longevity? How does spermidine or spermine affect longevity?

Aging is a pathophysiological process programmed at the genetic and epigenetic levels, the speed of which is determined by the ratio between damage factors, on the one hand, and body repair factors, on the other. The current lack of a universal theory of aging is the reason for new scientific research aimed at studying the fundamental mechanisms of aging in various animal species. Life expectancy in birds is significantly higher than in mammals when normalized by body size and standardized by the Rubner constant. Polyamines contribute to the longevity of birds due to the peculiarities of their metabolism and their higher levels in the body of birds compared to mammals. Currently, the study of the role of polyamines in the aging process is becoming particularly relevant.

The aim of our work is to develop a hypothesis of the leading role of polyamines in the longevity of birds compared with mammals. The study of the role of polyamines in the aging of various species of living organisms is an integral part of the research on the role of polyamines in the pathogenesis of age-related pathologies.

Keywords: *polyamines, spermidine, spermine, fe expectancy, longevity, age-related pathologies, genetic levels, epigenetic levels.*

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Introduction

Polyamines - putrescine, spermidine and spermine, are presented in all living organisms from viruses and up to mammals and humans. Despite all the diversity of functional activity in different tissues and organs and the differences in metabolic pathways in plants, birds and mammals, it is possible to note the commonality of their participation in the implementation of the stress-response and the regulation of aging [*Handa A et al. 2018; Jimenez Gutierrez G et al. 2023; Kolesnikov Y et al. 2024; Rossi M, Cervelli M 2024; Schibalski R et al. 2024*].

The anti-stress effect has been shown for all 3 main polyamines [*Jimenez Gutierrez G et al. 2023; Schibalski R et al. 2024*]. It is especially important to study spermidine, whose metabolism is associated with longevity [*Xu T et al. 2020; Díaz-Osorio Y et al. 2025; Jing Y et al. 2025*]. Spermidine has been shown to slow down the aging process, reduce the incidence and severity of age-related pathologies, and prolong life [*Bae D et al. 2018; Partridge L et al. 2020; Xu T et al. 2020; Jing Y et al. 2025*]. The effects of spermidine differ from those of spermine and putrescine, despite the fact that they can easily be metabolized into each other. Due to their excess positive charge, polyamines can interact with negatively charged high-molecular-weight compounds such as DNA, RNA, ATP, and proteins.These molecules perform a variety of functions in many physiological and pathophysiological processes, including cellular proliferation, differentiation, growth, tissue regeneration, and gene regulation [*Jaenne J et al. 1964; Minois N et al. 2011; Partridge L et al. 2020*]. Spermidine is involved in a number of biological events, including autophagy induction, apoptosis, transcription, and DNA stability [*Xu T et al. 2020; Jimenez Gutierrez G et al. 2023; Rossi M, Cervelli M 2024; Schibalski R et al. 2024; Díaz-Osorio Y et al. 2025; Jing Y et al. 2025*]. The concentration of spermidine and spermin decreases with age, and exogenous supplementation of spermidine reverses negative age-related changes and extends lifespan [*Eisenberg T et al. 2009; Eisenberg T et al. 2016*]. In this review, we summarize and update the latest data on how polyamine metabolism is associated with the aging process, and we explore its potential diagnostic and therapeutic applications in age-related diseases in animals and humans.

Polyamine content in birds and mammals in tissues.

A large group of polyamines includes putrescine, spermidine and spermine, acetylated derivatives of putrescine, spermidine and spermine, as well as cadaverine and agmatine, the formation of which is associated with decarboxylation of lysine and arginine. This article discusses the role and metabolism of polyamines - spermidine and spermine, the formation of which occurs with the participation of the enzyme ornithine decarboxylase (ODC), and for which their ability to influence life expectancy has been shown [Minois N et al. 2011]. Physiological concentrations of these polyamines are necessary for growth and development, survival and adaptation for all animal species, and therefore, over the past 50 years and currently, research is actively conducted on the mechanisms of their synthesis and decay, transport, etc. issues [Handa A et al. 2018; Jimenez Gutierrez G et al. 2023; Arthur R et al. 2024; Kolesnikov Y et al. 2024; Rossi M, Cervelli M 2024; Schibalski R et al. 2024].

Three routes of polyamine intake are known in birds and mammals: through their de novo synthesis [*Schipper R et al., 2000; Pegg A, 2009; 2016*], including under conditions of resident microorganism persistence [*Gerner E, Meyskens F, 2009; Hullar M, 2013]*, as well as by food intake [Zoumas-Morse C, 2007; Ali A, 2011; Avagyan S.A. 2023]. Numerous studies have been devoted to the study of polyamine content in food products and the assessment of the effect of probiotics on polyamine content in birds and mammals, as well as humans [*Bardócz S et al. 1995; Knut A et al. 2002; Kalac P, Krausová P 2005; Krausová P et al. 2006; Naoyoshi N et al. 2007; Atiya Ali M et al. 2011; Muñoz-Esparza N et al. 2021; Cantabrana B 2025*]. In particular, for certain somatic diseases, viral infections, cancerous tumors, neurodegenerative diseases and cardiovascular disorders, where elevated levels of polyamines are observed, it is proposed to use a polyamine-deficient diet or a polyamine-free diet [*Avagyan S.A. 2023*]

Species distribution of polyamines. The distribution of polyamines in the tissues of birds and mammals, as well as humans, has been studied in numerous laboratories [*Jiang D et al. 2024*]. In free form, spermidine and spermine are determined to

be 8-10% of their total content in the cell, while the transition from the bound form to the free form is easily accomplished depending on changes in the charge of the macromolecule with which they are bound, including ATP, proteins, phospholipids and nucleic acids. and are an available form for further metabolism. It has been established that the tissues of birds have a higher content of polyamines compared to mammals [*Jiang D et al. 2024*]. A comparative analysis of the lifespan and body size of birds and mammals allowed us to conclude that birds live significantly longer than mammals [*Travin D, Feniouk B 2017; Moreno-Borrallo A et al. 2024*]. It should be noted that the content of polyamines in birds is higher than in mammals, which is especially pronounced in the kidneys [*Furukawa K et al. 2021*]. Comparing the polyamine content in the kidneys of mammals and birds, it can be noted that in the kidneys of mammals the level of spermidine and spermine is lower (9.4–12.7 *mg/kg* and 38.4–82.8 *mg/kg*, respectively) [*Pegg A 2016*], and the content of spermidine and spermine in the kidneys of poultry (chickens and ducks) is higher (12.95–18.36 mg/kg and 238.56–261.08 *mg/kg*, respectively) [*Furukawa K et al. 2021*]. Moreover, the main differences are noted in the spermine content. Unlike mammals, in birds the synthesis of polyamines in tissues occurs not only from arginine, but also from proline.

A study of the polyamine content in the tissues of poultry (geese, ducks and chickens) showed that their content in bird tissues is specific to each species [*Furukawa K et al. 2021*]. However, general patterns were identified: the spermine content was higher than the spermidine and putrescine content in various tissues of three poultry species, which further confirmed that spermine is the main component of the polyamine pool in poultry tissues [*Furukawa K et al. 2021*]. General patterns include tissue distribution - the highest polyamine content was shown in immunocompetent tissues: spleen, thymus and bursa of fabric of birds and amounted to 3.24 – 29 for putrescine, 0.46 – 164 for spermidine and 64-489 for spermine, lower polyamine content in skeletal muscle tissues and in the heart [*Tabbaa et al, 2021*]. The widespread use of poultry liver as a human food product has generated interest in the polyamine content of the liver of various poultry species. The levels of putrescine, spermidine, and spermine in chicken liver were 2.0, 56.9, and 119.6 *mg/kg*, respectively, while in duck liver they were 21.1, 106.3, and 132.1 *mg/kg*, respectively [*Furukawa K et al. 2021*]. The spermine content (241 *mg/kg)* in goose liver is twice as high as in chickens and ducks [20].In humans, polyamine levels vary across tissues (muscle, kidney, prostate, and brain), with the prostate having the highest levels of spermine (24 *nmol/mg protein*), while the kidneys contain 2.18 and 6.85 *nmol/mg* protein of spermidine and spermine, respectively [*Arthur R et al. 2024*]. Heterogeneous distribution of polyamines has been recorded in the human brain, with high levels of spermidine in the white matter (20 nmol/mg protein) and in the thalamus (9.3 *nmol/mg protein*), and spermine in the cerebellar cortex (3.4 *nmol/mg protein*) [*Arthur R et al. 2024*]. Polyamines have been shown to be synthesized in neurons and accumulate in glial cells, which determines their high content in the white matter of the cerebral cortex [*Arthur R et al. 2024*]. The general patterns of polyamine distribution in the tissues of birds, mammals, and humans are:

1. Higher polyamine content in avian tissues compared to mammals; Spermidine and spermine content are 10-20 times higher in avian tissues compared to mammals, which determines their high anabolism.

2. Polyamine content varies across tissues. It is highest in immune tissues and the prostate.

3. Spermine levels are higher than those of other polyamines.

4. In the blood, polyamine levels are higher in red blood cells than in serum.

5. Spermidine levels in the blood are higher than spermine and putrescine, and are also significantly higher than acetylated derivatives of polyamines.

Polyamine Synthesis

Polyamines are formed by the decarboxylation of ornithine. Intracellular biosynthesis of spermidine and spermine begins with the diamine putrescine, which in turn is synthesized from ornithine.

The enzyme ODC [*Pegg A 2006*] is the rate-limiting enzyme for polyamine formation. Ornithine can be formed via several pathways: from the essential amino acid arginine via arginase, and from proline via proline oxidase and ornithine aminotransferase.In mammals, ornithine is synthesized in the cytosol from arginine (a con-

ditionally essential amino acid). During embryogenesis in the mammalian placenta, ornithine is synthesized from proline (a nonessential amino acid) in the mitochondria, which is associated with the need to maintain a high level of polyamines for the biosynthesis of proteins and nucleic acids during embryo growth and development [*Berezov T et al. 2012*]. Furukawa et al. (2021) found that when labeled [C-14]-arginine and [C-14]-proline were introduced into chicken kidneys, these amino acids were easily converted into polyamines. The authors found that the activities of the enzymes ornithine aminotransferase (OAT, mitochondrial) and ODC (cytosolic) were determined in chicken tissues, while the activities of arginase and proline oxidase (POX) were detected in the mitochondria of chicken kidneys. The concentration of polyamines in the blood plasma of chickens is 20-100 times higher than in mammals, which ensures their rapid delivery to various tissues and promotes rapid growth [*Furukawa K et al. 2021*].

In birds, polyamines are constantly synthesized from both arginine (a strictly essential amino acid) and proline, a nonessential amino acid [Furukawa. K et al, 2021]. Arginine is hydrolyzed to ornithine and urea by arginase II, and proline is converted to ornithine by the enzymes proline oxidase and ornithine aminotransferase. Glutamate, in turn, can participate in proline biosynthesis. Ornithine, formed in the mitochondria, enters the cytosol for subsequent synthesis of putrescine with the participation of ODC. Putrescine, spermidine, and spermine are secreted into the general circulation from the kidneys. The following enzyme activities were determined in chicken tissues: OAT-ornithine aminotransferase (mitochondrial) and ODC-ornithine decarboxylase (cytosolic), while the activities of arginase and proline oxidase (POX) were detected in the mitochondria of chicken kidneys. The concentration of polyamines in the blood plasma of chickens is 20-100 times higher than in mammals [*Furukawa K et al. 2021*]. .

Thus, the authors demonstrated two new differences between birds and mammals, which consist of the endogenous synthesis of polyamines [*Handa et al, 2018*] and their concentrations in blood plasma [*Kolesnikov et al., 2024*], which ensures rapid growth and development.

The next polyamine is a triamine - spermidine. Spermidine synthase (SpdSy) transfers the NH2 (CH2)3 fragment from S-adenosylmethionine to the amino group of putrescine, which leads to the formation of spermidine. Subsequent synthesis of spermine occurs by repeated transfer of this fragment to spermidine with the participation of the enzyme spermine synthase (SPMSy). The breakdown of polyamines is always associated with their conversion to lower molecular weight polyamines in the course of two successive enzymatic reactions. First, spermine or spermidine is acetylated by the enzyme spermidine/spermine N1-acetyltransferase 1 (SSAT), which is a key regulatory enzyme determining the breakdown of polyamines [*Pegg A 2013*]. The second is the acetylation of spermine and spermidine, which subsequently undergo oxidative cleavage between C3 and N4 to form lower molecular weight polyamines and 3-aminopropal. It is important to note that both the synthesis of polyamines and their degradation are accomplished with the transfer of the triatomic (CH2)3 fragment. Oxidation also leads to the degradation of polyamines. The oxidation products of polyamines are lower molecular weight polyamines, H2O2, 3-aminopropanal (3-AP), and 3-acetylaminopropanal [*Pegg A 2013*]. These aldehydes are unstable and spontaneously convert to acrolein after deamination. Acrolein, an unsaturated aldehyde, readily reacts with lysine residues of proteins to form protein-conjugated acrolein (PCAcrolein) [*Pegg A 2013*]. Acrolein, a highly toxic unsaturated aldehyde, interacts with lysine, proteins, lipids, and nucleic acids to produce systemic damage, leading to cell death. It has been shown that in experimental photo-induced stroke, acrolein levels in the necrotic zone increase 28-fold, which is associated with the activation of polyamine breakdown. Acrolein is a significantly more toxic compound than H_2O_2 [*Igarashi K, Kashiwagi K 2011; Park M, Igarashi K 2013*].

Regulation of polyamine metabolism

The activities of the enzymes of polyamine biosynthesis and degradation: ODC and SSAT - are regulated by changes in the concentrations of polyamines, as well as by various compounds: growth factors, hormones, etc. [*Pegg A 2016*]. At high concentrations of spermidine and spermine in cells, the activities of the enzymes of polyamine synthesis (ODC and SAMDC) are suppressed, while

the activity of the degradation enzymes (SSAT) increases. Conversely, when the cellular content of polyamines decreases, ODC and SAMDC are positively regulated and SSAT is suppressed. Regulation of the synthesis and degradation of polyamines occurs at the level of transcription and translation of the biosynthesis of these enzymes [*Pegg A 2006*]. With an increase in the content of polyamines inside the cell, ODC activity is suppressed by the induction of the antizyme protein (AZI), which forms a complex with the ODC monomer, leading to the inactivation of its enzymatic activity [*Kahana C 2018*]. The breakdown of this complex occurs in the 26S proteasomes. In addition, antizyme proteins are able to inhibit the absorption of polyamines or stimulate their secretion. The existence of 3 forms of AZI antizymes has been shown: AZI 1, AZI 2 and AZI 3 [*Ma R et al. 2015; Lambertos A et al. 2022; Feng Q et al. 2024*]. A more complex regulation of ODC activity is represented by proteins - antizyme inhibitors (AZIN), which are able to interact with AZI with a higher affinity than with ODC. Currently, 2 of their forms have been identified: AZIN 1 and AZIN 2 [*Ma R et al. 2015; Lambertos A et al. 2022; Feng Q et al. 2024*]. Previously, it was believed that the intracellular level of polyamines, putrescine, spermidine and Spermine levels are homeostatically maintained within a relatively constant range by three main systems: biosynthesis, acetylation/export, and transport [*Niu C et al. 2021*]. In vertebrate cells, biosynthesis is regulated by ornithine and S-adenosylmethionine decarboxylases (ODC2 and SAMDC); acetylation and export are regulated by spermidine/N1-acetyltransferase (SSAT); and transport is regulated by a group of membrane transporter proteins [*Minois N et al. 2011*]. Each of these enzymes responds to the intracellular pool of polyamines, with uptake and biosynthesis being negatively regulated by polyamines and acetylation being positively regulated [*Porter C, Bergeron R 1988; Shappell N et al. 1993; Kramer D et al. 2008*].

Acetylated polyamine derivatives

The content of acetylated polyamine derivatives (N1-acetylputrescine, N1-acetylspermidine, N1,N8-diacetylspermidine, N1-acetylspermine, and N1,N12-diacetylspermine) in blood plasma, urine, and saliva has been studied in various pathologies. A correlation has been established between the severity of a number of diseases, such as COVID-19 [*Avagyan S et al, 2022*], cancer [*Avagyan S et al, 2023*], and Parkinson's disease, and the content of acetylated polyamine derivatives [*Avagyan A et al., 2025*]. The content of N1,N12-diacetylspermine in urine and blood plasma is considered a biomarker for various forms of cancer in mammals. For example, it was previously found that N1-Acetylspermine increases in the saliva of patients with breast cancer [*DeFelice B, Fiehn O 2019*]. Recently, Burgen et al. (2021) showed that in patients with COVID-19, the content of acetyl derivatives of polyamines is significantly higher than in healthy individuals, and their level increased sharply as the patient's condition became more severe, while an increase in the ratio of N1-acetylspermidine to spermidine was also noted [*Bourgin M et al. 2021*]. Importantly, differences in the content of N1-acetylspermidine and N1, N8-diacetylspermidine in the serum were shown in patients carrying SARS-CoV-2 for different periods, with long-term carriers (more than 40 days) having significantly higher levels of these metabolites than patients with a shorter carriage period. The authors conclude that the inability to eliminate SARS-CoV-2 is associated with high levels of acetylpolyamines [*Vrijsen S et al. 2023*]. The content and metabolism of acetylated polyamines in the blood of patients with PD has been studied in several studies [*Roede J et al. 2013; Saiki S et al. 2019; Vrijsen S et al. 2023*]. It was established that the level of N1, N8-diacetylspermidine in the blood correlated with the cognitive status of PD patients. It is noteworthy that the level of N8-acetylspermidine in the blood was a marker of the rapid progression of Parkinson's disease [*Roede J et al. 2013*].

Disturbances in polyamine

Disturbances in polyamine homeostasis lead to severe metabolic disorders and neurological diseases, for example, mutations in spermine synthase and subsequent changes in spermine and spermidine levels cause Snyder-Robinson syndrome [*Murray-Stewart T et al. 2018*]. Similarly, mutation in the ODC1 gene leads to severe changes such as macrosomia, macrocephaly, developmental delay, alopecia, spasticity, hypotonia, cutaneous vascular malformations, visual impairment and

sensorineural hearing loss [*Murray-Stewart T et al. 2018*]. Research by Jain et al. 2018 showed that suppression of polyamine breakdown is associated with spermine-mediated airway epithelial damage and provokes the development of asthma [*Marcoli M et al. 2022*]. In mouse models with SMOX inactivation and combined SMOX and SSAT1 inactivation, increased spermine levels and decreased spermidine levels were found in the cerebral cortex and cerebellum of Smox-KO and Smox/Sat1-dKO mice compared to intact animals [*Marcoli M et al. 2022*]. Experiments with Smox/Sat1-dKO mice showed that long-term deficiency of polyamine catabolism caused TGM2 90 activation and increased α-synuclein expression, polyamination and protein aggregation, followed by activation of a chain of events that lead to cerebellar damage and ataxia in Smox/Sat1-dKO mice [*Marcoli M et al. 2022; Fan L et al. 2024*]. A significant contribution to the current understanding of the role of external factors, such as intestinal metabolites, in the regulation of polyamine metabolism was made by studies of the effect of small RNAs from Lactobacillus murinus in the intestine on polyamine metabolism in the body. It was found that small RNAs obtained from Lactobacillus murinus in the intestine, as part of extracellular vesicles, suppress polyamine metabolism in the body by inhibiting the expression of enzymes involved in the metabolism of the latter. The relationship between polyamine metabolism in the host and small RNAs of bacteria obtained from the intestinal microbiota is associated with the pathogenesis of diseases of the intestine, liver, and pancreas [*Jaenne J et al. 1964*].

Polyamines and Aging

All living organisms exhibit a characteristic decrease in polyamine levels with age; however, significant differences exist between animal species, tissues studied, and age groups compared [*Sturman J, Gaull G et al. 1975; Makletsova et al. 2013; Wirth A et al. 2021*]. The first sharp decline (35%) in tissue polyamine content in mammals is observed between birth and weaning, after which polyamine levels remain virtually stable throughout adulthood in rodents [*Sturman J, Gaull G et al. 1975*]. A study of polyamine metabolism in the brain of rapidly aging SAMP/SAMR mice showed that, even in the early stages of postnatal development, polyamine levels are lower in rapidly aging animals compared to controls [*Wirth A et al. 2021*]. A decrease in spermine and spermidine levels in humans and non-human primates begins after age 40 [*Vivó M et al. 2001*]. In the human brain, a negative correlation has been found between spermine/spermidine levels and aging in the cerebral cortex, basal ganglia, and cerebellar cortex [*Kiechl S et al. 2018*].

The effect of polyamine administration on lifespan has been demonstrated in vitro and in vivo. Administration of exogenous spermidine and spermine increases the lifespan of immune cell cultures [*Vrijsen S et al. 2023*]. In vivo experiments have demonstrated the gerontological efficacy of exogenous spermidine administration in yeast (by 40%), fruit flies (by 30%), nematodes (by 15%), and rodents (by 10%) [*Makletsova et al. 2013*]. In humans, a positive correlation has been recorded between increased dietary spermidine intake and longevity [*Makletsova M et al. 2022*]. Polyamines also prevent cognitive decline by stimulating autophagy and mitophagy, improving mitochondrial respiration, reducing neuroinflammation, and modulating mediator metabolism [*Eisenberg T et al. 2016; Wu X et al. 2017*].

Mechanisms of the geroprotective action of polyamines. One of the first proven positive protective mechanisms of polyamines for all animal species was their antioxidant effect [*Chai N et al. 2019; Clarkson A et al. 2004; Makletsova M et al. 2012*]. Model experiments on microorganisms, birds, and rodents have shown that exogenous administration of putrescine, spermidine, and spermine has a protective effect against toxic, highly reactive free radicals under conditions of oxidative stress induced by hypoxia, ischemia, hyperoxia, inflammation, etc. [*Tkachenko A, Nesterova L 2003; Clarkson A et al. 2004; Makletsova M et al. 2012; Jeong J et al. 2018; Chai N et al. 2019*].

Polyamines stimulate the expression of various factors of the antioxidant enzymatic defense system, such as superoxide dismutase (SOD), catalase, and glutathione metabolism enzymes [*Drolet G et al. 1986*], but they also act as antioxidants themselves, acting as a scavenger for reactive oxygen species [*Chai N et al. 2019*]. The higher the amino group, the higher the antioxidant capacity, with spermine being the most potent [*Lovaas E 1997; Ha H et al. 1998*]. Spermine functions as a free

radical scavenger, being oxidized during this process. Importantly, polyamines are capable of protecting against heavy metal toxicity, suppressing the formation of oxidative stress products caused by heavy metals, and directly chelating heavy metals [*Despotovic D et al. 2020*].It is also important to note that spermidine suppresses histone acetylation, thereby exerting a "rejuvenating" effect on the genome [*Eisenberg T et al. 2009*].

Polyamines act as chaperones. Polyamines enhance the activity of chaperones and also function as chaperones themselves [*Singh B et al. 2017; Schuber F. 1989*]. Polyamines promote the formation of α-helical structures in primary hyperacidic proteins, which may represent a conserved mechanism for polyamine-mediated protein regulation [*Singh B et al. 2017*], and in addition to improving the folding and stability of protein molecules, polyamines bind DNA [*Schuber F. 1989*]. thereby promoting DNA stability and homology-directed DNA repair by stimulating the activity of RAD51 recombinase [*Schuber F. 1989; Lovaas E 1997; Singh B et al. 2017*]. Polyamines also interact with lipids, thereby protecting membranes from osmotic shock [*Ballas S et al. 1983*], and preventing rupture of red blood cell membranes, which are subject to high tension under certain conditions [*Lagishetty C, Naik S 2008*]. Polyamines have an anti-inflammatory effect largely due to their modulating effect on the body's immune system [*Choi Y, Park H 2012*]. Spermidine has been shown to prevent lipopolysaccharide (LPS)-induced production of proinflammatory cytokines, iNOS and COX-2 expression, and NF-κB nuclear translocation [*Messerer J et al. 2023*]. In mice with accelerated aging (SAMP8), exogenous administration of spermine and spermidine reduces the level of NLRP3 and the content of proinflammatory cytokines IL-1β and IL-18 [*Xu T et al. 2020*]. The immune system plays an important role in the formation of the anti-inflammatory effect of polyamines, and polyamines effectively influence it [*Sánchez-Jiménez F et al. 2019; Van V et al. 2020*].

Polyamines modulate lysosomal homeostasis and autophagy pathways. Lysosomes play a central role in regulating the homeostasis of intracellular polyamine levels. Spermidine and spermine enter the lysosome via endocytosis and autophagy [*Hiasa M et al. 2014; Pavlova J et al. 2024*]. Autophagy is currently considered to be the central mechanism of the geroprotective action of polyamines, and especially spermidine [*Gupta V.K et al. 2013*]. Autophagy is a process during which defective proteins and other high-molecular compounds contained in cells, as well as dysfunctional organelles and cellular structures, are isolated and transported to lysosomes for subsequent degradation [*Gupta V.K et al. 2013*]. Spermidine is an autophagy inducer, modulating the expression of Atg genes and regulating the transcription factor elF5A (promoting the synthesis of the transcription factor TFEB). Spermidine inhibits EP300, which directly acetylates the Atg gene and indirectly stimulates tubulin deacetylation by inhibiting aTAT1 [*Gupta V.K et al. 2013; Pietrocola F et al. 2015; Puleston D et al. 2019; Baek A et al. 2020; 82 Yuan X et al. 2021*].

Furthermore, polyamine metabolism is regulated by mTORC1, a protein complex that is activated on the lysosomal membrane in the presence of abundant, rich nutrients, which in turn stimulates anabolic and simultaneously inhibits catabolic metabolic pathways. Activation of mTORC1 increases the activities of the enzymes AdoMetDC, SpdSyn, and SpmSyn, whereas inhibition of mTORC1 decreases SSAT activity [*Zabala-Letona A et al. 2017; Phadwal K et al. 2018*].

Spermidine inhibits EP300 acetyltransferase, promoting increased autophagy [*Baek A et al. 2020*]. Moreover, spermine increases microtubule acetylation, which promotes the retrograde movement of autophagosomes to the perinuclear region, a favorable site for the fusion of autophagosomes and lysosomes [*Qi Y et al. 2016*]. Furthermore, spermidine is critical for hypusination, a process that stimulates autophagy via TFEB, while ATP13A2 also modulates this TFEB pathway. Polyamines also influence mitophagy. Spermidine increases PINK1/Parkin-dependent mitophagy, which is modulated by ataxia-telangiectasia kinase (ATM) [*Hoshino K et al. 2005*]. Polyamines have a protective effect on mitochondria. Spermidine and spermine are present in mitochondria in mM concentrations [*Wu X et al. 2017*], where they counteract the formation of ROS. Polyamines effectively scavenge the toxic effects of H2O2, spermine can reduce superoxide production by inhibiting NADPH oxidase [*Yoshino M et al. 1991*], and also protect mitochondria from fragmentation [*Damuni*

Z et al. 1984; Wu X et al. 2017]. Polyamines have been shown to affect mitochondrial bioenergetics: spermine activates citrate synthase [*Damuni Z et al. 1984*] and regulates pyruvate dehydrogenase [*Igarashi K et al. 1989; Pezzato E et al. 2009*]. Spermine and spermidine can also inhibit F1-ATPase activity by directly binding to ATP [*Christian B et al. 2010*]. Polyamines regulate the expression of nuclear-encoded mitochondrial proteins, which are subsequently imported into the mitochondria [*Pietrocola F et al. 2015*]. Spermine is involved in the binding of mitochondrial 55S ribosomes to methionine-transferring tRNAs, thereby enhancing translation initiation in mitochondria [*Barba-Aliaga M, Alepuz P 2022*]. Spermine functions as an important regulator of mitochondrial Ca2+ uptake [*Igarashi K et al. 1989*]. Spermidine functions as the sole precursor of hypusine and is therefore required for hypusination and activation of eIF5A to drive cell growth, as polyamine depletion leads to translational abolition and growth arrest [*Mandal S et al. 2013*]. Importantly, mitochondrial functional activity is closely intertwined with the hypusination process [*Faundes V et al. 2021; Liang Y et al. 2021*]. Hypusinated eIF5A stimulates the expression of proteins involved in the Krebs cycle and oxidative phosphorylation [*Brenner S et al. 2015*].

An important aspect of spermidine's anti-aging effects on metabolism is its ability to regulate lipid metabolism. [*Korzun I et al. 2000; Duan H et al. 2024*]. Minua et al. found that elevated triglyceride levels, as well as altered phospholipid and fatty acid profiles, were associated with increased lifespan in spermidine-fed flies. Gao et al. demonstrated that spermidine regulates lipid metabolism by suppressing the expression of lipogenic genes through the AMP-activated protein kinase (AMPK) signaling pathway [*Arthur R et al. 2024*]. It is important to emphasize that spermidine can slow down aging by influencing certain signaling pathways, such as SIRT1/PGC-1α, insulin/IGF, AMPK-FOXO3a and CK2/MAPK signaling pathways [*Arthur R et al. 2024*]. Spermidine can regulate apoptosis and cell necrosis [*Jiang et al, 2023*], and polyamines are able to prevent the development of apoptosis [*Makletsova et al. 2013*]. The role of spermidine in the mechanisms of regulation of the cell necrosis process has been reported [*Drolet G et al. 1986*]. Experiments on yeast have shown that an increase in spermidine levels suppresses cell necrosis, thereby prolonging lifespan and improving metabolism in aging yeast [*Drolet G et al. 1986*]. It is important to note that the mechanism by which polyamines are able to effectively regulate the aging process in vertebrates is associated with the modulatory activity of neurotransmitter systems and receptor complexes (ionotropic glutamate receptors, NMDA, acetylcholine, GABA, etc.) [*Wu X et al. 2017; Zilfyan A.V., Avagyan S.A., 2023*]. Polyamines are key regulatory molecules for the activity of all systems in the vertebrate body.

The aging process is accompanied by a decline in the functional activity of organs and tissues. Currently, putrescine, spermidine, and spermine are considered key regulatory molecules in all tissues: muscle, skeletal, connective, nervous, endocrine, and adipose tissues [*Ou Q et al. 2024; Gautam P et al. 2025*] (Figure 1).

Decreased fertility as a factor in aging is associated with a decline in reproductive function in animals. The introduction of putrescine into the diet of birds significantly increases the number of follicles in the ovaries [*Ou Q et al. 2024*]. Importantly, polyamines are capable of regulating the endocrine system through releasing factors. Thus, putrescine acts as a factor regulating the splicing of gonadotropin-releasing hormone, thereby influencing the expression of gonadotropin-releasing hormone. Being a key regulator of reproductive function, gonadotropin-releasing hormone controls the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which are necessary for fertility [*Galasso L et al. 2023*]. Age-related changes in the musculoskeletal system are the most painful for aging organisms, so the study of the mechanisms that can affect this system is especially relevant. Skeletal muscles contain a significant amount of polyamines and their content decreases with aging. Polyamines regulate muscle mass of skeletal muscles, causing activation of autophagy and mitophagy [*Ren J., Zhang Y. 2018; Sung et al. 2021*]. Recent experimental studies in vitro and in vivo have shown that exogenous administration of spermidine reverses dysfunctional autophagy and stimulates mitophagy in skeletal and cardiac muscles, preventing atrophy of these tissues [*Sung et al. 2021*]. Compelling evidence has been obtained for the effectiveness of poly-

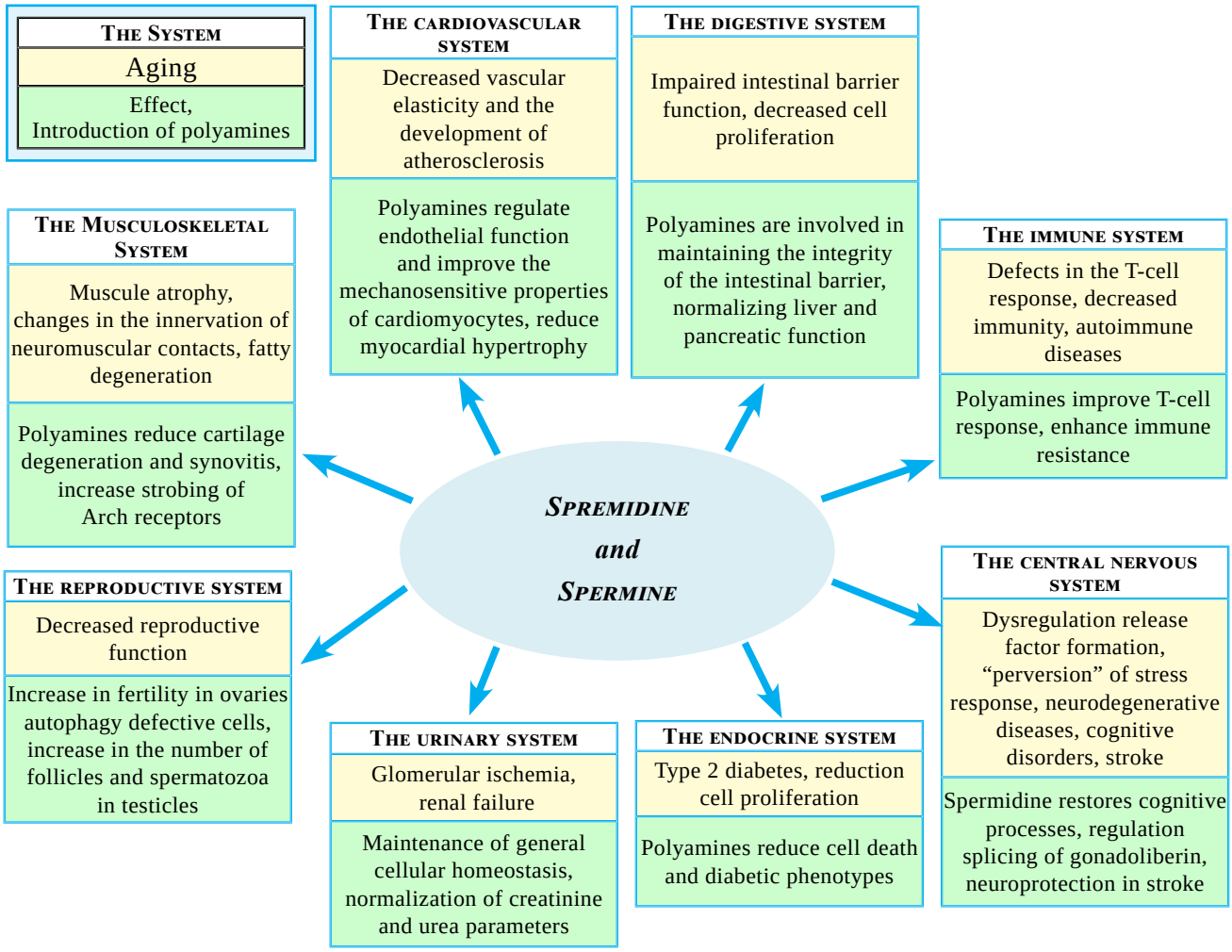

FIGURE 1. *The role of polyamines in animal and human bodies.*

amines and physical exercise as autophagy inducers, alone or in combination, which may contribute to the treatment of sarcopenia and musculoskeletal diseases, the pathogenesis of which is associated with aging [*Ren J., Zhang Y. 2018*]. Ou Q, et al. showed that administration of exogenous spermidine improves the condition in osteoarthritis by changing the polarization of macrophages [*Sung et al. 2021*]. Sung HK et al. suggest considering the level of spermidine in the blood serum as a predictor of fractures in the human musculoskeletal system [*Mahalingam S., Pandiyan P. 2024*]. High geroprotective activity has been established in relation to the effects of spermidine on the cardiovascular system. It has been established that spermidine reduces myocardial hypertrophy, normalizes blood pressure, and improves the mechanoelastic properties of cardiomyocytes due to the activation of autophagy [*Luo D et al. 2024*].

Currently, the study of the role of polyamines in the functional activity of the central nervous system is particularly important. Compelling evidence has been obtained for the involvement of polyamines in the process of neuroprotection during aging, which is especially important in the regulation of cognitive impairment observed in neurodegenerative diseases [*Wu X et al. 2017; Arthur R et al. 2024*]. Polyamines are found in relatively higher concentrations in the brain and have pleiotropic biochemical activity, including the regulation of ion mediator channels, gene expression, Ca2+ transport in mitochondria, and much more [*Wu X et al. 2017; Arthur R et al. 2024*]. A non-specific mechanism of the stress response by polyamines, called the PSO (polyamine stree-response), has been described [*Wu X et al. 2017; Arthur R et al. 2024*]. In their work, they emphasize the leading role of the regulation of synaptic plasticity by polyamines in the process of animal adaptation to extreme environmental conditions [*Wu X et al. 2017; Arthur R*

et al. 2024]. The gastrointestinal tract is particularly sensitive to disturbances in polyamine metabolism. Intestinal epithelial tissue contains high concentrations of polyamines, which is associated with the high proliferative activity of these cells. It is well known that disturbances in intestinal functional activity are age-dependent pathologies. Additional introduction of the polyamine putrescine into the diet of animals not only increases the level of polyamines directly in intestinal cells, but also affects the accumulation of spermidine in liver and muscle tissue [*Xu T et al. 2020; Díaz-Osorio Y et al. 2025*]. The endocrine system is particularly sensitive to metabolic changes in polyamine levels [*Dever T, Ivanov I 2018*]. Polyamines have a modulating effect on the endocrine system, which is confirmed by studies aimed at studying the mechanisms of spermidine's influence on the functional activity of the latter. It has been shown that polyamines directly affect the metabolism of endocrine cells, for example, the pancreas, where spermidine acetylates RIPK1, suppressing the development and progression of diabetes [*Duan H et al. 2024*]. It is important to note that polyamines are able to regulate the state of the endocrine system through releasing factors (as described above). Polyamines participate in the regulation of metabolic processes in adipose tissue, determining the quantitative and qualitative cellular composition of white adipose tissue, determining the number and ratio of white and beige adipocytes [*Berezov T et al. 2012; Fan L et al. 2024*]. Lipid metabolism in adipocytes is controlled by polyamines: activation of spermidine/spermine-N1-acetyltransferase (acceleration of polyamine metabolism) leads to a decrease in the energy reserves of fats in the cell, and deceleration, on the contrary, to an increase in intracellular concentrations of neutral fats. Polyamine metabolism ensures the regulation of adipose tissue mass by changing the balance between the processes of oxidation and biosynthesis of fatty acids [*Berezov T et al. 2012; Fan L et al. 2024*]. Polyamines play important and diverse roles in the immune system and can influence both innate and adaptive immune responses, including modulation of immune cell proliferation and differentiation, macrophage polarization, immune senescence and autophagy, and immunosuppression in cancer [*Eisenberg T et al. 2009*]. Although polyamines were initially thought to have immunosuppressive effects, it is now clear that their immunobiological properties are multifaceted and dependent on the context, cell types, and pathological conditions. Early studies identified a potential role for polyamines in the development of autoimmune diseases [*Luo D et al. 2023*]. Recent studies highlight the key role of polyamines in immune regulation. They enhance T cell activation and proliferation, and influence macrophage and dendritic cell functions [*Luo D et al. 2023*]. Decreased plasma spermine levels have been associated with impaired urinary tract function [*Luo D et al. 2023*]. Kidney cells respond to various forms of injury by decreasing polyamine synthesis and activating the polyamine degradation pathway. It has been shown that in mammalian renal fibrotic pathology, spermine oxidase is inducible in renal tubular epithelium with renal fibrosis, and spermine content in the kidneys also decreases. Moreover, SMOX expression in the kidneys positively correlates with renal fibrosis and decreased renal function in patients with chronic renal failure. Importantly, exogenous spermine administration significantly improves autophagy, delays aging, and attenuates fibrosis in mouse kidneys. Furthermore, downregulation of ATG5, a critical autophagy component, in tubular epithelial cells enhances SMOX expression and decreases spermine levels during TGF-β1-induced fibrogenesis in vitro and renal fibrosis in vivo. Mechanistically, ATG5 readily interacts with SMOX under physiological conditions and during TGF-β1-induced fibrogenic responses, preserving spermine levels in cells. The authors conclude that these results suggest that the SMOX/spermine axis is a potential new therapeutic for counteracting renal fibrosis, possibly by coordinating autophagy and suppressing pathological aging mechanisms [*Luo D et al, 2023*].

Changes in synaptic transmission, termed synaptic plasticity, are one mechanism by which neuronal activity reflects environmental changes and influences overall brain function [*Arthur R et al. 2024*]. Spermidine protects against age-related changes in interneuronal connections that contribute to age-related memory impairment [*Arthur R et al. 2024*]. Spermidine can prevent the loss of neuronal mitochondria, restore synaptic function in aged animals, and promote long-term potentiation, which is critical for learning and memory [*Arthur*

R et al. 2024]. Furthermore, it has been reported that active aging zones in the Drosophila nervous system reach their maximum capacity, which may limit synaptic plasticity and cause problems with memory formation [*Arthur R et al. 2024*]. The vast majority of studies on the effects of polyamines, especially spermidine, on synaptic plasticity emphasize their important role in maintaining and enhancing neuronal function.

As we learn more about the complex relationship between polyamine metabolism and synaptic plasticity, using this knowledge to develop treatments for neurological diseases in animals and humans and to develop methods for animal adaptation to environmental stressors is becoming increasingly important.

CONCLUSION

Polyamines are important molecules that determine cell longevity and death. Polyamines are compounds that, according to modern evolutionary theory, were inherited by modern life forms from a common ancestor. It is now known that nutritional supplementation with polyamines can reduce age-related pathology and increase the life span in a number of animal organisms as well as in humans. From the literature data presented above, it is clear that polyamines are not only markers of aging but can be considered predictors of longevity, as evidenced by the effectiveness of polyamines on all body systems.

In addition, applying polyanimes to animals prevents their senesecence. Even though this is a mature field, more work is needed to better understand and define the broad reach of polyamine metabolism in regulating life processes. In this paper we propose a hypothesis that longevity in birds compared to mammals is associated with higher levels of polyamines and their metabolic characteristics. From the literature data presented above, it is clear that polyamines are not only markers of aging but can be considered predictors of longevity, as evidenced by the effectiveness of polyamines on all body systems.

It is worth paying attention to the fact that the level of polyamines in food products can significantly affect the viability of microorganisms that do not have their own synthesis of polyamines.

It is also important to note that acetylated forms of polyamines may have important roles in regulation of polyamines system and effect on its ensymes , a perspective for future exploration.

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