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REVIEW

Recent advances in the research on biological roles of dietary polyamines in man

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Summary
The ubiquitous polyamines putrescine, spermidine and spermine fulfil an array of physiological roles in man. In particular, their participation in cell growth and proliferation has been of great interest in relation to their roles in tumour growth and in wound healing. Both endogenous and dietary polyamines take part in such processes. The deprivation of exogenous polyamines emerges as a promising strategy in tumour therapy. Thus, reliable information on their content in foods is needed for dieticians. This review continues our previous comprehensive review on the topic, summarising data on the polyamine content in foods published from 2005 to April 2009. Some new data has appeared. Bovine, porcine and chicken liver, kidney, spleen and heart all have a high content of spermine; bovine liver also of spermidine. Losses of spermidine and spermine up to one half of their original levels occur during both cold and frozen storage and during various thermal treatments. Cultivated mushrooms were reported to contain very high levels of spermidine. Recent results have proved that polyamine content varies widely within a food item, and this complicates the application of available data for the controlled nutrition of patients.

Key words: polyamines; food; putrescine; spermidine; spermine

INTRODUCTION

The biologically active polyamines putrescine [PUT, butane-1,4-diamine], spermidine [SPD, *N*-(3-aminopropyl)-butane-1,4-diamine] and spermine [SPM, *N,N′*-bis(3-aminopropyl)-butane-1,4-diamine] (Fig. 1) have traditionally been classified within the group of biogenic amines. However, they started to be considered separately during the 1990s, because of their roles in the growth and function of normal cells and due to their mode of formation (Kusano et al. 2008). Putrescine, though structurally a diamine, is also classified as a polyamine due to its role as the precursor of both physiological ("true") polyamines (PUT → SPD → SPM). Among their biological roles, participation in cell growth and proliferation has been of primary interest, as polyamines, both formed endogenously and taken from diet, can be involved in tumour development. The physiological research into polyamines has thus been very extensive and dynamic. The main roles of polyamines in health and disease have been reviewed (Gugliucci 2004, Moinard et al. 2005, Larqué et al. 2007), and, moreover, various aspects of the physiological roles of polyamine were covered in a recent book (Dandrifosse 2009).

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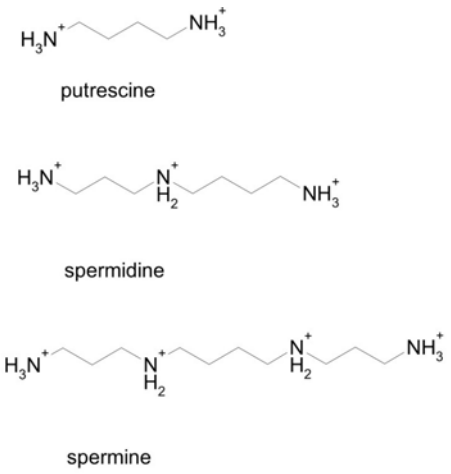

Fig. 1. **Formulae of polyamines in their cationic forms.**

The polyamine body pool is maintained by three primary sources: (i) endogenous (*de novo*) biosynthesis, (ii) production by intestinal microorganisms, and (iii) dietary intake. Diet provides a larger daily quantity of polyamines than does endogenous biosynthesis (Bardócz 1995). Information on the content of polyamines in foods and beverages would thus be of great interest for assessing their dietary intake (Zoumas-Morse et al. 2007).

The aim of the article is to review briefly current knowledge on the biological implications for human health of dietary polyamines and to collect recent data on polyamine content in foods, available notably during the five-year period since a review on the topic was last published (Kalač and Krausová 2005).

POLYAMINES FORMATION AND CATABOLISM

Polyamines are ubiquitous cell constituents of all eukaryotic organisms. Mammalian biosynthetic pathways are given in Figure 2. The biosyntheses from arginine and methionine are very effectively regulated by two key enzymes, ornithine decarboxylase and *S*-adenosylmethionine decarboxylase, respectively.

In healthy cells, polyamine levels are intricately controlled by the biosynthetic and catabolic enzymes. Catabolism of SPD and SPM proceeds as oxidase-catalysed oxidative deaminations and consecutive transformation of the primary reaction products (Seiler 2004, Wang and Casero 2006). Some of the final products, namely hydrogen peroxide, acrolein, 3-aminopropanal, 3-acetamidopropanal and 4-aminobutanal, may play pivotal roles in the development and progression of some grave neurodegenerative diseases (Wood et al. 2007).

BIOLOGICAL ROLES IN MAN

PUT, SPD and SPM under physiological conditions are flexible polycations exhibiting 2, 3 or 4 positive charges, respectively (see Fig. 1). This determines them as essential factors for the growth, maintenance and function of normal cells. Multiple abnormalities in the control of polyamine metabolism might be implicated in several pathological processes (Moinard et al. 2005).

Participation in tumour growth

Due to the above mentioned participation in cell growth and proliferation, polyamines accumulate in cancerous tissues and their content is elevated in the body fluids of cancer patients. Drugs which inhibit the biosynthesis of polyamines can prevent cancer and may also be used for therapeutic purposes. The chemopreventive or anti-neoplastic agents investigated mainly include inhibitors of ornithin decarboxylase and polyamine structural analogues and derivatives (Bachrach 2004, Casero and Marton 2007).

The second orientation is on polyamine catabolism and catabolic products. Among them, acrolein seems to be a key compound which is both carcinogenic and cytotoxic. The balance of amine oxidases and antioxidant enzymes appears to be a crucial point for cancer inhibition or progression. A long-lasting imbalance of these enzymes seems to be carcinogenic, while, for a short time, amine oxidases are cytotoxic for cancer cells (Toninello et al. 2006). The interest of researchers has recently been focused on spermine oxidase, the only catabolic enzyme able to oxidise spermine specifically (Amendola et al. 2009).

Nevertheless, tumour cells have the ability to uptake extracellular polyamines, both dietary and produced by intestinal bacteria, and to reduce the effects of the therapeutic agents referred to above. Another approach thus started in the 1990´s – deprivation of exogenous polyamines. Most of the reported results of this therapeutic strategy deal with laboratory experiments. However, preliminary clinical trials with prostate cancer patients show that the

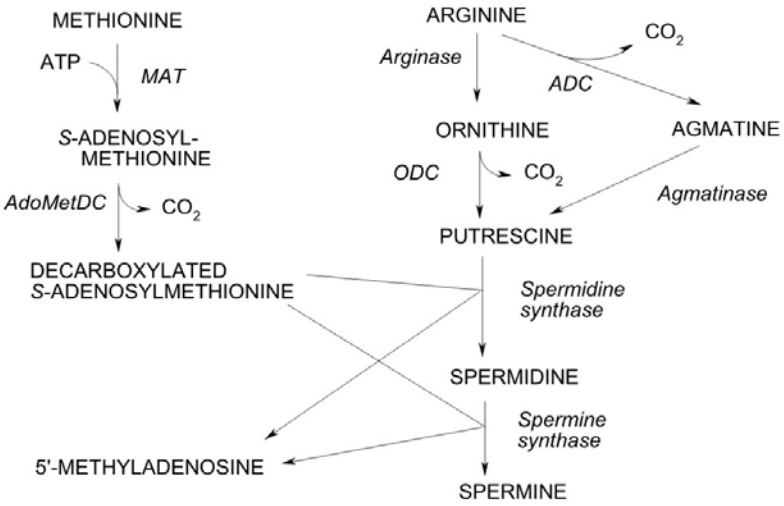

Fig. 2. **Mammalian polyamine biosynthetic pathway** (adapted from Hillary and Pegg 2003). The pathway via agmatin, existing in plants, was proposed also for mammals. The enzymes are written in italic (*ADC* – arginine decarboxylase; *AdoMetDC* – *S*-adenosylmethionine decarboxylase; *MAT* – methionine adenosyltransferase; *ODC* – ornithine decarboxylase).

reduction of dietary polyamine intake and partial intestinal decontamination is a well-observed and tolerated regimen, which seems to be beneficial for patient quality of life and pain control (Cipolla et al. 2007). Polyamines were identified as participating in almost all stages of colorectal tumorigenesis. Some components of diet, namely flavonoids, polyphenols and probiotics, can reduce the rate of hyperproliferation due to the effects on polyamine metabolism (Linsalata and Russo 2008).

Effects on intestinal tract

Dietary polyamines play a significant role in the growth and development of the digestive system of neonates and are necessary for the maintenance of the normal growth and general properties of the adult digestive tract (for a review see Deloyer et al. 2001).

The gastrointestinal tract can represent a significant source of polyamines originating from intestinal bacteria, sloughed cells and pancreatic bile and intestinal secretions. Considerable polyamine levels were observed in the lumen of human gut during the fasting state, which suggests endogenous secretion. A significantly higher content was determined in the jejunum than in the ileum, which suggests proximal absorption.

Initial studies deal with the ability of various microbiota species of human intestine to produce polyamines (Matsumoto and Benno 2007) and with the differences of such ability in healthy adults and patients with intractable adult-type atopic dermatitis (Matsumoto et al. 2007).

Studying inflammatory bowel disease, Weiss et al. (2004) observed an increased SPD content in colonic epithelial cells from the most severely inflamed mucosal areas, and enhanced SPD and SPM levels in acute colitis, whereas in chronic inflammation, SPM concentrations in colonic epithelial cells were decreased.

Antioxidant effects

Among other biological effects of polyamines, their antioxidant ability seems to participate in the reduction of cell membranes and DNA damage. Polyamines at physiological concentrations are potent scavangers of hydroxyl radicals and SPD and SPM can also quench both singlet oxygen at higher concentrations (Das and Misra 2004) and hydrogen peroxide (Rider et al. 2007).

The antioxidant and/or lysosomal stabilisation properties of polyamines apparently cause anti-inflammatory activity in acute and chronic inflammation (Lagishetty and Naik 2008).

Toxicity, risk of nitrosamines formation

The acute oral toxicity of individual polyamines, determined in Wistar rats, was observed to be 2000, 600 and 600 mg kg^{-1} body weight for PUT, SPD and SPM, respectively. The no-observed-adverse-effect level (NOAEL) was 180, 83 and 19 mg kg^{-1} body

weight for PUT, SPD and SPM, respectively (Til et al. 1997). Such extreme intakes of dietary amines cannot be imagined.

Spermidine or putrescine can react under acidic conditions with nitrous acid forming *N*-nitrosopyrrolidine. Nevertheless, information on this reaction in foods has been very scarce and nirosamine formation from polyamines does not seem to pose a health risk.

POLYAMINES IN FOODS

Besides the mostly adverse biological effects given above, dietary polyamines may be required in wound healing. Thus, reliable information on their content in foods has been needed for dieticians. Data available up to 2004 have been reviewed (Kalač and Krausová 2005) and only the more recently reported results will be discussed.

Polyamines are present in cells in free and conjugated forms. In plant tissues, polyamines are bound covalently to a partner molecule such as phenolic compounds or membrane phospholipids, and can be released by hydrolysis with a strong acid. Some binding, preferably with proteins, can be supposed in animal tissues; however, proven information is lacking. Most of the accessible data do not differentiate free and conjugated polyamines in foods.

Spermidine and spermine in foods originate from raw plant and animal tissues; a limited proportion may be formed by microbiota already present. Commonly, increased SPD and SPM levels may be supposed in young and quickly growing organisms and mainly in metabolically highly active tissues and organs (Nishimura et al. 2006). Higher PUT levels in fresh food raw materials are rare, but exist in some items of plant origin. Putrescine contents increase, even considerably, due to the high activity of several groups of bacteria, mainly *Enterobacteriaceae* and *Clostridium* spp. under inappropriate storage and handling conditions.

Unfortunately, daily cellular requirements for the polyamines have not yet been determined. The role of dietary polyamine intake increases in elderly people along with a limited ability to biosynthesise them (Larqué et al. 2007).

Intake of dietary polyamines

Mean daily intake of 18.7, 12.6 and 11.0 mg of PUT, SPD and SPM, respectively, was reported for the United Kingdom, Italy, Spain, Finland, Sweden and the Netherlands (Ralph et al. 1999). The values adopted for Japan were 9.9, 12.0 and 7.9 mg (Nishibori et al. 2007) and for a USA convenient sample diet 14.0, 7.9 and 7.2 mg were selected (Zoumas-Morse et al. 2007).

Comparing dietary polyamine intake in Europe (France, United Kingdom, Sweden, Italy, Germany and the Netherlands), USA and Japan, Weiger at al. (2005) reported high polyamine intake from similar European and USA diets (Western style nutrition), while the Japanese diet represented a significantly lower source. Putrescine was the major polyamine in all three diets, but at a lower level in Japan. Intake of SPM was comparable in all diets, and that of SPM was lowest again in Japan.

The cited papers state dairy products due to high PUT level as the main source of polyamine intake in Europe and USA, while in Japan, where there is a low consumption of cheese it is vegetables. Vegetables are the main source of SPD; meat and meat products the main source of SPM.

Recent original papers with overall data

Several papers dealing with polyamine content in a wide range of food items have been published in recent years (Nishimura et al. 2006, Cipolla et al. 2007, Larqué et al. 2007, Nishibori et al. 2007). Some of the published data confirmed previously available results, and some brought new information which will be discussed in the following sections.

However, the published data both in these and previously published papers mostly give the results of the analyses of a limited number of samples per food item. It should be noted here that polyamine contents vary widely within an item. Moreover, most of the data are given for fresh foods or raw materials, while information on the effects of various storage conditions and industrial and culinary treatments has been very limited. The possibility of setting up credible "tabular values" is thus presently very limited.

Polyamines in foods of animal origin

Spermine contents are commonly higher in foods of animal origin then those of SPD, which is an inverse relation to that observed in materials of plant origin.

Literature data on polyamine content in raw and processed beef, pork and meat products available up to 2005 have been reviewed (Kalač 2006). Recent results on fresh meat and pluck of warm-blooded animals are given in Table 1. Putrescine contents were mostly not detectable with bovine liver being an exception. Most of the pork and beef samples had SPD content below detection limits, while levels in all chicken meat samples were quantifiable. The content of both SPD and SPM in pluck or chicken giblets

analysed are considerably higher than in meat, and are among the highest levels observed in foods. Surprisingly, bovine liver has a higher content of SPD than of SPM; in porcine spleen the levels of both of the polyamines are comparable.

Data on polyamine changes in beef, pork, chicken meat and porcine liver and kidney under various storage conditions and thermal processing have became available during the period since 2006.

Under cold conditions, three ways of storage were tested (i) aerobic packaging in a foil, simulating household practice, (ii) vacuum packaging and (iii) packaging under a modified atmosphere up to 9, 21 and 21 days, respectively. Low SPM losses were observed in beef loin (Kozová et al. 2009b) and pork loin (Krausová et al. 2008), while losses of up to 40% (in all referred values given as % from the initial content in fresh packaged material) were noted in chicken meat (Kozová et al. 2009a). Losses of up to 40% were reported for porcine liver (Krausová et al. 2007) and kidney (Kozová et al. 2008).

Results on polyamine changes during several-month storage at –18 °C are not uniform. Spermine content in beef loin slightly increased during the initial two months of storage and then decreased by about 30% after a six-month storage period (Kozová et al. 2009b), while in pork loin, changes were insignificant (Krausová et al. 2008). Contradictory changes were reported for chicken meat. Kozová et al. (2009a) observed an increase of both SPD and SPM contents after six months of frozen-storage, whereas Moreira et al. (2008) determined heavy shrinkage of 70 and 80% for SPD and SPM, respectively, after a three-month storage. Krausová et al. (2007) reported losses of about 30% in porcine liver frozen for six months.

The effects of various culinary thermal treatments on changes in polyamine contents were reported for beef loin (Kozová et al. 2009b), pork loin (Paulsen et al. 2006, Paulsen and Bauer 2006, Krausová et al. 2008), chicken breast (Kozová et al. 2009a), porcine liver (Krausová et al. 2007) and porcine kidney (Kozová et al. 2008). Overall, losses of both SPD and SPM were usually about 40%. Shrinkage at lower temperature processing, such as boiling, stewing or grilling seems to be lower than that caused by frying or roasting. No polyamines were detected in broth and grease.

Unfortunately, no data are recently available on the nature of polyamine losses during meat – and indeed all food storage and processing. The knowledge available on polyamine catabolism in living cells cannot be applied to processes in food materials.

Following the previous review (Kalač 2006), research results on changes of polyamines during processing and storage of various meat products were miscellaneous. There were some reports mostly of an increase of PUT content, but of an increase or decrease in or stability of the content of SPD and SPM.

Only a few original papers have been published on the topic during the period since 2006, and these deal with traditional Spanish and Turkish meat products. The contents of SPD and SPM in freshly prepared products prior to fermentation and drying fit well with the data in Table 1 for beef and pork. Putrescine content usually increased to levels of tens or hundreds mg/kg in final products. In several types of dry-fermented sausages, an increase of SPD and SPM during processing was reported. However, the increase could be due to water losses, as the contents of both polyamines were not corrected to original dry matter content (Ruiz-Capillas et al. 2007, Genccelep et al. 2007, Lorenzo et al. 2008, Kurt and Zorba 2009).

In lacón, a Spanish product similar to dry-cured ham, SPD content remained stable during 84 days of ripening in both experimental variants, either produced with salt only or with additives (glucose, nitrite, nitrate, ascorbate and citrate). Spermine content decreased during the period by 42 and 13% in the variant without and with the additives, respectively (Lorenzo et al. 2007).

Polyamine content in the flesh of both sea and freshwater fish is very low after capture. Putrescine content can increase after inappropriate storage and handling conditions.

As reviewed by Michaelidou (2008), the content of all polyamines in bovine, caprine, ovine and also in human milks are very low. As in other proteinaceous materials, putrescine content can increase considerably by bacterial activity not only due to inappropriate storage conditions, but also by the activity of some lactic acid bacteria during the making of ripening cheeses (for a review see Kalač and Glória 2009).

As in fish and milk, polyamines occur in eggs at very low levels and this item remains at the edge of interest.

Polyamines in foods of plant origin

As mentioned above, vegetables and fruits are the main sources of PUT intake, and vegetables that of SPD intake. Spermine contents are usually low in foods of plant origin.

Some foods have a considerably high mean PUT level, usually above 40 m/kg, namely: oranges, orange juice (recently Vieira et al. 2007 with mean content 33.6 mg/l), mandarins, grapefruit juice, and

Table 1. **Content of polyamines (mg/kg) in fresh meat and pluck/giblets.** Putrescine contents were mostly below limits of quantification of the analytical methods used. Spermine contents were detectable only in a limited proportion of samples.

Product	Country	n	Putrescine			Spermidine			Spermine			Reference
			x	s_x	r	x	s_x	r	x	s_x	r	
Beef												
Sirloin	Czech Rep.	63	-	-	-	-	-	1.0–2.9	21.7	5.8	2.1–31.5	Krausová et al. 2006a
Rump	Czech Rep.	57	-	-	-	-	-	1.2–2.4	22.0	5.6	10.0–75.0	Krausová et al. 2006a
Pork												
Loin – barrows	Czech Rep.	15	-	-	-	-	-	1.1–6.6	26.1	7.0	7.7–35.1	Krausová et al. 2006a
Loin – gilts	Czech Rep.	12	-	-	-	-	-	-	22.3	10.6	4.3–41.4	Krausová et at. 2006a
Loin	Austria	72	-	-	-	3.0	1.1	-	20.7	5.9	-	Paulsen and Bauer 2007
Leg – barrows	Czech Rep.	15	-	-	-	-	-	1.3–5.3	28.4	8.5	8.2–42.2	Krausová et al. 2006a
Let – gilts	Czech Rep.	12	-	-	-	-	-	1.3–5.6	18.3	9.3	3.0–29.5	Krausová et al. 2006a
Chicken												
Breast	Brazil	30	1.0	-	-	27.4	1.9	-	38.7	2.4	-	Moreira et al. 2008
Breast	Czech Rep.	20	-	-	-	4.8	1.7	-	36.8	5.9	-	Kozová et al. 2009a
Thigh	Czech Rep.	20	-	-	-	10.2	2.2	-	38.0	3.7	-	Kozová et al. 2009a
Skin	Czech Rep.	10	-	-	-	11.4	1.7	-	24.3	3.8	-	Kozová et al. 2009a
Pluck/giblets												
Young bull liver	Czech Rep.	58	23.8	41.7	2.2–259	122	82.0	9.9–390	43.1	26.5	11.5–128	Krausová et al. 2006b
Cow liver	Czech Rep.	19	25.4	17.8	4.1–63.0	161	62.5	70.7–331	34.7	19.6	13.4–82.2	Krausová et al. 2006b
Barrow liver	Czech Rep.	19	-	-	-	32.1	11.6	15.7–56.6	115	49.4	65.4–207	Krausová et al. 2006b
Gilt liver	Czech Rep.	17	-	-	-	31.8	11.5	14.3–56.5	114	40.8	53.4–219	Krausová et al. 2006b

Lamb liver	Czech Rep.	9	-	-	-	22.2	16.1	7.7–57.0	113	30.4	63.2–165	Krausová et al. 2006b
Roe deer liver	Austria	39	2.4	-	ND-49.7	8.5	3.25	3.9–18.8	94.6	23.3	49.9–147	Paulsen et al. 2008
Brown hare liver	Austria	20	2.2	-	ND-4.4	37.2	12.4	22.2–63.4	111	24.9	60.3–169	Paulsen et al. 2008
Chicken liver	Czech Rep.	38	-	-	-	56.9	15.1	17.0–84.5	120	43.0	35.2–211	Krausová et al. 2006b
	Czech Rep.	20	-	-	-	48.7	8.8	-	133	18.0	-	Kozová et al. 2009a
Porcine kidney	Czech Rep.	40	-	-	-	9.4	3.4	5.7–17.7	53.1	14.0	32.8–88.5	Kozová et al. 2008
Roe deer kidney	Austria	39	-	-	-	10.7	5.3	4.2–38.6	79.9	15.0	27.9–117	Paulsen et al. 2008
Brown hare kidney	Austria	20	-	-	-	24.4	4.1	15.1–32.0	82.8	13.8	57.7–114	Paulsen et al. 2008
Porcine spleen	Czech Rep.	10	-	-	-	36.7	5.7	30.2–51.9	34.0	7.6	25.3–53.6	Kozová et al. 2008
Roe deer spleen	Austria	39	-	-	-	42.9	11.8	4.9–80.8	102	19.8	68.4–137	Paulsen et al. 2008
Brown hare spleen	Austria	20	-	-	-	52.0	13.9	23,5–75.5	91.1	23.5	50.6–139	Paulsen et al. 2008
Chicken heart	Czech Rep.	20	-	-	-	12.1	3.3	-	82.7	10.4	-	Kozová et al. 2009a

n – number of samples; x – mean; s_x – standard deviation; r – range; ND – below detection limit

sauerkraut, ketchup, frozen peas and fermented soy products (e.g. tofu and sauce, Righetti et al. 2008) among the processed products. Legumes, mainly soybean, pear, cauliflower and broccoli belong to the group of food items with SPD contents usually above 30 mg/kg. The same foods, especially legumes, have also the highest SPM levels (for detailed reviewed data see Kalač and Krausová 2005).

A decrease of SPD content in vegetables was observed during a three-week storage at 6–8 °C (Moret et al. 2005). In widely consumed spinach with initial SPD and SPM contents 28.9 ± 9.6 and 3.6 ± 1.8 mg/kg, respectively, the decrease during 15-day storage at 6 °C was considerable in SPD and less extensive in SPM (Lavizzari et al. 2007).

An increasing interest in the consumption of germinated seeds induced research into polyamine contents in sprouts. Glória et al. (2005) reported an increase of all polyamines in soy sprouts, with SPD and SPM accumulated in the cotyledon, and PUT in the radicle and hypocotyl. Similarly, the increase of both SPD and SPM during sprouting was observed in broccoli, radish (Martínez-Villaluenga et al. 2008) and alfalfa, but not in fenugreek (Frías et al. 2007).

Cultivated mushrooms

Very high SPD contents, often in the range of 100–200 mg/kg, were reported for common species of mushrooms cultivated in Japan (Nishimura et al. 2006, Nishibori et al. 2007). Spermine levels were considerably lower, usually below the limit of quantification, and PUT contents were mostly below 10 mg/kg. Thus, mushrooms currently seem to be the food item with the highest SPD level.

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