Bis(benzyl)polyamine Analogs as Novel Substrates for Polyamine Oxidase*

(Received for publication, January 6, 1989)

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N,N'-Bis(benzyl)polyamine analogs were found to be substrates for highly purified polyamine oxidase. Metabolism of these analogs was apparently dependent on molecular O2 and resulted in the formation of benzaldehyde, H2O2, and a polyamine analog with free terminal amines. The debenzylation reaction was optimal between pH 9 and 10, identical to the pH optimum for polyamine oxidase activity when N'-acetylspermine was used as the substrate. On a molecular sieve column the debenzylation activity co-eluted with N'-acetylspermine oxidizing activity, at an apparent molecular mass of approximately 65 kDa. The purified enzyme also appeared to have a molecular mass of approximately 65 kDa on sodium dodecyl sulfate-polyacrylamide gel electrophoresis. Debenzylation of the bis(benzyl)polyamines was competitively inhibited by N'-acetylspermine and N'-acetylspermidine. The specific irreversible inhibitor of polyamine oxidase, N3,N4,bis(buta-2,3-dienyl)butanediamine also inhibited the debenzylation, whereas inhibitors of diamine and monoamine oxidases did not. The evolution of benzaldehyde from bis(benzyl)polyamine analogs by polyamine oxidase allowed the development of a simple rapid spectrophotometric assay for use in the measurement of polyamine oxidase activity in partially purified tissue or cell extracts. Further, metabolism of a bis(benzyl)polyamine analog by polyamine oxidase was found to be an important element in the growth inhibitory properties of the compound in a mouse model of malaria.

We reported previously that micromolar concentrations of bis(benzyl)polyamine analogs inhibited the growth of Plasmodium falciparum, a human malaria parasite, in vitro and, in combination with α-difluoromethylnornithine, an irreversible inhibitor of polyamine biosynthesis, cured Plasmodium berghei infections in mice (1). The bis(benzyl)polyamine analogs were effective against both chloroquine-susceptible and chloroquine-resistant strains of P. falciparum and thus represent a potentially important new lead in malaria chemotherapy. We also found that the bis(benzyl)polyamine analogs were potent inhibitors of rat hepatoma (HTC) cell growth in vitro (2). In the course of studies aimed at elucidating the mechanism of this growth inhibition, it was found that a bis(benzyl)polyamine analog (N,N'-bis[3-(phenylmethyl)-amino]propyl]-1,7-diaminoheptane) was rapidly converted to its monobenzyl and free amine derivatives within the hepatoma cell by an enzyme which was tentatively identified as polyamine oxidase (2) because of its sensitivity to a specific irreversible polyamine oxidase inhibitor, N3,N4-bis(buta-2,3-dienyl)butanediamine, a compound originally described by Bey et al. (3, 4). Because the metabolism of the bis(benzyl)polyamine by polyamine oxidase appeared to be necessary for growth inhibition in the rat hepatoma cells, it was also possible that metabolism might be important in the compound's anti-malarial effects in vivo and in vitro. Additionally, the debenzylation reaction, tentatively identified as being catalyzed by polyamine oxidase, had not been associated previously with this enzyme and therefore was of considerable interest.

Polyamine oxidase (EC 1.5.3) is widely distributed in tissues and cells (5, 6) and has been purified to homogeneity from rat liver peroxisomes (7) and cytosol (8) as well as other sources (6, 9). The normal substrates of polyamine oxidase are considered to be N'-acetylspermidine and N'-acetylspermine, and therefore, it is believed that polyamine oxidase is involved in normal polyamine turnover (10). However, unlike the other enzymes of polyamine biosynthesis and interconversion, which are at extremely low levels in quiescent tissues (11), polyamine oxidase is present in tissues at constitutively high levels (5) and does not appear to be subjected to the stringent regulation that governs the rest of polyamine metabolism. It is thus possible that polyamine oxidase may serve roles in the cell other than to degrade polyamines and may have a broader substrate specificity than was previously thought.

We have found, as detailed in this report, that highly purified rat liver polyamine oxidase is capable of accepting bis(benzyl)polyamine analogs as substrates and oxidatively cleaving the terminal benzyl groups, to form polyamine analogs with free terminal amines. This type of substrate has not been described before for polyamine oxidase. These novel bis(benzyl)polyamines may be used for a simple rapid spectrophotometric assay of polyamine oxidase activity. Furthermore, the debenzylation of a bis(benzyl) analog is shown to be necessary for its antimalarial activity in mice.

EXPERIMENTAL PROCEDURES

Preparation of Rat liver Polyamine Oxidase—Polyamine oxidase was purified from rat liver using modifications of techniques described by Hölttä (7). Livers (175 g), taken from male Sprague-Dawley rats of approximately 300 g were homogenized in a Waring blender in 3 volumes of a solution of 10 mM Tris-HCl (pH 7.5) containing 0.25 M sucrose. The homogenates were centrifuged at 650 × g for 10 min, after which the supernatant was decanted and centrifuged at 15,000 × g for 30 min to obtain a peroxisomal pellet. The pellet was dispersed in 75 ml of a solution of 10 mM Tris-HCl (pH 7.5) containing 0.25 M...
sucrose and 0.8% CHAPS detergent, and after 60 min of gentle mixing in the cold, the preparation was centrifuged for 30 min at 20,000 × g. The supernatant (65 ml) was loaded onto a column of DEAE-cellulose (2.6 × 15 cm) which had been equilibrated with 10 mM Tris- HCl (pH 7.5) containing 0.25 M sucrose. The column was washed extensively overnight with 100 mM NaCl in the equilibrating buffer at a flow rate of 20 ml/h and polyamine oxidase was subsequently eluted at the same flow rate with 300 ml of 300 mM NaCl in the same buffer. The enzyme was then concentrated to 10 ml (38.4 mg protein/ml) using an Amicon ultrafiltration cell equipped with a PM-10 membrane. The concentrated DEAE eluate was applied to a column (2.6 × 63 cm) of Ultrogel AcA44 (Pharmacia LKB Biotechnology) equilibrated in a solution of 10 mM Tris- HCl (pH 7.2) containing 30 mM NaCl and eluted with the same buffer. Four fractions (24 ml total) which contained the highest polyamine oxidase activity were pooled and concentrated to 7 ml with an Amicon ultrafiltration cell equipped with a PM-10 membrane. Ammonium sulfate was added to aliquots (0.4 ml) of the Ultrogel AcA44-purified polyamine oxidase to 25% saturation, and these samples were further purified by hydrophobic interaction chromatography on a phenyl 5 PW column (0.8 × 7.5 cm, Waters Protein Pak HIC) which was equilibrated in a solution of 20 mM Tris- HCl (pH 7.64) containing 0.1 M EDTA and 25% (NH₄)₂SO₄. The column was eluted at 1 ml/min with a linear gradient of decreasing (NH₄)₂SO₄ concentration over 20 min. Polyamine oxidase was eluted shortly after the column was completed, with the column buffer being used in the absence of (NH₄)₂SO₄. The peak fraction of activity contained 90 µg protein/ml and had a specific activity of 120 nmol/min/mg protein. Multiple runs with the small phenyl 5 PW column were used to purify the entire batch of polyamine oxidase. Polyacrylamide gel electrophoresis (12) was carried out in the presence of sodium dodecyl sulfate on 8–16% gradient gels to check for purity of polyamine oxidase. The enzyme was stable stored frozen at −20 °C or in the refrigerator at 4 °C, without appreciable loss of activity, for at least 1 month. Protein concentration was estimated by the method of Lowry (13) using bovine serum albumin as a protein standard.

**Fluorometric Assay for H₂O₂ Formation.** The formation of H₂O₂ was measured using the method of Snyder and Hendley (14). Reactions contained various amounts of enzyme protein (see figure legends), 50 mM borate (pH 9.0), 0.02 mg/ml of horseradish peroxidase, 0.4 mM homovanillic acid, and various concentrations of either N₁,N₁-acetylserine or bis(benzyl)polyamine analog in a total volume of 0.25 ml. After 1-h incubation at 37 °C the reaction was terminated by the addition of 1.75 ml of water to each tube, after which fluorescence was measured at 425 nm (excitation at 315 nm) in a SLM-Aminco model SPF-500 spectrofluorometer.

**Spectrophotometric Assay for Polyamine Oxidase Activity, Measurement of Benzaldehyde Formation.** The discovery that a bis(benzyl)polyamine analog was a substrate for polyamine oxidase led us to develop a spectrophotometric assay for the enzyme activity based on the formation of benzaldehyde. A fluorimetric assay for H₂O₂ formation, bis(benzyl)polyamine analog substrates in a total volume of 0.25 ml. After 1-h incubation at 37 °C the reaction was terminated by the addition of 1.75 ml of water to each tube, after which fluorescence was measured at 425 nm (excitation at 315 nm) in a SLM-Aminco model SPF-500 spectrofluorometer.

**Measurement of Polyamine Analog Reaction Products**—For the determination of the stoichiometry of the production of polyamine products in the polyamine oxidase reaction, some of the reactions in the fluorometric assay and in the spectrophotometric assay were terminated by the addition of a volume of ice-cold 0.4 M perchloric acid equal to the volume of the reaction mixture. After deproteinization by centrifugation, the samples were mixed with dansyl chloride, and the derivatized polyamine products were separated by reverse-phase HPLC on a 4.6 × 250-mm Altex ODS-18 column and detected with a fluorometer (Kratos FS850). The elution conditions for the HPLC

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1 The abbreviations used are: CHAPS, 3-[3-cholamidopropyl]dimethylammonio]-1-propanesulfonic acid; HPLC, high performance liquid chromatography; MDL 72527 N₁,N₁'-bis(buta-2,3-dienyl)butanediamine; MDL 27696, N₁,N₁'-bis[3-(phenylimethyl)amino]propyl]-1,7-diaminohexane.

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**Polyamine Oxidase Oxidizes Bis(benzyl)polyamine Analogs**

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**P. berghei Infections in Mice**—The effects of the polyamine analogs on murine malaria were studied using a standard 4-day suppressive test described previously (18). Mice were infected by intravenous injection of 5 × 10⁵ P. berghei parasitized erythrocytes and then treated for the three consecutive days, three times per day, with either 10 mg/kg of MDL 27695 or MDL 27696. 15 mg/kg of MDL 27695. Some mice were pretreated for 2 days with 10 mg/kg of the polyamine oxidase inhibitor N₁,N₁'-bis(buta-2,3-dienyl)butanediamine. After the times indicated, mice were killed by asphyxiation with CO₂ and blood was obtained by cardiac puncture using EDTA as the anticoagulant. Leukocytes were removed from the blood by loading whole blood onto a 2-ml column of sulfoethyl cellulose (SERVA) which had been equilibrated previously with a solution of 10 mM potassium phosphate (pH 7.5) containing 5 mM MgCl₂, 138 mM NaCl, and 0.4 mM EDTA (17). Erythrocytes were eluted from the column with 4 ml of the equilibrating buffer, washed twice by suspension in equilibrating buffer followed by centrifugation, and an aliquot was removed for blood cell counting. Greater than 98% of leukocytes were removed by this column separation procedure.

The final red cell pellet was extracted with 2 volumes of 0.4 M perchloric acid and the polyamine analogs were measured by HPLC as detailed above. A mean corpuscular volume of 65 μl/10⁵ erythrocytes (determined by automated hematology analyzer) was used to calculate the intraerythrocytic concentration of the polyamine analogs.

**Results**

After incubation of partially purified polyamine oxidase, with a bis(benzyl)polyamine analog, N₁,N₁'-bis[3-(phenylimethyl)-amino]propyl]-1,7-diaminohexane (MDL 27695, see Scheme 2 for structures), the formation of the monobenzyl and free amine derivatives of this compound was demonstrated by HPLC (Fig. 1). Disappearance of the bis(benzyl) analog after a 4-h incubation was accounted for by the stoichiometric formation of the free amine analog. The degradation of the bis(benzyl)polyamine was completely prevented
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A number of bis(benzyl)polyamine analogs were tested as substrates for rat liver polyamine oxidase. DEAE-cellulose-purified rat liver polyamine oxidase (0.25 mg) was incubated with the bis(benzyl)polyamine analog N,N'-bis[3-[(phenylmethyl)-amino]propyl]-1,7-diaminoheptane, and the substrate and products were analyzed by HPLC as described under "Experimental Procedures." The bis(benzyl)polyamine analog; free amine polyamine analog; monobenzyl polyamine analog. Chemical structures of the polyamine analogs can be seen in Scheme 2 under "Discussion."

by preincubation of the polyamine oxidase with 0.01 mM of a specific irreversible inhibitor of the enzyme, N',N'-bis(buta-2,3-dienyl)butanediamine (3), whereas neither aminoguanidine, an inhibitor of diamine oxidase (19), nor pargyline, an inhibitor of monoamine oxidase (20), had any effect on the enzyme activity. This suggested that the degradation of the bis(benzyl)polyamine was, in fact, due to polyamine oxidase. Since the debenzylation of the bis(benzyl)polyamine by polyamine oxidase was unexpected, further characterization of this reaction was initiated.

Likely products of the polyamine oxidase reaction in addition to the two polyamine analogs were benzaldehyde and H2O2. Benzaldehyde has a strong UV absorbance maximum at 250 nm, and it was found that during incubation of a bis(benzyl)polyamine analog with partially purified rat liver polyamine oxidase at 37°C, the absorbance at 250 nm increased in a linear fashion suggesting that benzaldehyde was formed in the reaction. Additionally, the specific inhibitor of polyamine oxidase, N,N'-bis(buta-2,3-dienyl)butanediamine, abolished this change in absorbance. The formation of benzaldehyde and polyamine products in the polyamine oxidase reaction was examined and it was found that there was good agreement between the total actual amount of polyamine products measured by HPLC and the amount of benzaldehyde measured by spectrophotometry (Table I). The values in the column of Table I representing total polyamine products do not directly match with the theoretical benzaldehyde formed because 2 mol of benzaldehyde are formed for every 1 mol of free amine polyamine product formed and this is taken into account when the theoretical amounts of benzaldehyde or H2O2 are calculated. It was also found that there was good agreement between the formation of H2O2, measured in the spectrophotometric assay described under "Experimental Procedures" and the formation of polyamine products measured by HPLC (Table I).

The reaction of polyamine oxidase with bis(benzyl)polyamine was found to be dependent on molecular oxygen. Addition of glucose oxidase and glucose to the polyamine oxidase reaction resulted in a 70-80% decrease in the reaction rate, whereas glucose oxidase or glucose alone had virtually no effects on the reaction.

A number of bis(benzyl)polyamine analogs were tested as substrates for polyamine oxidase and benzaldehyde was released from all of them when they were mixed with partially purified rat liver enzyme (Table II). The monobenzyl derivative of MDL 27695 (Fig. 1) and benzylamine (Table II) were also shown to be substrates for polyamine oxidase.

To be certain that the oxidative metabolism of the bis(benzyl)polyamines was mediated by the same enzyme which acts in the catabolism of the normal polyamines and their acetyl derivatives, polyamine oxidase was highly purified from rat liver (Table III) and the purified enzyme was tested for activity with a bis(benzyl)polyamine substrate as well as with N'-acetyl spermine and N'-acetyl spermidine. The purified enzyme had a molecular mass of approximately 65 kDa as determined by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (Fig. 2), which was consistent with the ap-
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Polyamine oxidase was purified and enzyme activity was assayed with either N\(^1\)-acetylspermine (fluorimetric assay) or the bis(benzyl)polyamine analog (MDL 27695; spectrophotometric assay) as described under "Experimental Procedures." The crude homogenate and CHAPS extract were assayed with both substrates in the fluorimetric assay whereas the enzyme from subsequent purification steps was assayed with N\(^1\)-acetylspermidine in the fluorimetric assay and MDL 27695 in the spectrophotometric assay.

<table>
<thead>
<tr>
<th>Purification</th>
<th>Total protein</th>
<th>Total activity</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific activity(^*)</td>
<td>Ratio of AcSpm/MDL 27695(^*)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude homogenate</td>
<td>0.41</td>
<td>1</td>
<td>25,380</td>
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<tr>
<td>AcSpm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDL 27695</td>
<td>0.28</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>CHAPS extract</td>
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<td>1</td>
<td>2,613</td>
</tr>
<tr>
<td>AcSpm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDL 27695</td>
<td>0.34</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>CHAPS extract</td>
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<td>DEAE-cellulose</td>
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<td>1.5</td>
<td></td>
</tr>
<tr>
<td>AcSpm</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>MLD 27695</td>
<td>1.69</td>
<td>6</td>
<td>948</td>
</tr>
<tr>
<td>Ultrogel AcA44</td>
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<td>1.8</td>
<td>45</td>
</tr>
<tr>
<td>AcSpm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MLD 27695</td>
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<td></td>
<td>35.2</td>
</tr>
<tr>
<td>Phenyl 5PW</td>
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<td>498</td>
</tr>
<tr>
<td>AcSpm</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>MLD 27695</td>
<td>120</td>
<td></td>
<td>1.58</td>
</tr>
</tbody>
</table>

\(^*\) Specific activity is given as nanomoles H\(_2\)O\(_2\) or benzaldehyde \(\cdot\) min\(^{-1}\) \(\cdot\) mg protein\(^{-1}\).

Molecular weight determination of polyamine oxidase by molecular sieve chromatography. Molecular sieve chromatography was carried out and polyamine oxidase assays were performed using either the spectrophotometric assay with a bis(benzyl)polyamine analog (MDL 27695) as a substrate (○) or with N\(^1\)-acetylspermine as a substrate (×) in the fluorimetric assay as described under "Experimental Procedures."

The purified enzyme was also tested for its sensitivity to inhibitors of polyamine oxidase (MDL 72527), monoamine oxidase (pargyline), and diamine oxidase (aminoguanidine). As can be seen in Table IV, only the specific irreversible inhibitor of polyamine oxidase caused a marked decrease in the activity of the purified enzyme. It has been shown previously that MDL 72527 is inhibitory to neither monoamine nor diamine oxidases (3). The concentrations of aminoguan-
Polyamine Oxidase Oxidizes Bis(benzyl)polyamine Analogs

Because the bis(benzyl)polyamine analogs were known to inhibit the respective oxidases if these other activities had, the purified polyamine oxidase preparation was assayed using a bis(benzyl)polyamine analog (MDL 27695) as substrate at concentrations of 0.6-20 μM in the absence or presence of either 0.1 mM N-acetylspermine (A) or 2.5 mM N-acetylspermidine (B). A double-reciprocal plot of 1/V versus 1/S was used to analyze the data for competitive inhibition.

**Table IV**

<table>
<thead>
<tr>
<th>Addition</th>
<th>Concentration</th>
<th>Polyamine oxidase activity (nmol min⁻¹ mg protein⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td></td>
<td>90</td>
</tr>
<tr>
<td>MDL 72527</td>
<td>0.01</td>
<td>10</td>
</tr>
<tr>
<td>Aminoguanidine</td>
<td>1.0</td>
<td>86</td>
</tr>
<tr>
<td>Pargyline</td>
<td>0.1</td>
<td>94</td>
</tr>
</tbody>
</table>

**Fig. 4.** Competitive inhibition of the oxidation of a bis(benzyl)polyamine analog by N-acetylspermine and N-acetylspermidine. Polyamine oxidase activity, purified by hydrophobic interaction chromatography, was assayed using a bis(benzyl)polyamine analog (MDL 27695) at substrate concentrations of 0.6-20 μM in the absence (or) or presence of either 0.1 mM N-acetylspermine (A) or 2.5 mM N-acetylspermidine (B). A double-reciprocal plot of 1/V versus 1/S was used to analyze the data for competitive inhibition.

**SCHEME 1**

\[
\text{CH}_2=\text{CH}-\text{CNH(CH}_2\text{)}_2\text{NH(CH}_2\text{)}_2\text{NH}_2 + \text{O}_2 + \text{H}_2\text{O} \rightarrow \text{polyamine oxidase} \rightarrow \text{N-acetylspermine} \\
\text{O} \quad \text{O} \\
\text{CH}_2=\text{CNH(CH}_2\text{)}_2\text{CH} + \text{H}_2\text{N(CH}_2\text{)}_2\text{NH(CH}_2\text{)}_2\text{NH}_2 + \text{H}_2\text{O}_2 \\
3-\text{acetamidopropanal} \quad \text{sperrmidine}
\]

**Fig. 5.** Intracellular concentrations of polyamine analog after administration of a bis(benzyl)polyamine analog to mice. Mice were injected intraperitoneally with 15 mg/kg of bis[bis(benzyl)-N,N'-bis(N,N'-bis(buta-2,3-dienyi)butanediamine and the parent compound (O), the monobenzyl analog (A), the free amine product reached only 5 μM; the monobenzyl and free amine derivatives (Fig. 5A). The free amine metabolite reached a concentration of 46 μM by 1 h and remained as high as 30 μM even after 24 h. The mono- and bis(benzyl) analogs disappeared from the erythrocytes much quicker. The intraerythrocytic metabolism of MDL 27695 was prevented by pretreatment of the mice with an irreversible polyamine oxidase inhibitor (Fig. 5B). Although some residual polyamine oxidase activity was present, the free amine product reached only 5 μM even after 24 h. As before, the mono- and bis(benzyl) analogs were removed from the red cell more rapidly than the free amine analog.

**DISCUSSION**

The debenzylation of bis(benzyl)polyamine analogs by polyamine oxidase was unexpected since the oxidation of N-acetylspermine (or N-acetylspermidine) proceeds with a net loss of a 3-amino group from spermine or spermidine (Scheme 1). However, the oxidative catalysis of the bis(benzyl)polyamine analogs results in the loss of the ter-
Polyamine Oxidase Oxidizes Bis(benzyl)polyamine Analogs

The oxidation of a bis(benzyl)polyamine analog (MDL 27695) in mouse erythrocytes in situ appears to be a critical factor in the progression of *P. berghei* infections in mice treated with the bis(benzyl)polyamine analog. Following injection of MDL 27695 into mice, there was a rapid accumulation of the free amine derivative within the mouse erythrocytes. That the free amine analog arose within the erythrocyte due to metabolism therein was suggested by experiments in *vitro* which showed that the free amine analog does not readily penetrate the erythrocyte membrane but that the bis(benzyl) analog did readily enter the cell (23). The curative effects of MDL 27695 in the *P. berghei* model infections were blocked by pretreatment of mice with an irreversible inhibitor of polyamine oxidase. These data strongly suggest that metabolism of MDL 27695 to its free amine derivative within the mouse erythrocyte is, in fact, indispensable.

Metabolism of the bis(benzyl)analogs by polyamine oxidase is apparently not necessary for anti-malarial effects against *P. falciparum in vitro* (1). Neither the human erythrocytes which serve as host cells for *P. falciparum* nor *P. falciparum* itself degrade the bis(benzyl)polyamine analog to monobenzyl and free-amine derivatives. Thus, it is unclear whether or not the bis(benzyl)polyamine analogs would be effective against human *P. falciparum* infections. Only appropriate clinical trials would determine the efficacy of the analogs in man.

Polyamine oxidase activity is high in many tissues relative to the activity of other enzymes involved in polyamine metabolism (5) and does not appear to be highly regulated as are the enzymes for polyamine biosynthesis (11). It seems likely from the present data that polyamine oxidase is involved not only in the control of intracellular polyamine levels but has other functions in the cell with a wider range of substrate specificities than previously thought. In fact, the so-called polyamine oxidase may function as a broad specificity oxidase involved in general detoxification reactions and may also be involved in intermediary metabolic pathways as yet unidentified.

REFERENCES


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