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Review Article

Health Effects of Polyamines: An Overview of Polyamines as a Health-Promoting Agent for Human Health

Letchuman Sarvananda[1,2*], Danushka Madhuranga[3], Palihaderu Arachchige Dineth Supasan Palihaderu[1,2], Amal D Premarathna[4]

[1]Department of Basic Veterinary Sciences, University of Peradeniya, Peradeniya, Sri Lanka; [2]Molecular Nutritional and Biochemistry Laboratory, University of Peradeniya, Peradeniya, Sri Lanka; [3]Department of Biomedical Science, KAATSU International University, Battaramulla, Sri Lanka; [4]Department of Veterinary Pathobiology, University of Peradeniya, Peradeniya, Sri Lanka

ABSTRACT

Polyamines (PAs) are low molecular weight aliphatic nitrogenous base-containing molecules, are considered an organic compound having more than two amino groups, and they have potent biological activities. They play an important role in both eukaryotic and prokaryotic cells. In living organisms, PAs are mainly available as free PAs, covalently conjugated PAs, or non-covalently conjugated forms. The natural PAs, spermidine and spermine, are synthesized in every living cell and are therefore contained in foods, and their precursor, putrescine, are subcutaneous low molecular weight amines that contain multiple amino groups. Polyamines are synthesized within all living cells, in eukaryotes, polyamine synthesis begins with ornithine, which is synthesized through the urea cycle from arginine. The decarboxylation of ornithine catalyzed by Ornithine Decarboxylases (ODC) is the rate-limiting step in polyamine synthesis. In mammals, polyamines are involved in the most important physiological process. Cell proliferation and viability, nutrition, fertility, as well as nervous and immune system. In some instances where altered synthesis or metabolism of polyamines lead to several types of pathological conditions. Therefore, this review aims to collect and introduce data on the health effects of polyamines, concerning the biological roles of polyamine in humans. Such as its role in the intestine, as an antioxidant, in cancer, in the aging process, in the cardiac process, etc.

Keywords: Polyamines; Health effects; Spermidine; Spermine

INTRODUCTION

Polyamines have a long history in the biochemistry and physiology field, in an earlier study, Leeuwenhoek identified crystals that were composed of spermine phosphate in seminal fluid. Their further biosynthesis and catabolism pathways were revealed in the late 1950s. This finding led to immense interest in polyamines' physiological and biological functions in humans [1]. Polyamines (PAs) are low molecular weight aliphatic nitrogenous base-containing molecules, are considered an organic compound having more than two amino groups, and they have potent biological activities. They play an important role in both eukaryotic and prokaryotic cells [2]. Again, these covalently conjugated PAs can be divided into perchloric acid-soluble covalently conjugated polyamines and perchloric acid-insoluble covalently conjugated polyamines [3]. In plants, PAs are mainly present in their free form. As major PAs in the plants, there are three PAs, putrescine, spermidine, and spermine, and they are involved in the regulation of the diverse physiological process, such as flower development, embryogenesis, organogenesis, senescence, and fruit maturation and development [4]. The PAs are ubiquitous, and widespread from bacteria to mammals. Their participation in cell growth and proliferation has been of primary interest. The human body pool of the PAs is maintained by three sources. 1) Endogenous (*de novo*) biosynthesis, 2) Production by intestinal bacteria or from a constituent of epithelial cells shed into the gut lumen, and 3) Dietary intake. Diet is the main source of polyamines, it provides a larger daily quantity of PAs than endogenous biosynthesis. Dietary PAs are completely and easily absorbed in the body [5]. The natural PAs, spermidine and spermine, are synthesized in every living cell and are therefore contained in foods, and their precursor, putrescine, are subcutaneous low molecular weight amines that

Correspondence to: Letchuman Sarvananda, Department of Basic Veterinary Sciences, University of Peradeniya, Peradeniya, Sri Lanka, E-mail: sarvacool18@gmail.com

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contain multiple amino groups. Spermine and spermidine have four and three amino groups, respectively, and molecular weights of approximately 140 g/mol and 200 g/mol, respectively. A critical function of spermidine in eukaryotes is the activation of eukaryotic Translation Initiation Factor 5A (eIF5A) [6]. It is an essential protein for eukaryotic protein synthesis, and its activation requires post-translation modifications. During this process, a specific Eif5A lysine residue is changed to a hypusine residue by sequential reactions catalyzed by deoxyhypusine synthase, where spermidine is transferred to the lysine residue and deoxyhypusine hydroxylase. In another word, spermidine is deeply involved in protein synthesis because it acts as a substrate for the maturation of Eif5A [6].

Polyamines are positively changed under physiological PH conditions and weakly bind to the negatively charged intracellular molecules, such as nucleic acid, phospholipids, and ATP. Among these molecules also polyamines bind most frequently to RNA and regulate protein translation by influencing the structure of the mRNA [7]. The study revealed there are 17 proteins in *E.coli* and six proteins in eukaryotes that have been experimentally reported to be translationally controlled in this manner, and they are considered to be members of the "Polyamine modulation" [8]. These proteins are involved in cell proliferation, biofilm formation, enhancement of cell activity, and detoxification. And also importantly polyamines are essential for the maintenance of normal activities of organisms. Mainly three sources of polyamine sources were identified: Oral intake [9], intestinal microbiota [10], and biosynthesis in human cells. And also study indicated the polyamine biosynthesis ability decreased with age, and currently difficult to regulate. Therefore, to control and maintain a polyamine concentration in the body, it is necessary to control the number of polyamines derived from food and intestinal bacteria [9]. Many *in vivo* studies revealed the health benefit of polyamines using animals [11]. One report was, Soda et al. reported in 2009 about the effects of polyamines on extending healthy lifespans in mice [12]. In that report, the concentration of polyamines in the blood of 50-week-old mice fed with high polyamine chow containing spermidine and spermine at 374 nmol/g and 1540 nmol/g respectively. From 24 weeks of age was higher when compared to that of mice fed with low-polyamine chow containing spermidine and spermine at 143 nmol/g and 224 nmol/g, respectively. From 24 weeks of age. At 88 weeks of age, the incidence of glomerulosclerosis was lower, and the expression of the saneness marker protein -30, which decreases with aging, and also the survival rate of mice fed with high-polyamine chow was significantly higher than that of mice fed with low-polyamine chow. Therefore overall study concluded that oral intake of polyamines can improve overall health and promote healthy life expectancy [12]. Also there are many studies also concluded the effect of polyamines on the body [11]. Therefore, this review aims to collect and introduce data on the health effects of polyamines, concerning the biological roles of polyamine in men. Such as its role in the intestine, as an antioxidant, in cancer, in the aging process, in the cardiac process, etc.

LITERATURE REVIEW

Polyamine biosynthesis

Polyamines are synthesized within all living cells, in eukaryotes, polyamine synthesis begins with ornithine, which is synthesized through the urea cycle from arginine. The decarboxylation of ornithine catalyzed by Irnithine Decarboxylases (ODC) is the rate-limiting step in polyamine synthesis. Spermidine and spermine are then synthesized by the sequential addition of aminopropyl groups donated from Decarboxylated S-adenosylmethionine (dc-SAM), which is converted from S-adenosylmethionine (SAM) by the enzymatic activities of Adenosylmethionine decarboxylase (AdoMetDC) [13]. Polyamine biosynthesis, degradation, and transmembrane transport. The polyamines are synthesized from arginine. Arginase converts arginine to ornithine, and Ornithine Decarboxylase (ODC), a rate-limiting enzyme with a short half-life, catalyzes the decarboxylation of ornithine to form putrescine, a polyamine precursor containing two amine groups. ODC is inhibited by antizyme, and antizyme is inhibited by an antizyme inhibitor. S-adenosylmethionine decarboxylase (AdoMetDC) is the second rate-limiting enzyme in polyamine synthesis and is involved in the decarboxylation of S-adenosylmethionine (SAM). Spermidine synthetase and spermine synthase are constitutively expressed aminopropyl transferases that catalyze the transfer of the aminopropyl group from decarboxylated s-adenosylmethionine to putrescine and spermidine to form spermidine and spermine, respectively [13]. Polyamine catabolism is mediated by the back conversion pathway in which spermine or spermidine are first acetylated by Spermine/Spermidine N1-Acetyltransferase (SSAT) and then oxidized by N1-Acetylpolyamine Oxidase (APAO) to yield spermidine or putrescine, respectively. Spermine can be directly converted to spermidine *via* the Spermine Oxidase (SMO) reaction. Polyamines are transported across the membrane by the polyamine transporter [13]. This process can be showed as Figure 1. Other than the intracellular *de novo* synthesis, cells can take up polyamine from the extracellular space through a polyamine transporter in the cell membrane [13].

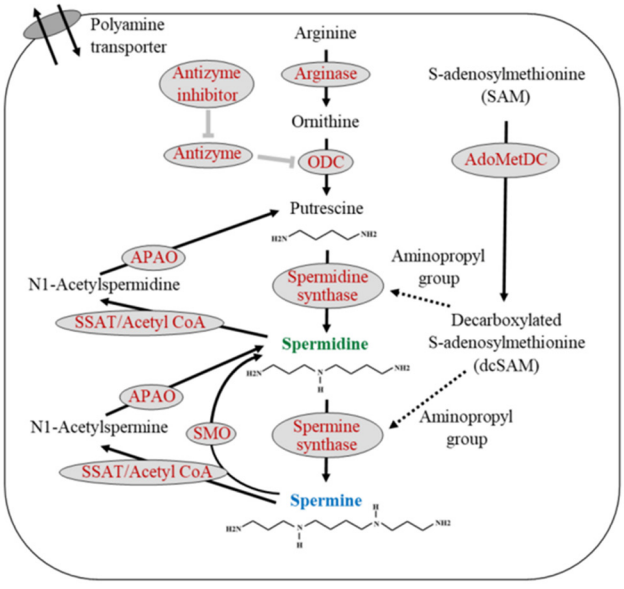

Figure 1: Polyamine biosynthesis pathway. **Note:** (■) The substance name; (■) Enzyme names; (■) Thick gray T-bars inhibitory activity on the target; (■) spermidine and spermine; (■) blue, respectively ODC: Ornithine decarboxylase; SSAT: Spermidine/spermine N1 -acetyltransferase; APAO: N1 -acetylpolyamine oxidase; SMO: Spermine oxidase; SAM: S-adenosylmethionine; AdoMetDC: Adenosylmethionine decarboxylase; dcSAM: Decarboxylated S-adenosylme

Biological roles of polyamines in man

There are 3 major types of polyamines in the body known as, Putrescine (PUT), Spermidine (SPD), and Spermine (SPM). These

have a different kinds of structural formulas, Figure 2 showed the structural classification of polyamines. Under the physiological conditions, are strong flexible polycations exhibiting 2, 3, or 4 positive chargers, respectively. They can interact with negatively charged macromolecules such as nucleic acids, phospholipids, and proteins. Which ionic interactions are reversible, and lead to the stabilization of DNA, RNA, membranes, and some proteins [5]. These revealed that polyamines are important in the growth, maintenance, and function of normal cells. These participate in several biological processes in humans, some of which are favorable and others injurious. In mammals, polyamines are involved in the most important physiological process. Cell proliferation and viability, nutrition, fertility, as well as nervous and immune system. In some instances where altered synthesis or metabolism of polyamines lead to several types of pathological conditions (Figure 3). Polyamines in the case of DNA and RNA, as well as protein fragments, and membranes also contain polyamines as negatively charged phospholipids and proteoglycans. Therefore alteration of polyamines in the systems can lead to several pathophysiological outcomes and various outcomes. Therefore maintenance of healthy levels in the body and constant uptake to the body is very important [14].

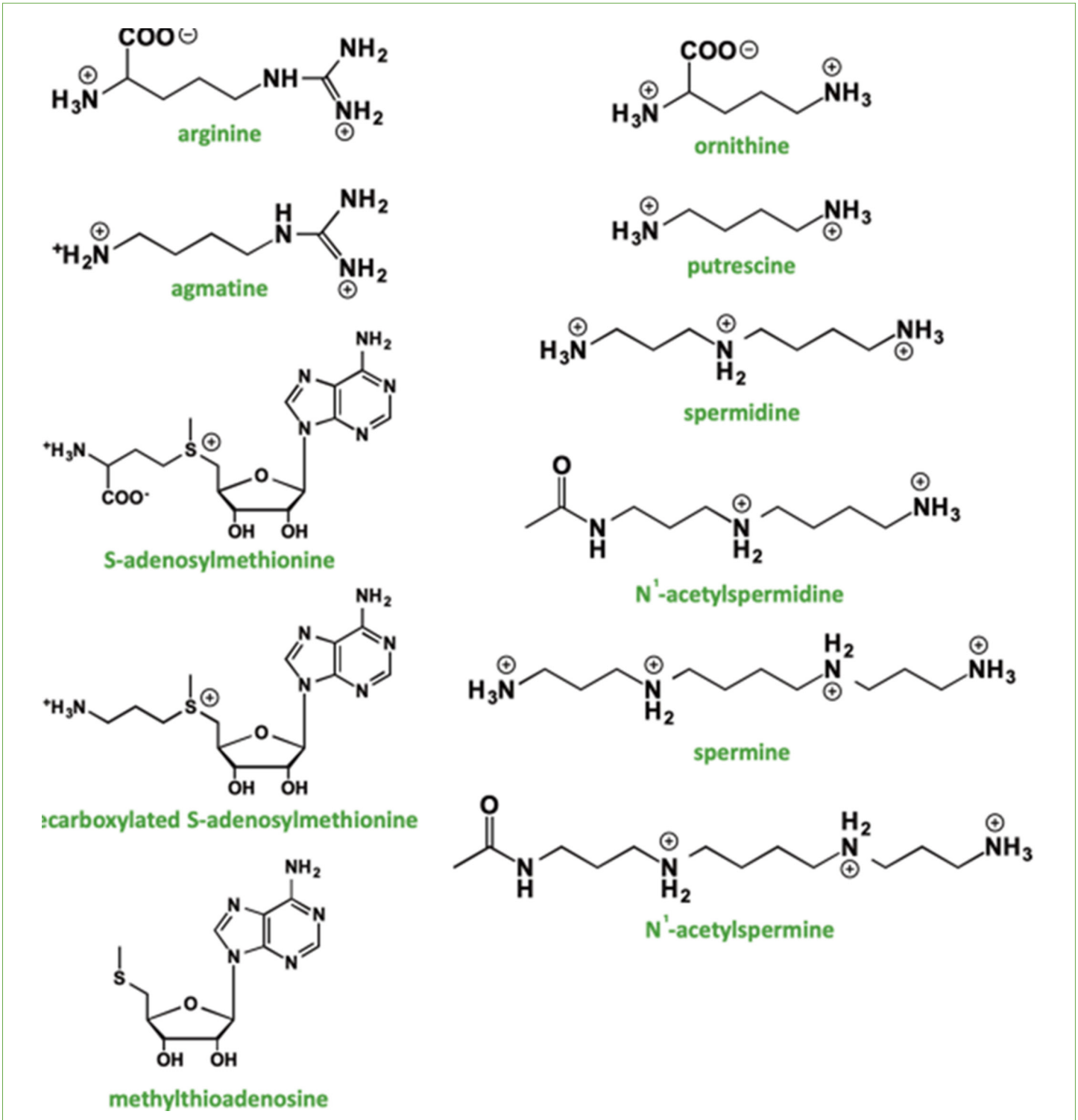

Figure 2: Structural classification of Polyamines

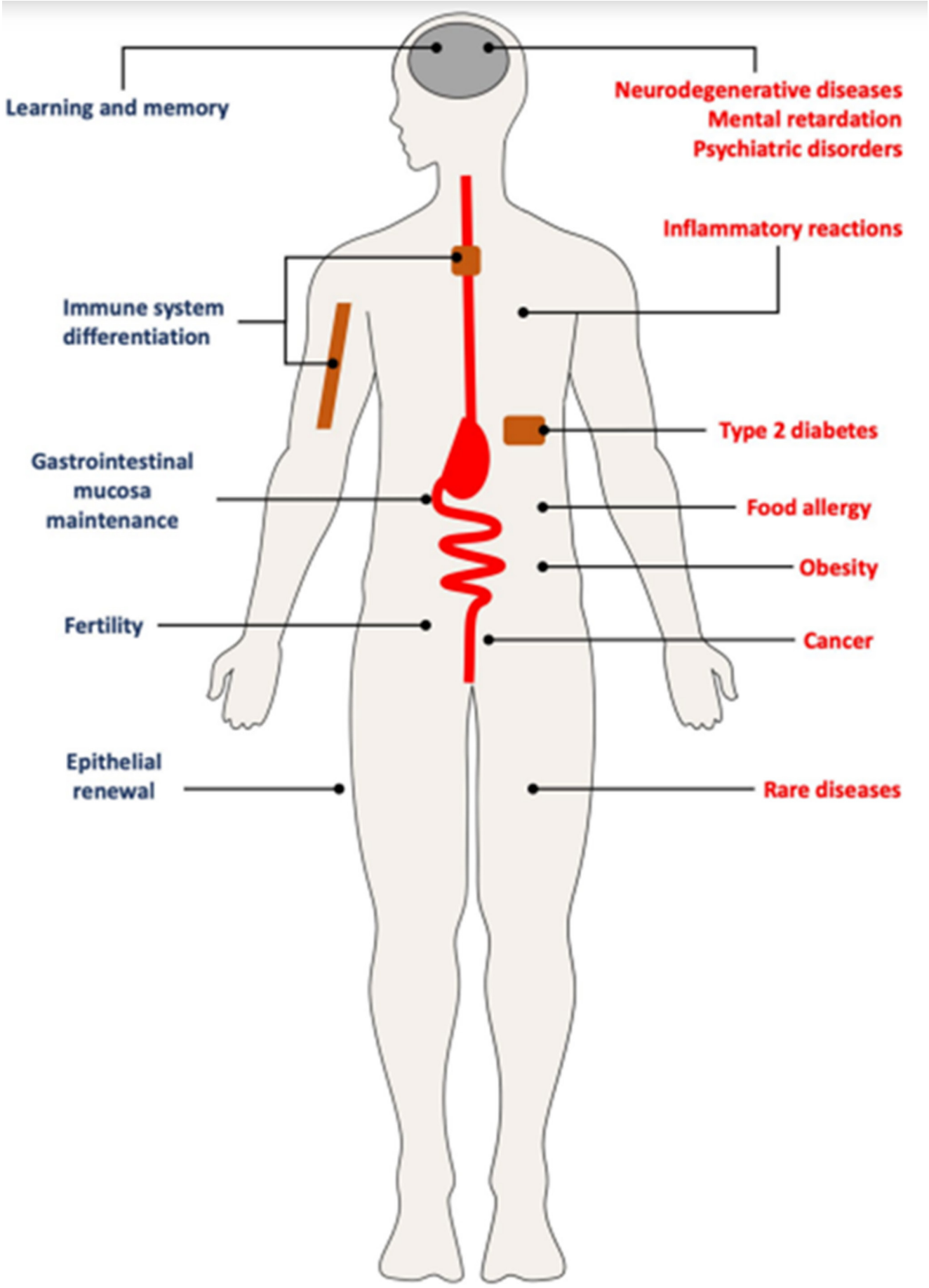

Figure 3: Some of pathophysiological conditions due to the alteration of polyamine metabolism in human.

Role in intestine

Dietary PAs (Polyamines), particularly SPM, significantly to the intestinal polyamine pool and they are importantly essential to the growth of small intestinal and colonic mucosal growth, maturation, and regeneration. It was proved using *in vivo* experiments [5]. Also considerable polyamine levels were observed in the lumen o the human gut during the fasting state, which suggests endogenous secretion. Relatively high PAs are found in the jejunum rather than the ileum, and dietary PAs are almost completely absorbed in the small intestine. The proportion of the PAs, which may affect the large intestinal mucosal tissue, is primarily of microbial rather than of dietary origin. Initial studies deal with the ability of various microbiota species of the human intestine to produce polyamines [15].

Ingested food is the major source of polyamines in the lumen, and the upper parts of the intestine absorb the majority of these compounds for the growth process throughout the body [16]. The gut microbiota is considered the main responsible for PAs levels in the lower part of the intestine [15]. PAs in the colonic lumen is transferred into the bloodstream *via* the colonic mucosa [17]. Intracellular polyamine levels are regulated by endogenous biosynthesis, degradation, and exogenous transport. Both endocytic and solute carrier-dependent mechanisms have been described for polyamine uptake in the gut lumen [18]. In eukaryotic cells, they are involved in several physiological functions [19]. In benign colonic or intestinal neoplasia, which can progress to invasive cancer. Adenomatous Polyposis Coli (APC) tumor suppressor gene contributes to normal GI tract development and APC alteration results in dysregulation of the pathways for the production of polyamines [20]. Especially the epithelium of the GI tract mucosa has the most rapid turnover rate of any tissue in the body and its integrity is preserved through the dynamic balance between cell migration, proliferation, growth arrest, and apoptosis [21-24]. Therefore, to maintain tissue homeostasis of the GI mucosa, the rates of epithelial cell division and apoptosis must be highly regulated by various extracellular and intracellular factors including special polyamines [25-27]. Natural PAs spermidine, spermine, and their precursor putrescine are organic cations in eukaryotic cells and are involved in the signaling pathways and the cell cellular functions [28,29]. Importantly normal intestinal epithelial growth depends on the available supply of polyamines to the dividing cells in the crypts, and polyamines also regulate intestinal epithelial cell apoptosis. Evidence indicated that polyamines regulate intestinal epithelium integrity by modulating the expression of various growth-related genes [30].

Role as the antioxidant

Free radicals are now accepted as important mediators of tissue injury in several neurodegenerative models [31]. High oxygen content and relatively low concentration of antioxidants enzymes and free radicals scavengers can lead to the formation and free radical damage. These radicals can attack the membrane lipids, proteins, and nucleic acids to cause cell damage or death [31], and cause to lipid peroxidation, these lipid peroxidation products contribute to the etiology of several chronic diseases including neurodegenerative conditions, chronic inflammatory diseases, alcoholic liver diseases, cardiovascular disorders, and diabetic complications. Therefore, the antioxidant properties of the drugs are very important for the treatment of these conditions and maintain a healthy life [31]. When it comes to PAs, spermine, spermidine, and putrescine, the primary and secondary amine moieties of PAs always carry a charge at physiological Ph., these amines are involved with numeric cellular functions, including free radical scavenger, antioxidant and anti-inflammatory properties [32], and as well as it has been reported that spermine inhibits both NADPH and ascorbic acid-dependent lipid peroxidation in liver microsomes [33]. PAs antioxidant activity seems to participate in the reduction of cell membranes and DNA damage. PAs at physiological concentrations are potent scavengers of hydroxyl radicals. SPD and SPM can also quench both singlet oxygen and hydrogen peroxide and can act as pro-oxidants and enhance oxidative damage to DNA components in the presence of free iron ions and hydrogen peroxide [34]. Polyamines antioxidant and/or lysosomal stabilization properties cause anti-inflammatory activity in acute and chronic inflammation [5]. Antioxidants act by two distinct mechanisms including scavenging effects on ROS (initiator and/or chain breaker of the per-oxidative reaction) and chelating action with transition metals (e.g. Cu^{2+} or Fe^{2+}) that catalyze ROS formation. It is now hypothesized that polyamines, due to their anti-oxidative properties, participate in the prevention of carcinogenesis by protecting cell DNA from ROS-induced damage, thereby preventing subsequent mutagenesis and cell transformation. High polyamine levels are required to protect healthy cells against ROS-induced damage [31].

Polyamine and cancer

Polyamines do not trigger cancer but accelerate tumor growth. Enhanced levels of PAs biosynthesis in cancer tissues arise from the increased activity of enzymes caused for their synthesis. In addition to the *de novo* synthesis, cells can uptake PAs from extracellular sources, such as cancer tissues, food, and intestinal microbiota [35]. The increased polyamine availability enhances cell growth. Cancer cells with a greater capability to synthesize PAs are associated with high production of proteins, which can lead to the degradation of the surrounding tissues. Immune cells in an environment with increased PAs levels, lose antitumor immune function. Therefore, the capability of cancer cells to invade and metastasize to new tissues is thus enhanced [35]. The freely available extracellular PAs are taken up into cancer cells *via* the polyamine transport system, an energy-dependent process that is upregulated in cancer cells. Deprivation of exogenous polyamines, therefore, started as a treatment approach in the 1990s. The reduction of dietary PAs intake and partial intestinal decontamination showed a well-observed and tolerated therapeutic regimen. Some compounds of diet, particularly flavonoids, polyphenols, ad probiotics, were reported to reduce the hyper proliferative role of PAs in colorectal cancer [36]. The naturally occurring polyamines, spermine, spermidine, and diamine putrescine are widespread. They have been implicated in the growth and differentiation process. Polyamines accumulate in cancerous tissues and their concentration is elevated in body fluids of cancer patients. Assays of urinary and blood polyamines have been used to detect cancer and to determine the success of therapy. Polyamine biosynthesis is up-regulated in actively growing cells, including cancer cells, therefore polyamine concentration as well as gene expression and activity of enzymes involved in polyamine biosynthesis, especially ODC, are higher in cancer tissues than in normal surrounding tissues [37]. Numerous reports have shown that both blood and urine polyamine concentrations are often increased in cancer patients. A close correlation between blood polyamine levels and the amount of urinary polyamines has also been found in cancer patients. Moreover, these levels decrease after tumor eradication and increase after relapse, indicating that

polyamines synthesized by cancer tissues are transferred to the blood circulation and kidney, where they are excreted into the urine [37]. Ornithine Decarboxylase (ODC), the first enzyme in the PAs biosynthetic pathway, exhibits increased enzyme activity in several cancers including breast, prostate, skin, and colon. Furthermore, ODC is itself an oncogene and is a target of several oncogenes such as c-MYC and Ras, which are amplified in multiple cancers. It revealed the strong association between increased PAs concentrations and elevated ODC activity [38].

Interplay of lipid metabolism and polyamines in aging

Aging is a multifaceted process, it is caused by a myriad of interacting factors and with consequences at all levels of the organism. Research into the subject has revealed that factors leading to aging are as varied as sustained exposure to cellular stress, chronic inflammation, dysregulation of lipid metabolism, autophagy, and cell survival and death. These factors will impinge upon each other in complex interactions. Effective interventions against aging will need to be able to impact as many as possible of the factors causing aging and their interactions [39]. Lipid metabolism has recently been found as a strong regulator of health and lifespan. A dysfunction or alteration in lipid metabolism can trigger deleterious consequences on health and ultimately aging and lifespan. On the other hand, many mutations increasing lifespan have been associated with increased levels of stored lipids and changes in lipid profiles (composition and saturation levels). The involvement of spermidine in adipogenesis combined with our results showing that spermidine alters lipid profile in fruit flies makes lipid regulation a likely contributor to the effect of spermidine on aging [39]. It is undoubted that cells senesce and lose with time-appropriate responses to growth and death signals. Unregulated cell growth or death will lead to tissue or organ dysfunction. However, how cellular senescence impacts whole organism aging is not fully understood and is still debated. Polyamines regulate cell growth and death. The decrease in polyamine levels with age could play a part in this cellular aging phenotype and polyamine supplementation may help lessen the effects of cellular aging [39].

The activity of ODC, the rate-limiting enzyme in polyamine synthesis, declines with age. ODC has been well characterized and has had a short half-life and is stimulated by various factors. The properties of spermidine synthase and spermine synthase have not been fully clarified, however, they seem to lack a regulatory or rate-limiting role in polyamine synthesis. The administration of arginine or ornithine stimulates putrescine levels; however, the subsequent synthesis of polyamines is not necessarily stimulated in elderly people or aged animals. These findings indicate that the activities of spermine and spermidine synthases decrease gradually with aging (Figure 4) [13].

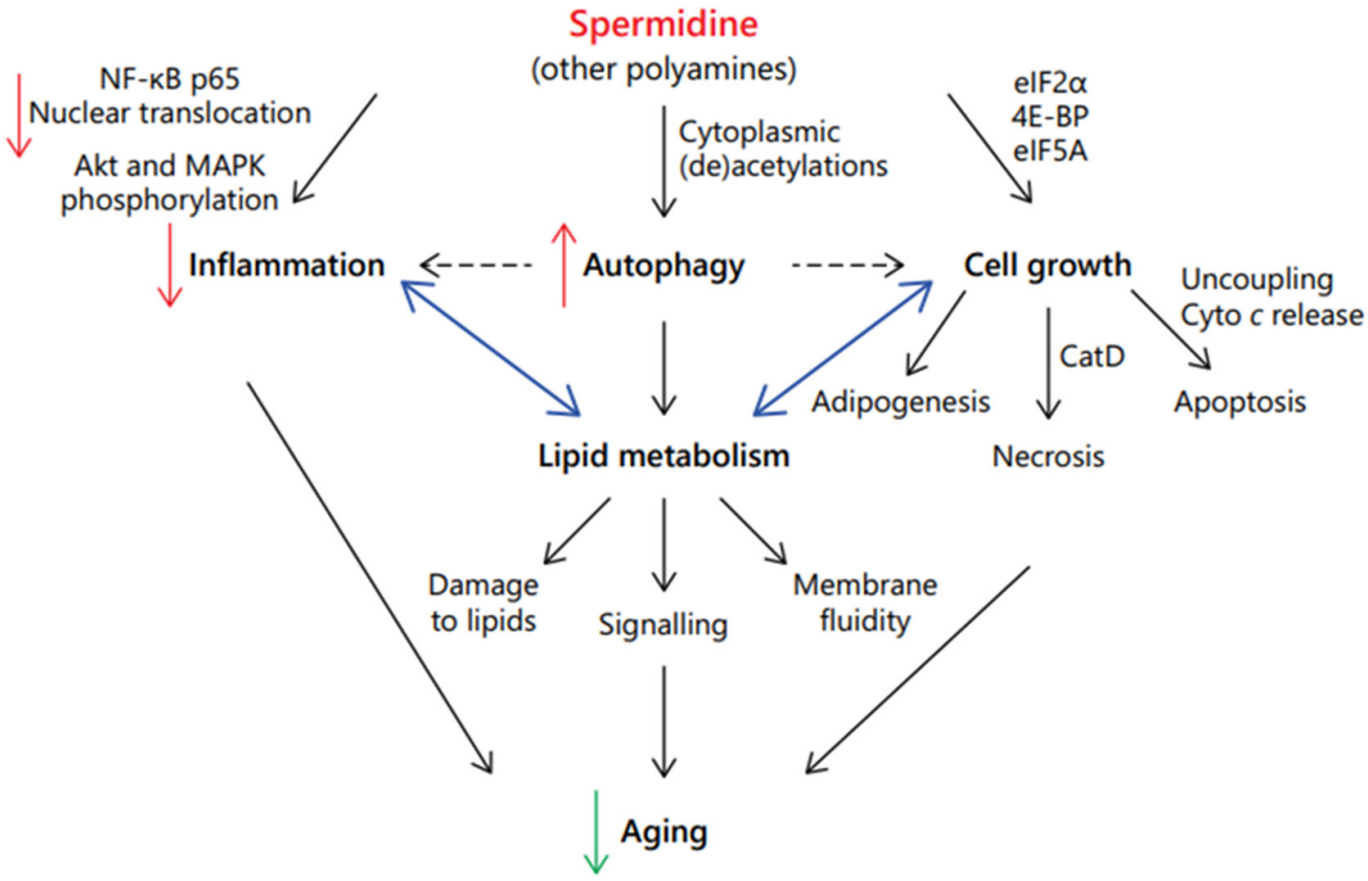

Figure 4: Syngthesis of the spermidine and its effects on aging

Polyamines in cardiac aging and mitochondrial function

Mitochondrial dysfunction is considered a major contributor to aging, and a dominant risk factor for the development of cardiovascular diseases. It has been shown that intracellular polyamine levels decrease with age in various species, and generally induced depletion of intracellular PAs decreased in yeast and mice. Polyamines have been shown to provide cardiovascular protection in humans. Because age-related cardiovascular dysfunction is often accompanied by impaired mitochondrial biogenesis and function, the ability of spermidine, a major mammalian polyamine, to attenuate cardiac aging through activation of mitochondrial biogenesis. Cardiac PAs levels were reduced in aged (24-month-old) rats [40].

Spermidine administration reduced lipid accumulation and necrotic core formation by inducing autophagy in an atherosclerosis mouse model. Polyamine exposure attenuated cardiac endoplasmic reticulum stress during acute myocardial infarction by inhibiting Reactive Oxygen Species (ROS) production in isolated, perfused rat hearts [41]. Interestingly, a large multi-center work showed that exogenous SPD administration enhanced mitophagy, promoted mitochondrial respiration, and improved diastolic function to delay cardiac aging in mice. In addition, the study revealed that high levels of dietary SPD were inversely correlated with cardiovascular disease in humans [42]. Our previous studies suggested that exogenous polyamines protect against myocardial reperfusion injury by inhibiting mitochondrial Permeability Transition Pore (mPTP) opening [43], and provided novel information derived from combined proteomics and metabolomics analyses on the cardio protective effects of polyamines in the aging heart [44]. Spermine plays an important role in many cardiac diseases including hypertrophy, ischemia, and infarction [45].

Role of polyamines in cognitive function

One of the major risk factors for poor health and shortened life expectancy among the elderly is known as the incidence and progression of diseases associated with cognitive decline and impaired cognitive function [46]. Individuals with cognitive impairment with or without definite neurodegenerative diseases have a higher mortality risk than healthy controls [47]. Therefore, it lead to the investigation of the possible role of increased polyamine intake, which extends the lifespan, in these aging-associated changes. The ability that spermidine is involved in memory function through a mechanism involving a novel memory-related molecule has been reported in insects such as Drosophila [11]. Polyamines cannot cross the BBB in normal conditions, reports have shown that BBB dysfunction is associated with the pathogenesis of several neurodegenerative disorders such as Alzheimer's disease [48], Parkinson's disease [49], multiple sclerosis, and amyotrophic lateral sclerosis, in addition to typical cerebrovascular disorders such as stroke and vascular dementia [13]. A study showed a close relationship between chronic inflammation and neurodegenerative diseases. Inflammation activates SSAT, an enzyme that breaks down spermine to spermidine and spermidine to putrescine, decreasing polyamine levels (Figure 5). Increased polyamine degradation and decreased concentrations of spermine and spermidine activate the polyamine recycling pathway [13].

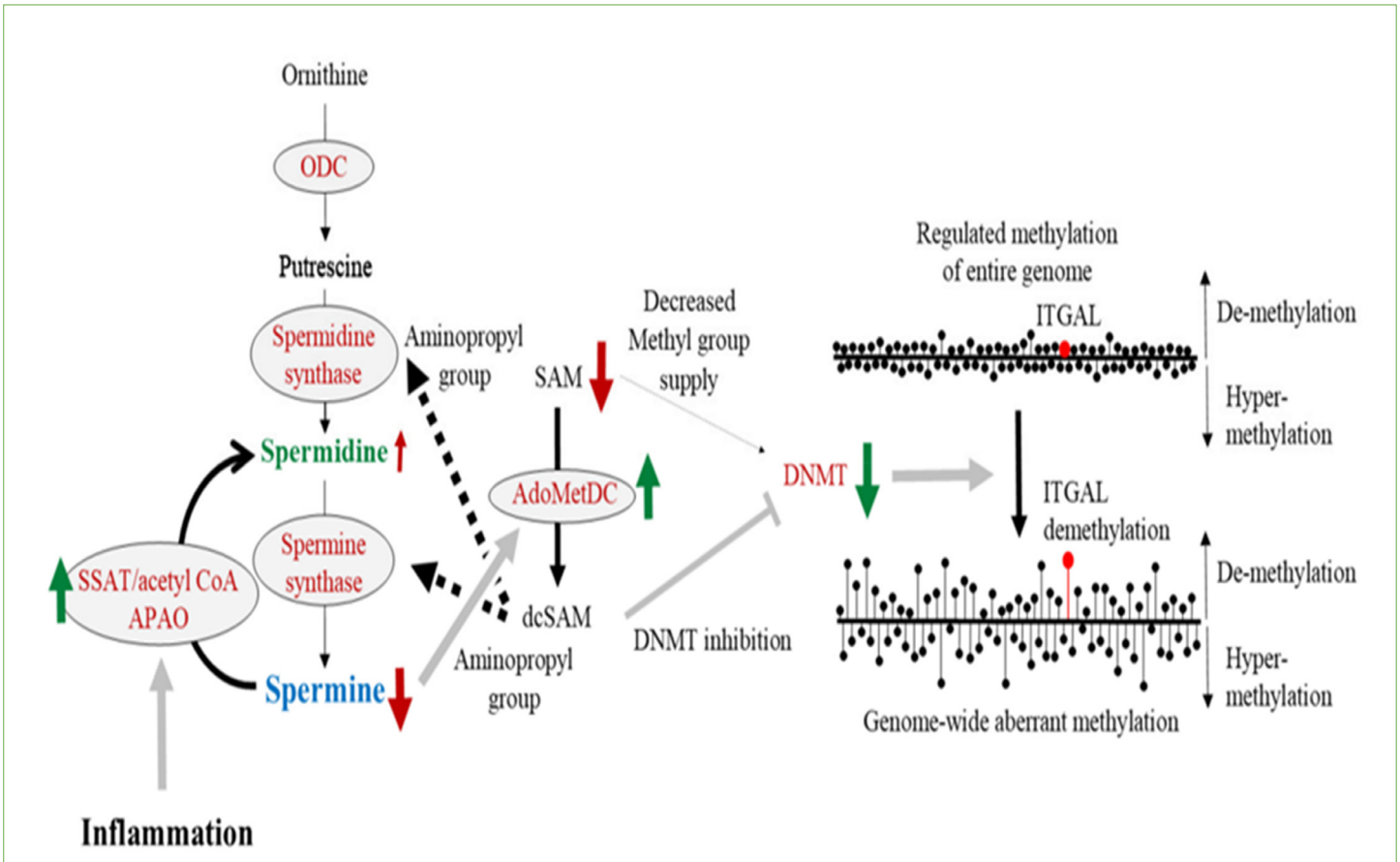

Figure 5: The effects of chronic inflammation on enzyme activities and substance levels related to polyamine metabolism and gene methylation

Polyamine localization in the body

Polyamines have a binding ability to DNA, RNA, and several protein molecules, and are involved in several types of cellular functions such as transcription, RNA modification, protein synthesis, and modulation of enzyme activities. A study showed that a high percentage of total polyamines is bound by ionic interactions with nucleic acids, proteins, and other negatively-charged molecules in the cell, while the free intracellular concentration of each polyamine is much lower (7%–15% of the total for spermidine and 2%–5% for spermine in tissues and organs) [50]. Therefore, most polyamines in circulating blood are present in blood cells. Copper et al. showed that spermidine and spermine concentrations in plasma account for only 1.0% (spermine) to 1.2% (spermidine) of whole blood [13]. When we measure serum or plasma polyamine concentration using HPLC, it is sometimes hard to detect the peak of spermine due to the low levels [13]. When the concentration of spermine is low, HPLC can only depict the peak of spermine as a shaking of the baseline. We consider that it is difficult to determine accurate polyamine concentrations using such an unclear peak. It is also important to note that even if a small amount of hemolysis occurs in the blood sample, the polyamines present in the cells leak out and have a significant effect on the polyamine concentration. The reason for measuring whole blood polyamine levels is to accurately measure all the polyamines present or attached to blood cells [13]. Blood cells circulate in organs and tissues throughout the body. Polyamine concentrations are increased in cancer tissues due to active polyamine synthesis, and blood polyamine concentrations are increased in cancer patients. These indicate that blood polyamine levels reflect polyamine concentrations in some organs and tissues in the body. Conversely, polyamines in blood cells can be passed to cells in tissues and organs, affecting their concentration. However, due to PAs water solubility, it cannot pass through the blood-brain barrier, but in dangerous brain injuries, PAs can enter the brain [13].

CONCLUSION

Polyamines have a long history in the biochemistry and physiology field, in an earlier study, Leeuwenhoek identified crystals that were composed of spermine phosphate in seminal fluid. Their further biosynthesis and catabolism pathways were revealed in the late 1950s. This finding led to immense interest in polyamines' physiological and biological functions in humans. Polyamines (PAs) are low molecular weight aliphatic nitrogenous base-containing molecules, are considered an organic compound having more than two amino groups, and they have potent biological activities. Polyamines are synthesized within all living cells, in eukaryotes, polyamine synthesis begins with ornithine, which is synthesized through the urea cycle from arginine. The decarboxylation of ornithine catalyzed by ornithine decarboxylases (ODC) is the rate-limiting step in polyamine synthesis. Spermidine and spermine are then synthesized by the sequential addition of aminopropyl groups donated from decarboxylated S-adenosylmethionine (dc-SAM), which is converted from S-adenosylmethionine (SAM) by the enzymatic activities of adenosylmethionine decarboxylase (AdoMetDC). In mammals, polyamines are involved in the most important physiological process. Cell proliferation and viability, nutrition, fertility, as well as nervous and immune system. In some instances where altered synthesis or metabolism of polyamines lead to several types of pathological conditions. Therefore, this review aims to collect and introduce data on the health effects of polyamines, concerning the biological roles of polyamine in humans. Such as its role in the intestine, as an antioxidant, in cancer, in aging processes, in cardiac process, etc.

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