Mescaline-Induced Changes of Brain-Cortex Ribosomes

ROLE OF SPERMIDINE IN COUNTERACTING THE DESTABILIZING EFFECT OF Mescaline ON BRAIN-CORTEX RIBOSOMES

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1. The effect of spermidine on the mescaline-induced changes of brain-cortex ribosomes was studied by adding spermidine during the treatment of goat brain-cortex slices with mescaline. 2. Mescaline treatment of brain-cortex slices removed a portion of the endogenous spermidine from ribosomes and this removal was significantly prevented when spermidine was present during mescaline treatment. 3. Spermidine present during mescaline treatment of brain-cortex slices counteracted, to some extent, the destabilizing effect of mescaline on ribosomes with respect to heat denaturation. 4. Mescaline treatment of brain-cortex slices made ribosomes more susceptible to breakdown, releasing protein and RNA, and resulting in loss of ribosomal enzymic activities. However, spermidine present during mescaline treatment counteracted moderately the mescaline-induced ribosomal susceptibility to breakdown and ribosomal loss of enzymic activities. 5. Ribosomes of mescaline-treated cortex slices were rapidly degraded by ribonuclease and trypsin. However, if spermidine was present during mescaline treatment of brain-cortex slices the rates of degradation diminished.

During the action of mescaline sulphate (3,4,5-trimethoxyphenethylamine sulphate) on brain-cortex slices, the ribosomal particles become susceptible to breakdown, releasing protein, RNA, acid-soluble nucleotides and ninhydrin-positive materials and resulting in loss of ribosomal enzyme activities (Datta & Ghosh, 1970a). Moreover, ribosomes of the mescaline-treated cortex slices undergo rapid degradation in the presence of trypsin and ribonuclease. On the other hand, polyamines such as spermidine and spermine partially decrease the temperature-dependent and the pH-dependent breakdown of ribosomes into protein, RNA and acid-soluble nucleotides, and make ribosomes less susceptible to enzymic digestion by crystalline ribonuclease and trypsin (Datta, Sen & Ghosh, 1969b). In the present study, we study the effect of polyamines in counteracting the destabilizing effect of mescaline on ribosomes. The results presented in this paper appear to indicate that the polyamines are, to some extent, capable of counteracting the destabilizing effect of mescaline on brain-cortex ribosomes.

METHODS AND MATERIALS

Treatment of brain-cortex slices with mescaline. The cortex portions of brain tissue obtained from freshly slaughtered goats were carefully removed and cut in the

cold into slices 0.5 mm thick. Approximately 10 g wet wt. of cortex slices was suspended in 100 ml of Krebs-Ringer buffer (0.15 M-NaCl-3 mM-KCl-2 mM-CaCl₂-0.2 M-NaHCO₃), containing 0.5 M-glucose, pH 7.0, previously saturated with O₂ + CO₂ (95:5). Unless stated otherwise, the concentration of mescaline was 10 µg/g wet wt. of brain-cortex slices. The respiring conditions of the slices were periodically checked by separate manometric experiments performed under similar conditions. After incubation at 37°C for 2 h the slices were collected by centrifugation and washed four times with 100 ml portions of Krebs-Ringer buffer. Unless otherwise stated, 'mescaline-treated' cortex slices indicates glucose-mescaline-treated slices, whereas 'untreated' (control) slices indicates slices treated with glucose alone.

Treatment of brain-cortex slices with spermidine. The procedure described above was used, and 50 mM-spermidine was present during the treatment. Unless otherwise stated, 'spermidine-treated' cortex slices indicates glucose-spermidine-treated slices.

Treatment of brain-cortex slices simultaneously with mescaline and spermidine. The procedure described above was used, but mescaline (10 µg/g wet wt. of brain-cortex slices) and spermidine (50 mM) were present during the treatment. Unless otherwise stated, 'mescaline-spermidine-treated' cortex slices indicates glucose-mescaline-spermidine-treated slices.

Preparation of ribosomes. Ribosomes were prepared from untreated and treated brain-cortex slices by using deoxycholate and further purified by sucrose-density-gradient centrifugation and characterized as described by Datta & Ghosh (1963b, 1970a).

Extraction of ribosomal RNA. Ribosomal RNA was extracted by the method of Kirby (1956) as described by Littauer & Eisenberg (1959). The precipitated RNA was dissolved in water and further purified by passage through a column (2 cm $\times$ 30 cm) of Sephadex G-25 that had been equilibrated with water as described by Martin (1966).

Chemical determinations. Protein was determined by the method of Lowry, Rosebrough, Farr & Randall (1951), with crystalline bovine serum albumin as a standard. RNA was determined by the orcinol method of Meibaum (1939) and also by a u.v.-spectrophotometric procedure (Hotchkiss, 1957). The concentrations of acid-soluble nucleotides were determined spectrophotometrically on the basis of $E_{260} = 33$ for a solution containing a nucleotide mixture obtained from complete hydrolysis of 1 mg of yeast RNA/ml. Nitrogen was determined by the method of Ma & Zuazaga (1942). The organic phosphorus compounds were digested by the procedure of King (1932) and the inorganic phosphorus was determined by the method of Lowry, Roberts, Wu, Hixon & Crawford (1954). Ribosomes and ribosomal RNA were extracted three times with 0.5M-HClO₄. From the combined extracts polyamines were separated by paper electrophoresis, and spermidine was determined by the Amido Black method (Raina, 1963; Janne, Raina & Siimes, 1964).

Enzymic assays. Ribonuclease activity was measured by the method of McDonall (1955) as described by Datta, Bhattacharyya & Ghosh (1964). Phosphomonoesterase activity was measured by the method of Bessey, Lowry & Brock (1946) as described by Datta & Ghosh (1964). Phosphodiesterase activity was measured by the method of Frisch-Niggemeyer & Reddi (1957) as described by Datta & Ghosh (1963a) and Datta, Ghosh & Bhattacharyya (1969a). Trypsin digestion was performed by the method of Anson (1938) as described by Marks, Datta & Lajtha (1968).

Determination of stability of ribosomes. The stability of ribosomes was determined on the basis of degradation into smaller components such as protein and RNA released into the suspension medium. Ribosomes suspended in a

suitable buffer were incubated at 37°C under different conditions as described in the Results and Discussion section. At the end of the incubation, the suspensions were cooled in ice and centrifuged at 105 000g in a Spinco model L ultracentrifuge for 3 h. The supernatants were very carefully collected. The protein and nucleic acid contents of the supernatant were determined in the 5% trichloroacetic acid-precipitated residues of the supernatants.

Thermal denaturation profiles. A dilute suspension of ribosomes (E_{260} 0.3–0.4) in magnesium cacodylate-sucrose buffer, pH 7.0, was heated in 1 cm cuvettes for 15 min at different temperatures in a thermostatically controlled heating chamber (sensitivity $\pm 0.5^\circ\text{C}$) attached to a Beckman model DU spectrophotometer. The E_{260} values were measured over a range of temperatures between 30°C (room temperature) and 85°C during heating. The percentage increase in E_{260} or thermal hyperchromicity between 30°C and 85°C was calculated on the basis of the E_{260} at 30°C. Proper corrections were made for changes in concentrations of ribosomes as a result of thermal expansion of water. The temperatures recorded were those of the ribosomal solutions in the cuvettes.

Buffers. Magnesium cacodylate (MC) buffer, pH 7.0 (5 mM), was prepared as described by Gillochrist & Bock (1958). MC-sucrose buffer comprises 5 mM-magnesium cacodylate buffer containing 0.25 M-sucrose, pH 7.0. Acetate-veronal buffers, pH 2.5–9.6 (28 mM), were prepared as described by Michaelis (1931).

Materials. Spermidine trihydrochloride, spermine tetrahydrochloride, putrescine dihydrochloride and cadaverine dihydrochloride were purchased from Nutritional Biochemicals Corp., Cleveland, Ohio, U.S.A., and were neutralized before use. Crystalline pancreatic ribonuclease and crystalline ($\times 2$) trypsin were purchased from Sigma Chemical Co., St Louis, Mo., U.S.A. Trypsin was checked for the absence of ribonuclease activity by the procedure described by Piatigorsky (1968). Crystalline mescaline sulphate was obtained from Hoffmann-La Roche and Co. Ltd., Basle, Switzerland, and was neutralized before use.

Table 1. *Spermidine contents of ribosomes isolated from brain-cortex slices after various treatments*

The treatments of brain-cortex slices, isolation of ribosomes and determination of spermidine were as described in the Methods and Materials section. Mean values $\pm$ S.E.M. of three different experiments are given.

Treatment	Spermidine content ($\mu\text{mol}/100 \text{ mg}$ of ribosomes)
Control (untreated)	11.5 $\pm$ 1.2
Mescaline (10 $\mu\text{g/g}$ wet wt. of slices)	8.0 $\pm$ 1.2
Mescaline (50 $\mu\text{g/g}$ wet wt. of slices)	2.2 $\pm$ 0.3
Spermidine (10 mM)	22.5 $\pm$ 2.0
Spermidine (50 mM)	28.5 $\pm$ 3.0
Mescaline (10 $\mu\text{g/g}$) and spermidine (10 mM)	16.2 $\pm$ 2.0
Mescaline (10 $\mu\text{g/g}$) and spermidine (50 mM)	21.2 $\pm$ 1.9

RESULTS AND DISCUSSION

Spermidine contents of ribosomes after treatment of brain-cortex slices. Datta *et al.* (1969b) demonstrated that endogenous and exogenous spermidine was attached to cerebral ribosomes, and therefore attempts were made to study the effects of mescaline treatment of brain-cortex slices on the spermidine contents of ribosomes isolated from brain-cortex slices so treated. The spermidine contents of purified ribosomes of brain-cortex ribosomes were determined after brain-cortex slices were treated with mescaline and spermidine separately and in combination (Table 1). It was observed that the mescaline treatment lowered the endogenous spermidine content of ribosomes and this effect of mescaline was dose-dependent. On the other hand, the spermidine treatment increased the spermidine content of ribosomes. The treatment with mesca-

Table 2. *Specific activities of ribosomal enzymes isolated from brain-cortex slices after various treatments*

Treatments of brain-cortex slices with mescaline, spermidine and their combination and the preparation of ribosomes were as described in the Methods and Materials section. The isolated ribosomes were assayed for enzymic activities at their respective optimum pH values. The ribonuclease assay systems contained 0.5 mg of ribosomal protein, 2.5 mg of purified and dialysed yeast RNA and 14 mM-acetate-veronal buffer, pH 5.4, in a total volume of 1 ml. Other details were as described by Datta *et al.* (1964). The phosphomonoesterase assay systems contained 0.5 mg of ribosomal protein, 5 mM-*p*-nitrophenyl phosphate and 14 mM-acetate-veronal buffer, pH 8.1, in a total volume of 2 ml. Other details were as described by Datta & Ghosh (1964). The phosphodiesterase assay systems contained 0.5 mg of ribosomal protein, 0.5 mM-bis-*p*-nitrophenyl phosphate and 14 mM-acetate-veronal buffer, pH 8.9, in a total volume of 2 ml. Other details were as described by Datta & Ghosh (1963b) and Datta *et al.* (1969a). Mean values $\pm$ s.e.m. of five different experiments are given. The specific activity of ribonuclease is expressed as μ g of yeast RNA hydrolysed/h per mg of ribosomal protein. The specific activity of phosphomonoesterase is expressed as nmol of *p*-nitrophenol liberated/h per mg of ribosomal protein. The specific activity of phosphodiesterase is expressed as nmol of *p*-nitrophenol liberated/h per mg of ribosomal protein.

Treatment	Specific activity (mean $\pm$ s.e.m.)		
	Ribonuclease	Phosphomonoesterase	Phosphodiesterase
Control (untreated)	170 $\pm$ 12	400 $\pm$ 25	50 $\pm$ 3
Mescaline (10 μ g/g wet wt. of slices)	144 $\pm$ 15	260 $\pm$ 23	35 $\pm$ 3
Spermidine (1 mM)	163 $\pm$ 15	368 $\pm$ 30	45 $\pm$ 4
Spermidine (10 mM)	165 $\pm$ 11	372 $\pm$ 33	45 $\pm$ 4
Spermidine (50 mM)	167 $\pm$ 13	380 $\pm$ 35	46 $\pm$ 5
Mescaline (10 μ g/g) and spermidine (1 mM)	146 $\pm$ 10	276 $\pm$ 20	37 $\pm$ 2
Mescaline (10 μ g/g) and spermidine (10 mM)	150 $\pm$ 11	320 $\pm$ 27	40 $\pm$ 3
Mescaline (10 μ g/g) and spermidine (50 mM)	153 $\pm$ 14	340 $\pm$ 29	44 $\pm$ 4

line and spermidine combined increased the spermidine content of ribosomes above that produced by the mescaline treatment, but less than that produced by the spermidine treatment. This increment of spermidine content was dependent on the concentration of the spermidine used during the treatment. The results thus suggested that mescaline treatment removed a portion of endogenous spermidine from ribosomes and this removal was significantly prevented if spermidine was present when mescaline acts on brain-cortex slices.

Enzymic activities of ribosomes after treatment of brain-cortex slices. Datta & Ghosh (1970a) observed general decreases in the specific activities of ribonuclease, phosphomonoesterase and phosphodiesterase in the ribosomes isolated from the mescaline-treated slices. In the present experiment, attempts were made to study the effect of the concurrent presence of spermidine during the mescaline treatment on the activities of these ribosomal enzymes. As shown in Table 2, spermidine had little or no inhibitory action on the activities of ribosomal enzymes, but mescaline had a marked inhibitory effect. The inhibitory effect of mescaline on ribosomal enzymes was counteracted, to some extent, if spermidine was present during the action of mescaline on brain-cortex slices. This

counteracting effect of spermidine was dose-dependent.

Hyperchromicity profiles of ribosomes after various treatments of brain-cortex slices. Several findings indicated the stabilizing effect of polyamines on secondary structures of RNA and suggested that the removal of endogenous polyamines from RNA-containing cellular macromolecules might lead to the disorganization of secondary structure of these macromolecules (Friedman, Axel & Weinstein, 1967; Mangiantini, Tecce, Toschi & Trentalance, 1965; Muench & Saffile, 1968; Cohen, Morgan & Streibel, 1969). As the mescaline treatment of brain-cortex slices removed a portion of endogenous spermidine from ribosomes (Table 1) it was of interest to follow the effect of mescaline treatment of brain-cortex slices on the thermal hyperchromicity (heat denaturation) profiles of ribosomes isolated from brain-cortex slices after treatment with mescaline and spermidine both separately and in combination. Fig. 1 shows the thermal hyperchromicity profiles of ribosomes isolated from brain-cortex slices after various treatments. The 'melting' temperatures, T_m , were 63°C for the 'untreated', 60°C for the 'mescaline' ribosomes, 68°C for the 'spermidine' ribosomes and 64°C for the 'mescaline-spermidine' ribosomes.

Fig. 1. Thermal hyperchromicity (heat-denaturation) profiles of ribosomes isolated from brain-cortex slices after various treatments. Treatments of brain-cortex slices with mescaline, spermidine and their combination and determination of thermal hyperchromicity values of isolated ribosomes are as described in the Methods and Materials section. —, Untreated (control) ribosomes; ----, 'mescaline-treated' ribosomes; — · — ·, 'spermidine-treated' ribosomes; · · · ·, 'mescaline-spermidine-treated' ribosomes.

These T_m values suggested that, whereas the mescaline treatment of brain-cortex slices caused instability of ribosomes, the spermidine treatment enhanced the thermal stability of ribosomes but spermidine present during the action of mescaline on brain-cortex slices counteracted, to some extent, the destabilizing effect of mescaline. Thus spermidine present during the action of mescaline on brain-cortex slices partially prevented the destabilizing effect of mescaline with respect to disorganization of secondary structure of ribosomes as measured by thermal hyperchromicity. Evidence was presented previously that mescaline, when

acting on respiring brain-cortex slices, lowered the hydrogen-bonded structures of ribosomal total RNA and 28S RNA species of the drug-treated brain-cortex slices (Datta & Ghosh, 1970b). This effect of mescaline on the hydrogen-bonded structures may be mediated through the removal from ribosomes of endogenous polyamines that are known to assist in the organization of helical structures of ribosomal RNA.

Stability of ribosomes after treatment of brain-cortex slices. We showed that ribosomes isolated from the mescaline-treated brain-cortex slices released increased amounts of RNA, protein, acid-

Table 3. Release of components from ribosomes isolated from brain-cortex slices after various treatments

Treatments of brain-cortex slices with mescaline, spermidine and their combination and the preparation of ribosomes were as described in the Methods and Materials section. Portions (20 mg) of ribosomes containing 14 mg of protein and 6 mg of RNA were suspended in 5 ml portions of 5 mM-magnesium cacodylate buffer, pH 7.0, in which the agents listed in the table were dissolved with the pH adjusted where necessary and incubated at 37°C for 3 h with suitable controls. The suspensions were then spun at 105 000 g_{av} for 1 h and the supernatants were carefully decanted and collected. Protein and RNA were determined in the 5% trichloroacetic acid-precipitated residues. Mean values $\pm$ s.e.m. of determinations with six different preparations are given.

Treatment	Component released Medium ...	Amount of component (μ g/5 ml) released in suspension medium				
		Control (5 mM-magnesium cacodylate buffer, pH 7.0)	NaCl (0.5 M)	Urea (4 M)	EDTA (0.1 M)	Spermidine (5 mM)
Control (untreated)	Protein	202 $\pm$ 16	1353 $\pm$ 102	2078 $\pm$ 140	404 $\pm$ 35	140 $\pm$ 10
	RNA	94 $\pm$ 10	322 $\pm$ 30	353 $\pm$ 40	398 $\pm$ 35	41 $\pm$ 5
Mescaline (10 μ g/g wet wt. of slices)	Protein	663 $\pm$ 50	2144 $\pm$ 225	3824 $\pm$ 340	870 $\pm$ 65	402 $\pm$ 38
	RNA	312 $\pm$ 25	600 $\pm$ 65	650 $\pm$ 60	675 $\pm$ 55	215 $\pm$ 20
Spermidine (10 mM)	Protein	202 $\pm$ 15	1325 $\pm$ 122	2075 $\pm$ 170	375 $\pm$ 30	137 $\pm$ 10
	RNA	107 $\pm$ 9	362 $\pm$ 25	415 $\pm$ 30	468 $\pm$ 40	33 $\pm$ 3
Spermidine (50 mM)	Protein	200 $\pm$ 15	1310 $\pm$ 110	2005 $\pm$ 175	352 $\pm$ 30	123 $\pm$ 10
	RNA	100 $\pm$ 7	350 $\pm$ 30	400 $\pm$ 31	453 $\pm$ 32	29 $\pm$ 2
Mescaline (10 μ g/g) and spermidine (10 mM)	Protein	499 $\pm$ 45	1543 $\pm$ 120	2508 $\pm$ 200	470 $\pm$ 27	235 $\pm$ 20
	RNA	280 $\pm$ 21	541 $\pm$ 45	590 $\pm$ 45	650 $\pm$ 56	181 $\pm$ 15
Mescaline (10 μ g/g) and spermidine (50 mM)	Protein	405 $\pm$ 29	1848 $\pm$ 150	3104 $\pm$ 210	614 $\pm$ 45	315 $\pm$ 25
	RNA	209 $\pm$ 12	498 $\pm$ 42	553 $\pm$ 50	603 $\pm$ 40	148 $\pm$ 12

soluble nucleotides and amino acids into several suspension media compared with the ribosomes of the untreated slices (Datta & Ghosh, 1970a). In the present study, attempts were made to examine the effect of combined treatment of brain-cortex slices with mescaline and spermidine on the extent of release of ribosomal components such as protein and RNA. Ribosomal particles are susceptible to degradation in the presence of high concentrations of sodium or potassium chloride (Shigera & Chargaff, 1960; McQuillen, 1961) and of urea (Kihara, Halvorson & Bock, 1961) or in the absence of Mg^{2+} ions (Shigera & Chargaff, 1960; Ts'o & Vinograd, 1961). Datta *et al.* (1969b) observed that polyamines prevented the breakdown of brain-cortex ribosomes into smaller components. In the present study, the relative stability of ribosomal particles isolated from variously treated slices was assayed in terms of the release of protein and RNA, in suspension media containing sodium chloride, urea, EDTA and spermidine, which were chosen in view of the above results. The release into different suspension media of protein and RNA from ribosomes of variously treated brain cortex slices (Table 3) gave a general idea of the degree of stability of ribosomal particles. In these suspension media, there was release of more protein and RNA from ribosomes of the mescaline-treated slices. The ribosomes from the spermidine-treated slices appeared to be nearly as stable as those of the untreated slices. The rate of release of

components from ribosomes of the mescaline-spermidine-treated slices was less than that of such release from ribosomes of slices treated with mescaline alone. These results indicated that the destabilizing effects of mescaline on ribosomes, as measured by the release of ribosomal protein and RNA in some suspension media, were partially counteracted if spermidine was present during the action of mescaline. However, once the macromolecular structure of ribosomes was affected by mescaline, it could not be completely reversed or restabilized by polyamines, though their breakdown might be lessened to some extent by providing polyamines in the suspension medium (Table 3).

Degradation of ribosomes by ribonuclease and trypsin. Polyamines inhibit the enzymic degradation of ribosomes (Erdman, Thomas, Norton & Herbst, 1968) and aggregate ribosomal subunits into 70S and 100S ribosomal particles (Cohen & Lichtenstein, 1960; Colbourn, Witherspoon & Herbst, 1961). Hence, the susceptibility to ribonuclease and trypsin degradation of ribosomes isolated after mescaline and spermidine treatment was determined. As in a previous study (Datta & Ghosh, 1970a), the susceptibility of ribosomes isolated after aforesaid treatments to enzymic degradation was determined by incubating ribosomes with pancreatic ribonuclease and trypsin, and by estimating the extent of degradation of RNA and protein

Fig. 2. Ribonuclease digestion of ribosomes isolated from brain-cortex slices after various treatments. Treatments of brain-cortex slices with mescaline, spermidine and their combination are as described in the Methods and Materials section. The incubation system contained 10mg equivalent of ribosomal RNA, 1mg of crystalline pancreatic ribonuclease and 14mM-acetate-veronal buffer, pH 7.5, in a total volume of 10ml. During the incubation at 37°C samples were withdrawn and the rate of degradation of ribosomal RNA was determined. —, 'Untreated' (control) ribosomes; ----, 'mescaline-treated' ribosomes; — — —, 'spermidine-treated' ribosomes;, 'mescaline-spermidine-treated' ribosomes.

Fig. 3. Trypsin digestion of ribosomes isolated from brain-cortex slices after various treatments. Treatments of brain-cortex slices with mescaline, spermidine and their combination are as described in the Methods and Materials section. The incubation system contained 10mg equivalent of ribosomal protein, 1mg of crystalline trypsin and 14mM-acetate-veronal buffer, pH 7.6, in a total volume of 10ml. During incubation at 37°C samples were withdrawn and the rate of degradation of ribosomal protein was determined. —, 'Untreated' (control) ribosomes; ----, 'mescaline-treated' ribosomes; — — —, 'spermidine-treated' ribosomes;, 'mescaline-spermidine-treated' ribosomes.

constituents of the ribosomes. The results are expressed as percentage of total RNA or protein in the ribosomes that was degraded by the enzymes (Figs. 2 and 3). Ribosomes of the mescaline-treated cortex slices were more rapidly degraded by pancreatic ribonuclease and ribosomes of the spermidine-treated slices were less rapidly degraded by pancreatic ribonuclease than those of the untreated brain-cortex slices (Fig. 2). However, ribosomes isolated from the mescaline-spermidine treatment were less rapidly degraded by pancreatic ribonuclease than those of the mescaline-treated slices.

Similarly, ribosomes of mescaline-treated cortex slices were more rapidly degraded by trypsin and ribosomes of the spermidine-treated slices were less rapidly degraded by trypsin than those of the untreated brain-cortex slices (Fig. 3). However, ribosomes isolated from the mescaline-spermidine treatment were less rapidly degraded by trypsin than those of the mescaline-treated slices. This study thus indicated that the susceptibility to ribonuclease and tryptic degradation of ribosomes as induced by mescaline treatment might be counteracted, in part, by spermidine present during the treatment of brain-cortex slices.

Results presented herein suggest that one of the mechanisms by which mescaline induces instability in brain-cortex ribosomes may involve partial removal of endogenous polyamines from ribosomes. This suggestion is strengthened by the observations that spermidine added during the mescaline treatment of brain-cortex slices counteracts, to some extent, the destabilizing effect of mescaline (Tables 2 and 3, Figs. 1, 2 and 3). That the destabilizing effect of mescaline on brain-cortex ribosomes is mediated through the removal of endogenous polyamines from ribosomes of the mescaline-treated slices as suggested in this communication is comparable with the observation of Simon, Cohen & Raina (1966), who reported that levorphanol, a morphine derivative, influenced the metabolism of *Escherichia coli*, through selective inhibition of the synthesis of ribosomal RNA (Simon & Van Praag, 1964), by forcing the leakage of polyamines from the levorphanol-treated cells and that spermidine reversed inhibition by levorphanol of RNA synthesis.

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