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Review

Modulation of cellular function by polyamines

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ABSTRACT

Polyamines (putrescine, spermidine and spermine) are essential for normal cell growth. The polyamine levels in cells are regulated by biosynthesis, degradation, and transport. Polyamines can modulate the functions of DNA, nucleotide triphosphates, proteins, and especially RNA because most polyamines exist in a polyamine–RNA complex in cells. Thus, the major focus on this review is on the role of polyamines in protein synthesis. In addition, effects of polyamines on B to Z conversion of DNA, transcription, phosphorylation of proteins, cell cycle progression, apoptosis and ion channels, especially NMDA receptors, are outlined. The function of eIF5A is also briefly discussed. Finally, a correlation between acrolein, produced from polyamines by polyamine oxidases, and chronic renal failure or brain stroke is summarized. Increased levels of polyamine oxidases and acrolein are good markers of chronic renal failure and brain stroke.

Contents

1. Introduction

Polyamines [putrescine, $NH_2(CH_2)_4NH_2$; spermidine, $NH_2(CH_2)_3NH(CH_2)_4NH_2$; and spermine, $NH_2(CH_2)_3NH(CH_2)_4NH(CH_2)_3NH_2$] are essential for cell growth from bacteria to mammalian cells (Cohen, 1998; Igarashi and Kashiwagi, 2000; Tabor and Tabor, 1984). Because polyamines are fully protonated under physiological conditions, they can interact with nucleic acids, especially with RNA, ATP, specific kinds of proteins, and phospholipids (Miyamoto et al., 1993; Watanabe et al., 1991). In this review, the physiological functions of polyamines are discussed mainly with a focus on their interactions with RNA and subsequent effects on protein synthesis. Interactions of polyamines with DNA, ATP and specific kinds of proteins are also discussed. Polyamines have characteristics which are different from those of K^+ and Mg^{2+} for their interaction with RNA and other acidic substances. In this context, it is also of interest to know why, among polyamines, putrescine and spermidine predominate in prokaryotic cells, which grow rapidly, whereas spermidine and spermine predominate in eukaryotic cells, which proliferate

Abbreviations: ODC, ornithine decarboxylase; SAMDC, *S*-adenosylmethionine decarboxylase; SSAT, spermidine/spermine N^1-acetyltransferase; NMDA, *N*-methyl-D-aspartate; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; eIF5A, eukaryotic translation initiation factor 5A; PC-Acro, protein conjugated acrolein; IL-6, interleukin-6; CRP, C-reactive protein; SD, Shine–Dalgarno; SBI, silent brain infarction.

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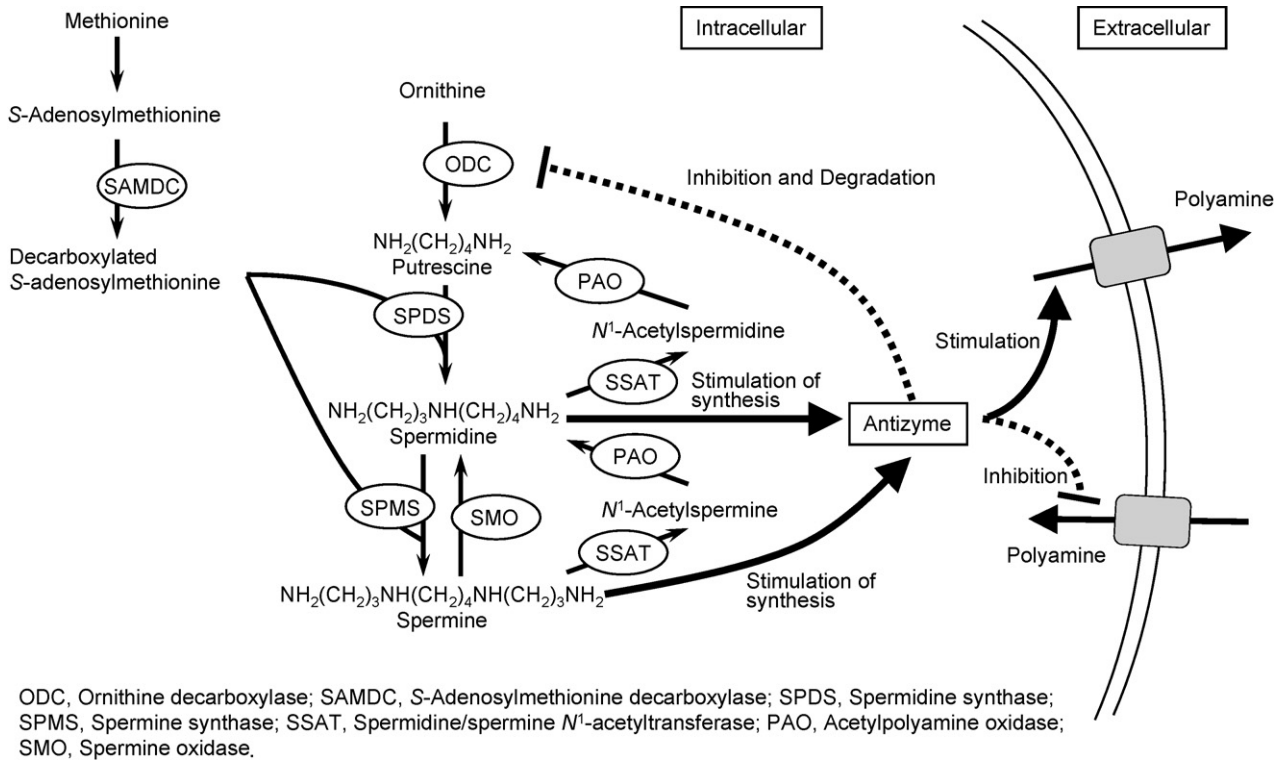

Fig. 1. Regulation of polyamine content in mammalian cells.

relatively slowly. We propose a hypothesis about this aspect of polyamine biology.

2. Regulation of polyamine contents in cells

The polyamine content of cells is elaborately regulated by biosynthesis, degradation, uptake and excretion (Igarashi and Kashiwagi, 1999; Pegg, 1988; Wallace et al., 2003). In both prokaryotes and eukaryotes, polyamine levels are increased during cellular responses to proliferative stimuli (Igarashi et al., 1975; Kakinuma et al., 1988; Marton and Pegg, 1995). Fig. 1 shows the metabolism of the polyamines in mammalian cells. Putrescine is synthesized from ornithine by ornithine decarboxylase (ODC), and decarboxylated *S*-adenosylmethionine is synthesized from *S*-adenosylmethionine by *S*-adenosylmethionine decarboxylase (SAMDC). These two enzymes, ODC and SAMDC, are rate-limiting enzymes in polyamine biosynthesis. It has been found that knockout of either ODC or SAMDC in mice is lethal, pointing to a crucial role for these enzymes (Nishimura et al., 2002a; Pendeville et al., 2001). Spermidine is synthesized from putrescine, and spermine from spermidine, by transfer of the aminopropyl moiety of decarboxylated *S*-adenosylmethionine. The enzymes catalyzing these reactions are spermidine synthase and spermine synthase (Fig. 1). Three different enzymes exist to convert spermine to spermidine, and spermidine to putrescine. Spermine oxidase (SMO) directly catalyzes the conversion of spermine to spermidine, and both spermidine/spermine N^1-acetyltransferase (SSAT) and acetylpolyamine oxidase (PAO) catalyze the conversion from spermine to spermidine and spermidine to putrescine (Casero and Pegg, 1993; Hölttä, 1977; Jänne et al., 2004; Pegg, 1988; Vujcic et al., 2002). For adjustment of cellular polyamine content, a unique protein, antizyme, is also strongly involved. Antizyme not only directly inhibits the activity of ODC, but also stimulates degradation of ODC (Coffino, 2001; Hayashi et al., 1996; Heller et al., 1976). The synthesis of antizyme is increased by polyamines through enhancement of ribosomal frameshifting of a termination codon in open reading frame of antizyme mRNA (Matsufuji et al., 1995), and ODC is degraded by antizyme–26S proteasome complex rather than ubiquitin–26S proteasome complex (Murakami et al., 1992). Antizyme also inhibits polyamine uptake and enhances polyamine excretion (Mitchell et al., 1994; Sakata et al., 2000; Suzuki et al., 1994), although the molecular basis for this is not yet known because polyamine uptake proteins in mammalian cells have not yet been identified at a molecular level. Recently, a diamine exporter, the complex of SLC3A2 and y^+LAT, has been identified to catalyze the excretion of putrescine and possibly acetylpolyamines in colon epithelial cells (Uemura et al., 2008). Thus, antizyme is a key player to adjust polyamine content in mammalian cells.

In *Escherichia coli*, the most widely studied experimental prokaryote, putrescine is synthesized by two pathways (Fig. 2A); one from ornithine catalyzed by ODC as in mammalian cells, and the other from arginine catalyzed by arginine decarboxylase and agmatine ureohydrolase (Tabor and Tabor, 1985). Spermidine is synthesized from putrescine and decarboxylated *S*-adenosylmethionine by SAMDC and spermidine synthase as in mammalian cells, but there is no mechanism for synthesis of spermine in eukaryotes. Spermidine acetyltransferase, equivalent to SSAT in mammalian cells, catalyzes either N^1- or N^8-acetylation of spermidine (Fukuchi et al., 1994). Polyamine transport in *E. coli* has been well characterized (Igarashi and Kashiwagi, 1999, 2006a). There are two polyamine uptake systems that function at neutral pH, both of which belong to the family of ATP-binding cassette transporters. Those are a spermidine-preferential uptake system consisting of the PotA, PotB, PotC and PotD proteins, and a putrescine-specific uptake system consisting of the PotF, PotG, PotH and PotI proteins (Fig. 2B). Two other polyamine transporters, comprising single proteins each with twelve transmembrane segments, are PotE and CadB, which function as antiporters of putrescine/ornithine and cadaverine/lysine. The genes for PotE or CadB constitute an operon with genes for inducible ornithine decarboxylase (iODC) or inducible lysine decarboxylase (iLDC),