Catabolism of polyamines

Review Article

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Summary. Owing to the establishment of cells and transgenic animals which either lack or over-express acetylCoA:spermidine N1-acetyltransferase a major progress was made in our understanding of the role of polyamine acetylation. Cloning of polyamine oxidases of mammalian cell origin revealed the existence of several enzymes with different substrate and molecular properties. One appears to be identical with the polyamine oxidase that was postulated to catalyse the conversion of spermidine to putrescine within the interconversion cycle. The other oxidases are presumably spermine oxidases, because they prefer free spermine to its acetyl derivatives as substrate. Transgenic mice and cells which lack spermine synthase revealed that spermine is not of vital importance for the mammalian organism, but its transformation into spermidine is a vitally important reaction, since in the absence of active polyamine oxidase, spermine accumulates in blood and causes lethal toxic effects.

Numerous metabolites of putrescine, spermidine and spermine, which are presumably the result of diamine oxidase-catalysed oxidative deaminations, are known as normal constituents of organs of vertebrates and of urine. Reasons for the apparent contradiction that spermine is in vitro a poor substrate of diamine oxidase, but is readily transformed into N8-(2-carboxyethyl)spermidine in vivo, will need clarification.

Several attempts were made to establish diamine oxidase as a regulatory enzyme of polyamine metabolism. However, diamine oxidase has a slow turnover. This, together with the efficacy of the homeostatic regulation of the polyamines via the interconversion reactions and by transport pathways renders a role of diamine oxidase in the regulation of polyamine concentrations unlikely. 4-Aminobutyric acid, the product of putrescine catabolism has been reported to have antiproliferative properties. Since ornithine decarboxylase and diamine oxidase activities are frequently elevated in tumours, it may be hypothesised that diamine oxidase converts excessive putrescine into 4-aminobutyric acid and thus restricts tumour growth and prevents malignant transformation. This function of diamine oxidase is to be considered as part of a general defence function, of which the prevention of histamine and cadaverine accumulation from the gastrointestinal tract is a well-known aspect.

Keywords: Polyamines – Putrescine – Spermidine – Spermine – Polyamine oxidase – Diamine oxidase – AcetylCoA:spermidine N1-acetyltransferase (SAT)

Abbreviations: ADH, aldehyde dehydrogenase; AdoMet, S-adenosyl-methionine; AdoMetDC, S-adenosylmethionine-decarboxylase; dAdoMet, decarboxylation product of AdoMet; BE 333, N1,N11-bis(ethyl)norspermine; BE 343, N1,N12-bis(ethyl)spermine; cAMP, cyclic adenosine monophosphate; CuAO, copper-amine oxidase; DAO, diamine oxidase; DFMO, (D,L)-2-(difluoromethyl)ornithine; GABA, 4-aminobutyric acid; MAO, monoamine oxidase; MDL 72527, N1,N4-bis(2,3-butadienyl)-1,4-butenediamine; NacPut, N-acetylputrescine; N1acSpd, N1-acetylspermidine; N8acSpd, N8-acetyspermidine; N1acSpm, N1-acetyl spermine; N1,N12diacSpm, N1,N12-diacetylspermine; ODC, ornithine decarboxylase; Orn, ornithine; PA, polyamine; PAO, polyamine oxidase (FAD-dependent) Put putrescine (1,4-butanediamine); SAO, bovine (ruminant) serum amine oxidase; SAT, acetylCoA:spermidine N1-acetyltransferase; SMO, spermine oxidase; Spd, spermidine (4-aza-1,8-octanediamine); Spm, spermine (4,9-diaza-1,12-dodecanediamine)

1 Introduction

The first enzymes that were recognised as polyamine (PA)-related, namely diamine oxidase (DAO) (Zeller, 1938a, b) and ruminant serum amine oxidase (SAO) (Hirsch, 1953), were catabolic enzymes. Since, however, PA biosynthesis attracted much more interest than PA degradation, physiological and pathological roles of these oxidases are still less well understood than functions of all other enzymes of PA metabolism. About 36 years ago it became obvious that the stepwise formation of spermine (Spm) from putrescine (Put) and spermidine (Spd) can be reversed (Siimes, 1967). Although the formation of Spd from Spm by an SAO-catalysed reaction had been demonstrated already in 1960 (Bachrach and Bar-Or, 1960), neither DAO nor SAO appear to play a significant role in the physiological back conversion of Spm to Put. As
was first suggested in 1979 at a workshop (Seiler, 1981) acetylation and oxidative degradation of N1-acetylsperrmidine (N1acSpd) and N1-acetylsperrmine (N1acSpm) by a FAD-dependent polyamine oxidase (PAO) are the steps, which catalyse the conversion of Spm to Spd, and of Spd to Put. Together with the aminopropylation of Spd and Spm these reactions form the so-called interconversion cycle (Fig. 1). The regulated uptake and release of the PAs together with the interconversion pathway are the elements, which control PA homeostasis of most cells (Seiler, 1987).

It is a key aspect of PA interconversion, that Put and Spd, which were formed by degradation from Spd and Spm, can be re-utilised. The rate of the re-formation of Spd and Spm depends on the availability of dAdoMet. Therefore, the activity of S-adenosylmethionine decarboxylase (AdoMetDC) and the activity of acetylCoA: spermidine N1-acetyltransferase (SAT) limit the flux rate through the cycle. Ornithine decarboxylase (ODC) has the function to provide Put at a rate, at which diaminobutane moieties are irreversibly lost by excretion or by oxidative deaminations (Seiler, 1987). The interconversion cycle appears to be the general system of PA regulation. Oxidative deaminations of the PAs are confined to those cell types, which are rich in DAO.

Basically the principles of PA regulation are the same in single cells and in the mammalian organism as an entity. Uptake of PAs from the gastrointestinal tract and their distribution into the individual organs by the bloodstream corresponds to the energy dependent, transporter mediated uptake from the cellular environment. The urinary excretion of PAs and of PA-derived amino acids corresponds to the controlled secretion through the cellular plasma membrane.

Uptake and de novo synthesis on one hand, and release and transformation into excretory products by oxidative deamination (“terminal catabolism”) on the other, fulfil the same purpose. The importance of uptake and release, vs. de novo synthesis and degradation differs from cell type to cell type, and changes with the physiological and pathological situation. As a rule, in rapidly proliferating cells the proportion of Put formed by degradation of N1acSpd is small compared with its formation by decarboxylation of Orn. In contrast, slow or non-growing cells produce PAs at a slow rate, and ODC activity is correspondingly low.

Since this sketchy picture of PA catabolism is in essence generally accepted, this overview will concentrate on less well known observations, which support or complete our pertinent knowledge of PA catabolism. Uptake and release, although intimately entangled with PA regulation will not be a topic of this review.

2 The catabolic branch of the interconversion pathway

The first step of the catabolic branch of the interconversion pathway is the SAT – catalysed acetylation of the aminopropyl moieties of Spd and Spm (Casero and Pegg, 1993). The N1-acetyl-PAs are substrates of a PAO, which removes the aminopropyl moiety as an aldehyde (3-acetamidopropanal) (Bolkenius and Seiler, 1981). Figure 2 shows the reactions of Spd acetylation and oxidative deaminations of the acetyl derivatives of Spd. The analogous reactions of Spm are shown in Fig. 3. 3-Acetamidopropanal is metabolised by an aldehyde dehydrogenase (ADH) – catalysed reaction to form N-acetyl-β-alanine. After its deacetylation by a selective hydratase, β-alanine may be further metabolised by transamination. In situations of enhanced PA acetylation