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Gender-related differences in polyamine oxidase activity in rat tissues

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Summary. Variations in level of polyamines and their related enzymes are frequently observed in response to some treatments which affect in a different way male and female. The possibility of a gender-related difference in the oxidation of polyamines was investigated in rats by measuring the activity of polyamine oxidase, a ubiquitous enzyme of vertebrate tissues, which transforms spermine into spermidine and spermidine into putrescine. The study was carried out on thymus, spleen, kidney and liver of young rats of both sexes, and female rats showed a lower polyamine oxidase activity than male rats in all the tissues. We also found higher values of spermidine acetylation in female than male rats in thymus and liver. Owing to these gender-related differences, a higher spermidine N-acetyltransferase/polyamine oxidase ratio was found in female than in male rats. A second gender-related difference was a higher spermidine/spermine ratio in female than in male, the only exception being the thymus. These basal differences possibly account for the gender-related differences of polyamine metabolic enzyme activities in response to some treatments, including drugs or hormones.

Keywords: Amino acids – Polyamine oxidase – Polyamines – Gender – Rat

Introduction

It has been well established that intracellular polyamine content is regulated by the activities of biosynthetic enzymes, ornithine decarboxylase (EC 4.1.1.17, ODC) and S-adenosylmethionine decarboxylase (EC 4.1.1.50, SAMD), and of the catabolic enzyme spermidine/spermine N^1-acetyltransferase (EC 2.3.1.57, SAT) (Seiler, 1987; Porter et al., 1992; Casero and Pegg, 1993; Seiler, 1995; Pegg et al., 1995). However, there is another step of polyamine metabolism that involves oxidative deacetylation of monoacetyl derivatives of polyamines by the action of the flavin-containing polyamine oxidase (EC 1.5.3.3, PAO), the importance of which has only been recently

assessed. However, changes in PAO activity have been demonstrated in tissues during postnatal development or ageing and after treatment with certain drugs, hormones or hyperplastic factors (Hayashi et al., 1989; Sessa et al., 1995; Dimitrov et al., 1996; Ferioli et al., 1996). All these data suggest an important role also for PAO in the regulation of intracellular levels of polyamines, as previously postulated (Hölttä, 1977; Morgan, 1981).

It is well known that there is a sexual dimorphism of the response to some dietary, toxic or carcinogenic agents in female and male rats (Cameron et al., 1990; Saito et al., 1991; Tessitore et al., 1992). However, although polyamines play a role in all these conditions (Porter et al., 1992; Shappell et al., 1993), the sex has been shown to have a considerable influence on polyamine urinary excretion both in humans (Beninati et al., 1980) and in rodents (Seiler et al., 1981), and it has been found that the therapeutic effect of difluoromethylornithine (DFMO) was much better for female than for male mice (Ask et al., 1992), most of the studies on polyamine metabolism carried out on rats used male animals. When we compared the data in relation to sex, differences in ODC activity, with higher values in males than in females were found in rat kidney (Henningsson and Rosengren, 1975; Manteuffel-Cymborowska et al., 1995) and liver (Richards, 1975). Moreover, the half-life of ODC activity in vivo was slightly longer in male than in female mice (Loeb et al., 1984; Murakami et al., 1988). More recently, Tanaka et al. (1993) showed gender-related differences in ODC and SAT levels in liver regeneration in ethanol-treated rats. In addition, female rats showed higher basal values of SAT activity than male animals (Tanaka et al., 1993). A sexual dimorphism in hepatic S-adenosylmethionine content and S-adenosylmethionine synthetase activity, with higher values in female than in male rats has been reported (Franchino et al., 1996). In rat thymus, we found that prolactin induced SAT activity in male rats but had no effect in female rats, and the basal thymic activity of the enzyme was higher in female than in male rats (unpublished results). To investigate whether there was also a similar gender-related difference for the second enzyme of polyamine interconversion, i.e., PAO, in the present study the activity levels of the two enzymes involved in the polyamine acetylation/oxidation process were compared in some tissues of young male and female rats. Polyamine levels were also determined in the same tissues of rats of both sexes.

Materials and methods

Chemicals

[acetyl-l-^{14}C]Acetylcoenzyme A (58 mC/mmol) was purchased from Amersham International (Amersham, Bucks., UK). Polyamines and acetylpolyamines, in their HCl salt forms, histones (calf thymus, Type AS-II), peroxidase, o-phthaldialdehyde and octanesulfonic acid were from Sigma (St. Louis, MO, USA). HPLC-grade acetonitrile was obtained from Merck (Darmstadt, Germany). All other chemicals were analytical-grade products.

Animals

Male and female Wistar rats (Nossan, Italy) were used in all experiments. Since it is known that PAO activity changes during development (Hayashi et al., 1989), we used rats about 2 months of age, i.e., when enzyme activity in the liver has reached a plateau level (Bolkenius and Seiler, 1986). The animals were housed in a constant light-dark cycle (light between the hours of 06.00 and 18.00) and temperature (23–25°C)-controlled room. Laboratory chow and water were freely available. The rats were killed by decapitation, and the tissues were excised as rapidly as possible and frozen at −80°C until the enzyme determinations and polyamine levels were performed.

Assays of SAT activity

The tissues were homogenized in 10 vol of the medium as described by Matsui and Pegg (1980). The cytosolic extract resulting from 1 h centrifugation at 100,000 × g was used as a source of enzyme, and the activity was determined at 30°C for 10 min by the measurement of transposition of the acetyl radical of [acetyl-^{14}C] acetyl CoA into spermidine according to the method of Matsui and Pegg (1980).

Assays of PAO activity

The tissues were homogenized in water (1:10, wt:v), and enzyme activity was assayed at 37°C for 30 min, according to the method described by Suzuki et al. (1984). H_2O_2 produced by the action of PAO on the substrate N^1-acetylspermine was measured by converting homovanillic acid into a highly fluorescent compound in the presence of peroxidase.

Estimation of polyamine levels

The tissues were homogenized in 10 vol of 0.2 N perchloric acid and then centrifuged at 3,000 × g for 30 min. Portions of the supernatant were filtered with Millex-GS (0.22 μm) (Millipore) and analyzed for polyamines according to Löser et al. (1988) with a Perkin-Elmer apparatus for HPLC.

Protein determination

Protein content was determined by the method of Geiger and Bessman (1972), using crystalline bovine serum albumin as standard.

In the case of enzyme activities, the data were expressed as pmoles of N^1-acetylspermidine or of H_2O_2 formed per mg of protein per min of incubation, for SAT and PAO, respectively. Polyamine levels were expressed as nmoles per g of tissue.

Statistical analysis

The results are the means ± S.E. The significance of differences in assay values was evaluated by analysis of variance (ANOVA). Differences with $P < 0.05$ were considered as significant.

Results

The activity levels of SAT in several tissues of young rats are shown in Fig. 1. Each point represents the mean values of duplicate determinations on 8–10 animals. The enzyme activity in tissues of male rats was in accordance with known data, with low levels of SAT activity in liver and high levels in kidney

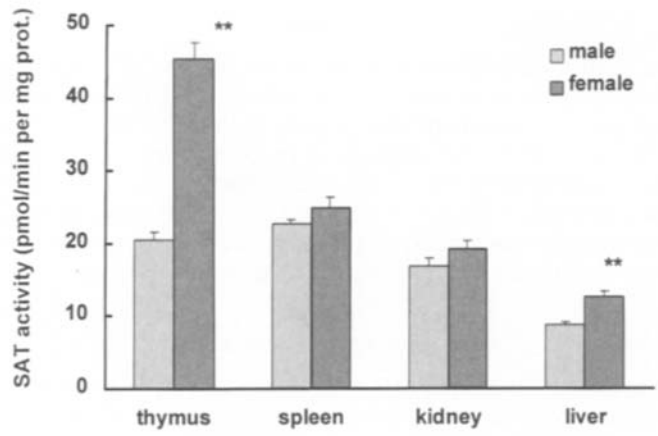

Fig. 1. SAT activity in tissues of male and female rats. Enzyme activity was measured as described in "Materials and methods". Data represent the mean values ± S.E. of 8–10 rats per group. ** $P < 0.001$ vs. male rats

and spleen (Grillo et al., 1984). In addition, the thymus showed a high level of SAT activity. Compared with male rats, female rats presented higher values of SAT activity, particularly in thymus and liver, in which the enzyme activity was significantly higher than in males. Thymus of female rats showed the highest values of SAT activity among the tissues tested in both sexes. Our results on SAT activity in liver are in agreement with those of Tanaka et al. (1993), with significantly higher levels of enzyme activity in female than in male rats. However, it is well known that the cytosolic fraction of rat tissue homogenate contains some spermidine-acetylating proteins (which selectively acetylate the N^1 terminus of spermidine) and others that prefer the N^8 terminus of the polyamine and also acetylate histones (Libby, 1978; Seiler, 1987) and the method used does not discriminate between these enzymes. It may therefore be that in male and female rats there was a different ratio of the specific and unspecific acetyltransferases. This may be particularly true in the case of the liver, in which unspecific acetyltransferases account for a large part of the so-called SAT activity (Pegg et al., 1985). Unfortunately, the specific antiserum (Persson and Pegg, 1984), which was very useful to discriminate authentic SAT in the case of induction of the enzyme in response to various stimuli, cannot be used in basal conditions because of the very small amount of protein in the resting state of the cells. Experiments were therefore carried out to determine substrate specificity. The ability of thymus and liver, the tissues showing a significant sex-related difference in spermidine acetylating activity, from male and female rats to catalyse the acetylation of various substrates is shown in Table 1. In our thymic and hepatic extracts, spermidine was prevalently acetylated; histones (the preferred substrate of nuclear N^8-SAT (Libby, 1978; Wallace et al., 1992)) were also acetylated to a high degree, whereas putrescine (another substrate for nuclear enzyme (Wallace et al., 1992)) was only slightly acetylated in male and in female rats. These results

indicate that two enzymes acetylating spermidine in the N^1 and the N^8 position, respectively, were present in our cytosolic extracts, as previously reported (Wallace et al., 1992; Ferioli et al., 1996).

The activity levels of PAO in several tissues of young rats is shown in Fig. 2. Also for this enzyme activity, each point represents the mean values of duplicate determinations on 8–10 animals, or more in the case of the thymus. The enzyme activity in tissues of male rats was in accordance with previously reported data, with lower values among the tissues tested in the thymus (Seiler et al., 1980). Female rats presented significantly lower values of enzyme activity in all the tissues tested than male rats. Interestingly, when SAT and PAO activities were different in male and female rats, as in the thymus and the liver, the differences were contrasting, with higher SAT values and lower PAO values in female than in male rats. Thus, the SAT/PAO ratio in females was increased (about 3 fold) with respect to the same ratio in male rats.

Table 1. Substrate specificity of spermidine N-acetyltransferase activity of thymus and liver of rats in relation to the sex

	Thymus		Liver	
	Male	Female	Male	Female
Spermidine	15.0 (100)	38.3 (100)	5.6 (100)	7.9 (100)
Putrescine	1.6 (10)	0.5 (1.3)	1.1 (20)	1.5 (19)
Histones	9.4 (63)	27.0 (70)	4.2 (75)	6.5 (82)

Cytosolic extracts of tissues were incubated in the presence of 3 mM polyamine or histones (0.5 mg/ml). The results are the means of three experiments. In parentheses the percentage activity with respect to spermidine.

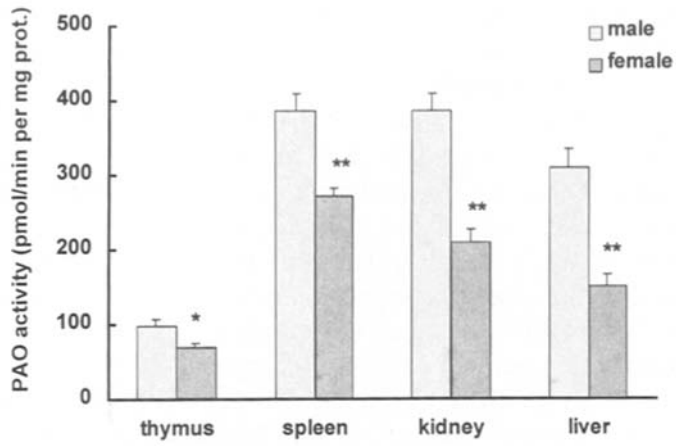

Fig. 2. PAO activity in tissues of male and female rats. Enzyme activity was measured as described in "Materials and methods". Data represent the mean values ± S.E. of 8–10 rats per group. * $P < 0.05$; ** $P < 0.0001$ vs. male rats

Table 2. Polyamine levels in tissues of male and female rats

Tissue	Putrescine		Spermidine (nmol/g tissue)		Spermine	
	Male	Female	Male	Female	Male	Female
thymus	54 ± 2.7	75 ± 4.3*	481 ± 28	417 ± 31	346 ± 22	337 ± 32
spleen	12 ± 2.1	26 ± 3.2**	234 ± 25	352 ± 58	266 ± 24	235 ± 39
kidney	18 ± 1.9	25 ± 1.7*	218 ± 13	296 ± 31*	246 ± 13	201 ± 23
liver	12 ± 1.1	24 ± 1.1**	390 ± 32	499 ± 20**	415 ± 34	258 ± 42*

The results are expresses as mean values ± S.E. of 8–10 rats. * $P < 0.05$, ** $P < 0.005$ vs. male rats.

Table 2 shows the levels of putrescine, spermidine and spermine in some tissues of male and female rats. The major changes in polyamine levels were found in putrescine, which was always significantly higher in female than in male rats. With respect to spermidine, significantly higher values were observed in liver and kidney of female than of male rats. A higher level of spermine in female than in male rats was found in liver. All these results cause a higher spd/sp ratio, which was about twice as high in female as that in male rats in liver, kidney and spleen. In the thymus, however, spd/sp ratio was about the same in males and females.

Discussion

Over the last few years, considerable interest has been directed to the catabolic processes of polyamines, particularly the acetylation/oxidation step, which is considered a means to adjust cellular polyamine levels according to metabolic needs (Seiler, 1987; Porter et al., 1992; Shappell et al., 1993; Casero and Pegg, 1993; Seiler, 1995; Pegg et al., 1995). In particular, as regards the properties and the functions of PAO, the current knowledge has been summarized in a recent review (Seiler, 1995).

The data presented here show that PAO activity, although present in all tissues, was always lower in female than in male rats. More interestingly, the two enzymes of the acetylation/oxidation process of polyamines, when compared in relation to the sex of the animals, showed an opposite trend, with higher SAT activity and lower PAO activity in female than in male rats. Very few researchers have reported comparative data on polyamine metabolism in relation to the sex of the animals. As regards ODC activity, there are some conflicting data on this point. Lower ODC activity in liver, but not in kidney, of female than male rats of the same age has been reported (Richards, 1975). In contrast, by using a different rat strain, Tanaka et al. (1993) found higher hepatic ODC activity in female than in male rats. Conversely, higher values of ODC activity in males than in females have been shown in kidney (Henningsson and Rosengren, 1975; Murakami et al., 1988; Manteuffel-

Cymborowska et al., 1995). Among the few data on polyamine catabolism, a gender-related difference in hepatic SAT activity, with female rats showing higher basal values than male rats, has been reported (Tanaka et al., 1993), although ethanol metabolism in vivo has been found not different between the genders (Iimuro et al., 1997). The present results confirm the data of Tanaka et al. (1993) on the sex-related difference in hepatic SAT activity and extend the knowledge by reporting the same gender-related difference in the activity of the second catabolic enzyme, PAO. This enzyme has been scarcely investigated, in contrast to the key enzymes of polyamine biosynthesis and SAT, and the availability of pure PAO from tissues other than the liver (Hölttä, 1977) would be of great interest in understanding the role of the enzyme in polyamine metabolism, since changes in PAO activity in different experimental conditions have been shown (Hayashi et al., 1989; Sessa et al., 1995; Dimitrov et al., 1996; Ferioli et al., 1996). No reasons for the gender-related differences in PAO activity can be given on the basis of the present study. Although sex hormones may have a role in these gender-related differences in enzyme activities, we found the same differences in younger and sexually immature rats (results not shown). Moreover, previous data showed that in rat liver polyamine metabolism is not under estrogenic control (Branham et al., 1988; Dimitrov et al., 1996). However, a similar gender-related difference, with higher enzyme activity in male than in female rats has been reported for other hepatic enzymes (Rikans et al., 1991; Catania et al., 1995; Zhu et al., 1995). By using a polarographic method, Pavlov et al. (1991) showed a relatively high level, but a different subcellular distribution, of PAO activity in liver and kidney of female rats. Further investigations could take into consideration this different subcellular distribution of the enzyme in various tissues (Pavlov et al., 1991; Van den Munckhof et al., 1995), and also the different level of its activity in male and female rats. For this purpose, the contrasting results previously obtained in PAO activity after partial hepatectomy or carbon tetrachloride by Hölttä (1977) and Hayashi et al. (1989) might be due not only to the difference in the enzyme preparations, but also to the different sex of the rats used.

Our results are in agreement with the notion that PAO is not a rate-limiting enzyme, because of its high activity in most tissues (Seiler et al., 1980). One can suppose that in thymus and liver, which showed higher SAT activity and lower PAO activity in female than in male rats, the relatively low level of PAO in females seems to be sufficient to reconvert spermine and spermidine to putrescine. This was suggested by the higher values of the diamine in female rats, although female rodents presented a greater urinary excretion of putrescine than male rats (Seiler et al., 1981). However, in female rats, PAO activity was generally lower than in males, and in thymus and in liver SAT activity was higher in females than in males, which resulted in a higher SAT/PAO ratio in female than male rats. The higher SAT/PAO ratio represents one of the gender-related differences observed and may be in part responsible for the inability of some treatments (such as hormones and ethanol) known to be active in male rats to induce SAT activity in female. More generally, the higher SAT/PAO ratio and spd/sp ratio may contribute to the sexual dimor-

phism of the response to toxic, proliferative or inhibitory agents in female and male rats.

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