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Review

Aliphatic polyamines in physiology and diseases

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SUMMARY

Aliphatic polyamines are a family of polycationic molecules derived from decarboxylation of the amino acid ornithine that classically comprise three molecules: putrescine, spermidine and spermine. In-cell polyamine homeostasis is tightly controlled at key steps of cell metabolism. Polyamines are involved in an array of cellular functions from DNA stabilization, and regulation of gene expression to ion channel function and, particularly, cell proliferation. As such, aliphatic polyamines play an essential role in rapidly dividing cells such as in the immune system and digestive tract. Because of their role in cell proliferation, polyamines are also involved in carcinogenesis, prompting intensive research into polyamine metabolism as a target in cancer therapy. More recently, another aliphatic polyamine, agmatine, the decarboxylated derivative of arginine, has been identified as a neurotransmitter in mammals, and investigations have focused on its effects in the CNS, notably as a neuroprotector in brain injury.

1. Introduction

Aliphatic polyamines (simply quoted as polyamines throughout this paper) classically refer to three molecules: putrescine, spermidine and spermine. They are found ubiquitously in the body. They are the focus of intensive research due to their involvement in many physiological functions such as immunity and intestinal function, but especially due to their involvement in carcinogenesis. Agmatine, the decarboxylated derivative of arginine, was recently found in mammals, and several studies have investigated its potential functions, especially in the CNS.

2. Metabolism of putrescine, spermidine and spermine

2.1. Structure and metabolism

Polyamines are ornithine derivatives that form a small family of three members: putrescine, spermidine and spermine. Their chemical structure is shown in Fig. 1. Polyamine metabolic pathways (synthesis, interconversion and catabolism) are shown in Fig. 2. The first step of polyamine synthesis is the enzymatic decarboxylation of ornithine into putrescine by ornithine decarboxylase (ODC). Spermidine is derived from putrescine by addition of an aminopropyl group via spermidine synthase. Spermine is derived from spermidine by addition of another aminopropyl group catalyzed by spermine synthase. In both reactions, the aminopropyl group donor is S-adenosyl-S-methyl-homocysteamine (SAMHC). SAMHC is synthesized by the enzymatic decarboxylation of S-adenosylmethionine (SAM) by SAM decarboxylase (SAMdc). Polyamine catabolism involves acetylation by spermidine/spermine acetyltransferase (SSAT) and oxidation of acetylated derivatives by polyamine oxidase.[1] Putrescine is catabolized by diamine oxidase. Note that spermine can be directly oxidized by spermine oxidase.[2]

2.2. Regulation of polyamine metabolism: key enzymes and transport systems

The regulation of polyamine metabolism involves three critical enzymes: ODC, SAMdc and SSAT (Fig. 3). These enzymes have a short half-life (less than 1 h) and their cellular content is tightly controlled at multiple steps of their synthesis and degradation. Furthermore, cell polyamine content is also controlled by transport systems involving both uptake and efflux[2,3] (see also [S1] supplemental material).

2.2.1. Ornithine decarboxylase (ODC)

ODC (EC 4.1.1.17) catalyzes the decarboxylation of ornithine into putrescine, the first step of polyamine biosynthesis. This

Abbreviations: DFMO, difluoromethylornithine; ODC, ornithine decarboxylase; SAM, S-adenosylmethionine; SAMdc, SAM decarboxylase; SAMHC, S-adenosyl-S-methyl homocysteamine; SSAT, spermidine/spermine acetyltransferase.

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Putrescine $H_2N\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}NH_2$

Spermidine $H_2N\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}NH\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}NH_2$

Spermine $H_2N\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}NH\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}NH\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}NH_2$

Agmatine $H_2N\text{-}C(=NH)\text{-}HN\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}NH_2$

Fig. 1. Structure of polyamines: putrescine, spermidine, spermine and agmatine.

decarboxylation reaction requires pyridoxal phosphate which is lysine-bound to the enzyme by formation of a Schiff base. The active form of ODC is a homodimer. Each monomer contains two domains: an N-terminal domain, with an α/β barrel structure including the cofactor binding site, and a C-terminal β-sheet domain. The active sites are formed by interaction of the barrel domain of one monomer with the sheet domain of the other. The active dimers and inactive monomers are in equilibrium.[4]

ODC has a high turnover, and its degradation rate is tightly regulated. Catabolism of ODC involves the non-covalent binding of ODC monomer to a specific protein, antizyme, which inactivates ODC and targets it towards degradation by proteasome 26S. Conversely, another protein, antizyme inhibitor, can displace ODC from the ODC/antizyme complex and thus prevent its degradation. Antizyme inhibitor is an inactive analog of the ODC monomer, but with more affinity for antizyme.[2,4] High cellular polyamine levels increase ODC degradation by inducing antizyme ARNm translation via a frameshifting process. The antizyme mRNA contains two overlapping open reading frames (ORFs), a short one, ORF1, and a long one, ORF2. ORF2, which is in the +1 frame relative to ORF1, does not have an initiation codon. Synthesis from ORF2 therefore requires a failure of the ribosome to terminate at the end of ORF1 and a polyamine-induced shift to the +1 reading frame, allowing synthesis of the functional

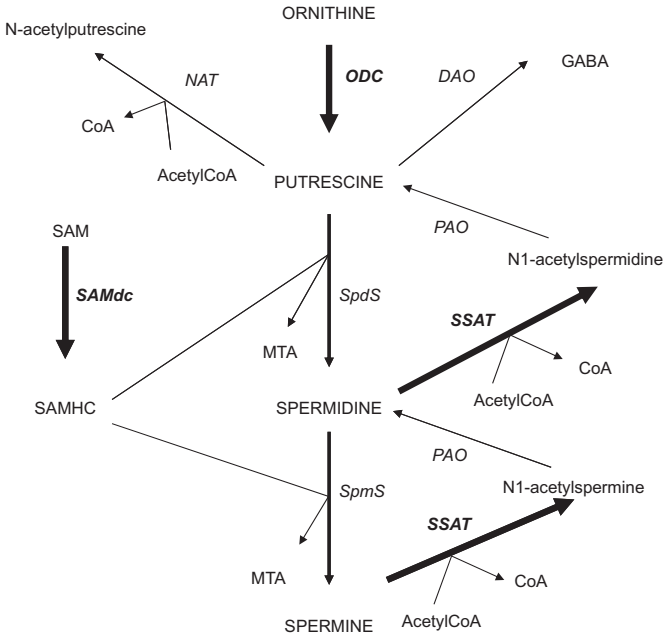

Fig. 2. Polyamine metabolism (adapted from[1]). Key steps and enzymes are shown in bold. ODC: ornithine decarboxylase; SpdS: spermidine synthetase; SpmS: spermine synthetase; SSAT: spermidine/spermine N1-acetyl-transferase; PAO: polyamine oxidase; NAT: N8-acetyl-transferase; DAO: diamine oxidase; SAMdc: SAM decarboxylase; SAM: S-adenosyl-methionine; SAMHC: S-adenosyl-S-methyl homocysteamine; MTA: 5-methylthioadenosine; CoA: Coenzyme A; GABA: Gamma aminobutyric acid.

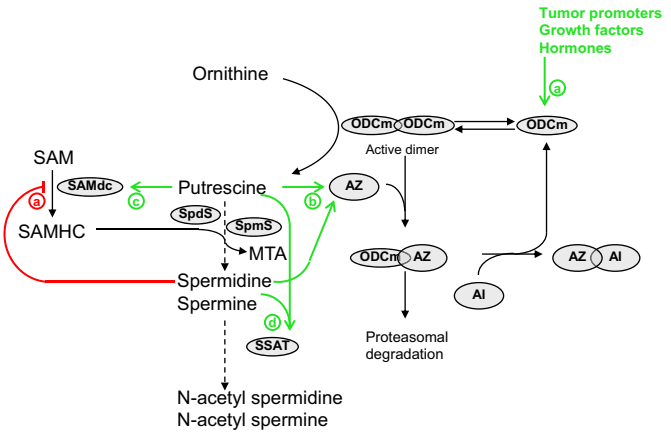

Fig. 3. Regulation of polyamine metabolism. AZ: antizyme; AI: antizyme inhibitor; MTA: 5-methylthioadenosine; ODCm: monomer of ornithine decarboxylase; SSAT: spermidine/spermine N1-acetyl-transferase; SAMdc: SAM decarboxylase; SAM: S-adenosyl-methionine; SAMHC: S-adenosyl-S-methyl homocysteamine; SpdS: spermidine synthetase; SpmS: spermine synthetase. Green arrows denote activatory regulation, red ones inhibitory regulation. Small circled letters identify the targets of these regulations; a: transcription and translation, b: transcription (frameshifting), inhibition of protein degradation, c: SAMdc autoprocessing and activation, d: transcription (polyamine response element), mRNA processing and translation, protein stabilization. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

protein. Moreover, polyamines inhibit antizyme ubiquitinylation and degradation.[2,4]

ODC transcription is also regulated by many stimuli. The *Odc* gene promoter region contains sequences that allow response to hormones, growth factors and tumor promoters. Note that ODC mRNA synthesis is increased by the *c-Myc* oncogene. The *Odc* gene promoter contains two E-boxes that are activated by the Myc/Max transcription factor when c-Myc levels are increased.[4]

Lastly, ODC is regulated at the translational level. ODC mRNA translation is induced by high levels of the translation factor eIF4E. Furthermore, the *ras* oncogen increases ODC expression by inducing both its transcription and translation.[2,4]

2.2.2. S-adenosylmethionine decarboxylase (SAMd)

SAMdc (EC 4.1.1.50) catalyzes the decarboxylation of SAM into SAMHC. This reaction is the limiting step of the conversion of putrescine into spermidine and spermine, since SAMHC is the aminopropyl donor. SAMdc structure is that of a dimer $(\alpha\beta)_2$ with a pyruvoyl group in its active site; the two protomers are derived from a unique inactive proenzyme of 334 amino acids. Proenzyme activation involves an autoprocessing step, with serinolysis of the peptidic bond between residues Glu67 and Ser 68 leading to a cleavage of the proenzyme into two subunits, α (C-terminal part) and β (N-terminal part), with the pyruvoyl group at the N-terminal of the α chain. Each $\alpha\beta$ unit contains a putrescine-binding site. Catalysis proceeds via the formation of a Schiff base between SAM and the pyruvoyl group, decarboxylation of SAM, protonation of its Cα carbon, and hydrolysis of the Schiff base.[5] Alternatively, misprotonation of the pyruvoyl group leads to its transamination into alanine, which results in SAMdc inactivation and degradation by the proteasome after ubiquitinylation.[2]

Like ODC, SAMdc activity is tightly regulated at multiple levels. Putrescine activates SAMdc by inducing proenzyme autoprocessing and enhances its catalytic activity. Adversely, spermidine and spermine decrease enzyme synthesis by inhibiting SAMdc gene transcription and mRNA translation. The mechanism of translational inhibition involves a small ORF in the 5′untranslated region of the mRNA encoding a MAGDIS hexapeptide. Increased