The Sensitivity of Rat Liver and Yeast Mitochondrial Ribosomes to Inhibitors of Protein Synthesis*

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SUMMARY

Amino acid incorporation by isolated intact rat liver mitochondria was severely inhibited by chloramphenicol, carbomycin, or sparsomycin, partially inhibited by emetine, and unaffected by erythromycin or lincomycin. By contrast, amino acid incorporation by inner membrane-matrix fractions prepared from rat liver mitochondria by digitonin was strongly inhibited by emetine, erythromycin, and lincomycin. These results suggest that the mitochondrial membrane acts as a permeability barrier to these drugs thus preventing their inhibitory effects on protein synthesis in intact mitochondria.

Ribosomes with a sedimentation coefficient of 55 S were isolated from rat liver mitochondria. When incubated with supernatant factors from Escherichia coli, these ribosomes catalyze poly(U)-dependent polyphenylalanine synthesis at rates comparable to those obtained with ribosomes isolated from yeast mitochondria. Protein synthesis on ribosomes isolated from both rat liver and yeast mitochondria was inhibited to the same extent by carbomycin, chloramphenicol and erythromycin over a wide concentration range of drug. Hence, mitoribosomes from yeast or rat liver do not differ in their sensitivity to these inhibitors of protein synthesis.

The binding of radioactive chloramphenicol to yeast mitoribosomes and E. coli ribosomes was blocked by erythromycin, carbomycin, or lincomycin. Carbomycin and lincomycin partially prevented the binding of radioactive chloramphenicol to rat liver mitochondrial ribosomes, while erythromycin only inhibited 10 to 20% of the binding. These results suggest that significant differences may exist in the binding sites for these antibiotics on rat liver and yeast mitoribosomes.

Several groups have shown that the mitochondrial ribosome from animal cells has a sedimentation coefficient in the range of 55 to 60 S (1). The observation that labeled nascent protein chains were associated with these particles in lysates of purified mitochondria suggested that these small ribosomes were actually the ribonucleoprotein particle involved in mitochondrial protein synthesis (2-5). More convincing evidence for the role of this small ribosome in protein synthesis was obtained by Swanson and Dawid (6), who demonstrated the poly(U)-dependent synthesis of polyphenylalanine using the 60 S mitochondrial ribosome obtained from Xenopus eggs; however, the sensitivity of this protein synthesis to inhibitors was not examined. Subsequently, DeVries et al. (7) reported the isolation of rat liver mitochondrial ribosomes which retained peptidyltransferase activity, indicating that the 55 S ribosome was able to catalyze this critical reaction of protein synthesis sensitive to inhibition by certain antibiotics. Recently, we reported the isolation of rat liver mitochondrial ribosomes highly active in poly(U)-dependent polyphenylalanine synthesis in a cell-free system (8). Greco et al. (9) also have succeeded in the isolation of ribosomes from rat liver mitochondria which are active in protein synthesis.

A phylogenetic difference between the mitochondrial ribosome of mammals and yeast has been claimed on the basis of sensitivity to erythromycin (10, 11). Amino acid incorporation by isolated yeast mitochondria is strongly inhibited by the macrolides erythromycin, carbomycin, and lincomycin (12), while incorporation by intact rat liver mitochondria is completely resistant to erythromycin and lincomycin but is inhibited by very low concentrations of carbomycin. This difference has been attributed by Linnae's groups (10, 11) to a change in the mitochondrial ribosome during evolution so that the 55 S ribosomes of mammalian mitochondria can still bind erythromycin, although peptide bond formation is not affected. In contrast, Kroon and DeVries (13) have suggested that the lack of sensitivity of mammalian ribosomes to erythromycin results from a selective permeability barrier in the mitochondrial membrane since erythromycin inhibited incorporation in swollen liver mitochondria. The present study was undertaken in an attempt to distinguish clearly between these two alternatives. Protein synthesis on isolated ribosomes from both rat liver and yeast mitochondria was inhibited to the same extent by three different inhibitors: carbomycin, chloramphenicol, and erythromycin. The binding of [3H]chloramphenicol to yeast mitochondrial ribosomes was prevented to the same extent by erythromycin, carbomycin and lincomycin as was the binding to Escherichia coli ribosomes; however, all three antibiotics were less effective inhibitors of the binding of [3H]chloramphenicol to rat liver mitochondrial ribosomes.

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EXPERIMENTAL PROCEDURE

Growth of Escherichia coli and Preparation of Ribosomes—An E. coli mutant (Q4) which is low in ribonuclease (obtained from F. L. Chang, Temple University, Philadelphia, Pa.) was grown in a liquid medium containing 8 g of nutrient broth, 5 g of peptone, 5 g of NaCl and 1 g of glucose per liter. The cells were harvested at late log phase and ground vigorously with alumina in a chilled mortar and pestle in the cold room. As the cells underwent breakage, additional alumina was added slowly. After 10 min of grinding, 0.44 ml of freshly prepared buffer containing 10 mM Tris-Cl, pH 7.8, 14 mM magnesium acetate, 60 mM KCl, and 6 mM mercaptoethanol were added to the mortar. The subsequent preparation of ribosomes and S-100 fraction was exactly as described by Nirenberg (14).

Preparation of Ribosomes from Rat Liver Mitochondria—Rat liver mitochondria were prepared from 40 to 60 Sprague-Dawley rats weighing 125 to 150 g in 0.34 M sucrose containing 5 mM Tris-Cl, pH 7.6, by the procedure of O'Brien and Kalf (2). Sterility of glassware and solution was maintained at all steps. The mitochondrial pellet obtained after seven washes was resuspended at a concentration of 5 mg per ml in Medium A (0.1 M KCl, 5 mM Tris-Cl, pH 7.6, and 30 mM MgCl2). The mitochondria were lysed by the addition of 0.1% (v/v) Triton X-100. Deoxyribonuclease, free of ribonuclease, then was added at a final concentration of 5 pg per ml and the solution was kept on ice for 5 min. The suspension then was centrifuged for 10 min at 60,000 X g in the Spincino 30 rotor. The resultant supernatant was layered on 2 ml of Medium A containing 24% sucrose and centrifuged for 3 hours at 230,000 X g in the Spincino 65 rotor. The crude ribosomal pellet was resuspended in 2 ml of Medium A containing 6 mM mercaptoethanol and centrifuged at 3,000 X g for 5 min. The supernatant was layered on a 10 to 30% sucrose gradient containing Medium A supplemented with 6 mM mercaptoethanol. After 16 hours at 20,000 X g in the Spincino SW 27 rotor, 1-ml fractions were collected and the absorbance at 260 nm was measured for each fraction.

The fraction corresponding to the mitochondrial ribosomes was diluted with medium and centrifuged at 230,000 X g for 3 hours in the Spincino 65 rotor. The pellet containing ribosomes was resuspended in the same medium. The absorbance ratio (A260:A165) of the purified ribosomes was 1.1:1.4.

Preparation of Yeast Mitochondrial Ribosomes—A diploid wild type strain of Saccharomyces cerevisiae was grown in liquid medium (15) containing 1% glucose as carbon source. The cells were harvested at late log phase and suspended in water at a concentration of 1 g per ml. Then, 0.5 ml of thioglycolic acid (57 mg per ml) and 0.5 ml of 0.1 M EDTA were added per ml of medium and the pH of the suspension was adjusted to pH 7.0 with NaOH. The suspension was incubated at 33° for 30 min with gentle stirring and then centrifuged at 3,000 X g for 5 min. The pellet was resuspended at a concentration of 1 g per ml of cells in a medium containing 1.8 M sorbitol, 0.25 mM citrate-phosphate buffer, and 1.0 ml of Glusulase (Endolaboratories) per 3 g of cells as described by Kovace et al. (16). The mixture was incubated at 33° for 30 to 60 min with gentle stirring. The conversion to spheroplasts was monitored by measuring the absorbance at 600 nm. The digestion was stopped by chilling the suspension as soon as the turbidity decreased to a value 20% of the initial value. The spheroplasts were collected by centrifugation at 3,000 X g for 10 min. The cells were washed twice with medium containing 1.5 M sorbitol, 10 mM Tris-maleate, pH 6.7, and 0.1 mM EDTA. The protoplasm then was resuspended in Medium B (0.44 mM mannitol, 5 mM Tris-Cl, pH 7.4, and 0.1 mM EDTA) at a concentration of 0.2 g per ml. The suspension was dispersed two times in a Waring Blendor at high speed for 20 sec. The cellular debris and nuclear fragments were removed by two centrifugations at 2,000 X g for 5 min. Mitochondria were sedimented by centrifugation at 12,000 X g for 10 min and the pellet was washed four times by resuspension in Medium B. The mitochondrial ribosomes were described by Grivett et al. (17).

Preparation of Mitochondria for Amino Acid Incorporation—Rat liver mitochondria were prepared under sterile conditions in 0.25 M sucrose containing 10 mM Tris-Cl, pH 7.4, and 1.0 mM EDTA as previously described. Inner membrane-matrix fractions were prepared with digitonin (18). Yeast mitochondria were prepared from cells in late log phase in Medium C (0.25 M mannitol, 10 mM Tris-Cl, pH 7.4, and 1.0 mM EDTA) as described previously (19).

Protein Synthesis—Amino acid incorporation was assayed in rat liver mitochondria (20) and yeast mitochondria (19) by previously described methods. Cell-free protein synthesis was assayed by the method described by Ibrahim and Beattie (8).

Binding of [3H]Chloramphenicol to Ribosomes—Radioactive chloramphenicol was added at a final concentration of 3.0 μM to a 2.0-ml suspension of ribosomes (0.5 mg per ml) in 0.2 M KCl containing 10 mM magnesium acetate and 10 mM Tris-Cl, pH 7.6. In the experiments with rat liver mitochondria, the concentration of magnesium acetate was raised to 20 mM. After a 5-min incubation at 4°, the suspension was centrifuged at 150,000 X g for 80 to 100 min. The pellet was rinsed four times with 2.0 ml of buffer and then suspended in 1.0 ml of water for determination of radioactivity. In the controls, 0.3 mM unlabeled chloramphenicol was present during the incubation and 3.0 μM [3H]chloramphenicol was added immediately before centrifugation. The radioactivity in these tubes provided a correction for the [3H]chloramphenicol present in fluid trapped in the ribosomal pellet (21).

Materials—Sucrose (ribonuclease-free) was obtained from Mann, poly(U) from Miles Laboratories; erythromycin, chloramphenicol and other nucleotides from Sigma; lincomycin and sparsomycin from Upjohn; rifampicin and valinomycin from Calbiochem and actinomycin D from Merek, Sharpe and Dohme. Uniformly labeled [3H]leucine (270 μCi per mmole) was obtained from Amer sham-Searle, 1,2-[14C]chloramphenicol (5 μCi per mmole) and uniformly labeled [14C]cyclophycinoline (400 μCi per mmole) from New England Nuclear. Carbamyacin was a generous gift from Pézer.

RESULTS

Effects of Antibiotics on Amino Acid Incorporation by Isolated Mitochondria—To study the effect of various inhibitors of mitochondrial protein synthesis, it is necessary to study amino acid incorporation under optimal conditions. In a previous study (20) we explored the ionic and energy requirements for maximum rates of incorporation. The concentration dependence of leucine also has been investigated to ensure that the substrate amino acid is not rate-limiting for a reaction occurring on the mitochondrial ribosome. As seen in Fig. 1, an optimal rate of amino acid incorporation was observed at a leucine concentration of 60 μM. A slight decrease in the incorporation rate was observed at higher concentrations of leucine.

The effects of various inhibitors of protein synthesis on amino acid incorporation by rat liver and yeast mitochondria are listed in Table I. Low concentrations of chloramphenicol, carbamyacin, and sparsomycin inhibited completely the incorporation by intact mitochondria, while a 0.75 mM concentration of emetine inhibited by nearly 60% the incorporation rate. In contrast, the addition of erythromycin and lincomycin had no effect on amino acid incorporation by intact rat liver mitochondria.

One possible explanation for the inability of certain antibiotics to inhibit protein synthesis is that the mitochondrial membrane acts as a permeability barrier to the drug. The inner membrane-matrix fraction prepared by use of digitonin (18) has altered permeabilities to many substances and yet is still active in amino acid incorporation (22). Both macrolides, erythromycin and lincomycin, caused a 70% inhibition of amino acid incorporation in the inner membrane-matrix fraction. In addition, emetine was an effective inhibitor of incorporation in this fraction at much lower concentrations than in intact mitochondria. Similar inhibitory effects of erythromycin, carbamyacin, and emetine were obtained when the inner membrane-matrix fraction was incubated in the presence of valinomycin when maximum rates of amino acid incorporation are obtained (20).

The various inhibitors also were tested in rat liver mitochondria which had been suspended in 2.5 mM sucrose at 0° at a concentra-
the inner membrane-matrix fraction has retained some permeability to these drugs so that the internal concentration of the drug is much lower than that of the medium. A clear choice between these two explanations can be obtained only by comparing the antibiotic sensitivities of isolated ribosomes from both types of mitochondria in a cell-free system for protein synthesis.

These results indicate that protein synthesis on rat liver mitochondrial ribosomes has retained sensitivity to the macrolides erythromycin and lincomycin. However, it is imperative that amino acid incorporation be studied in mitochondria which have been treated so as to lose some permeability barriers to various drugs and yet maintain an incorporation rate equal to or greater than that of the intact mitochondria. The effects of the various inhibitors also were tested on amino acid incorporation by isolated yeast mitochondria. The data of Table I indicate that much lower concentrations of erythromycin inhibit protein synthesis in isolated yeast mitochondria than are effective with the inner membrane-matrix fraction obtained from rat liver mitochondria. For example, addition of 50 μg per ml of erythromycin caused a 90% inhibition in yeast mitochondria but only a 40% inhibition in the inner membrane fraction. The maximum inhibition by erythromycin observed with liver mitochondria was only 70% even with much greater concentrations of erythromycin.

This difference in sensitivity to the macrolides of rat liver and yeast mitochondria may result because a change in the properties of the mitochondrial ribosome has occurred so that certain macrolides are less effective inhibitors of protein synthesis, as suggested by Linnane’s group. An alternative explanation might be that the inner membrane-matrix fraction has retained some permeability barriers to these drugs so that the internal concentration of the drug is much lower than that of the medium. A clear choice between these two explanations can be obtained only by comparing the antibiotic sensitivities of isolated ribosomes from both types of mitochondria in a cell-free system for protein synthesis.

The sedimentation profile of ribosomes extracted from rat liver mitochondria is compared with that of ribosomes extracted from yeast mitochondria (Fig. 2). The rat liver mitoribosomes sediment at 55 S with almost no contaminating material of higher buoyant density. As discussed in a previous publication (8), the concentration of Mg²⁺ in the gradient was maintained at 20 mM to prevent dissociation of the 55 S ribosomes to the two subunits of 39 S and 20 S. As seen in Fig. 2, the yeast mitoribosomes sediment at 74 S and clearly can be differentiated from the rat liver mitoribosomes in the gradient. As seen in Fig. 3, the liver mitoribosomes also can be distinguished from the bacterial 70 S ribosomes. Tubes 16 to 20 of the gradient of Fig. 3 were pooled and this fraction was used for all further studies involving rat liver mitochondrial ribosomes. Hence, the slight amount of contaminating material of buoyant density greater than 55 S was not used. It is unlikely that this material represents bacterial contamination since our mitochondrial preparations contain less than 100 bacterial colonies per ml of a mitochondrial suspension containing at least 10 mg of protein.

Both liver and yeast mitoribosomes isolated in this way were highly active in cell-free protein synthesis measured with poly(U) and phenylalanine. The extent of incorporation was dependent
Fig. 2. Sucrose density gradient centrifugation of ribosomes isolated from rat liver and yeast mitochondria as described under "Experimental Procedure." The yeast mitoribosomes (O--O) sediment at 74 S, while the rat liver mitoribosomes (●—●) sediment at 55 S.

Fig. 3. Sucrose density gradient centrifugation of ribosomes isolated from rat liver mitochondria and Escherichia coli as described under "Experimental Procedure." The rat liver mitoribosomes (●—●) sediment at 55 S, while the E. coli ribosomes (O—O) sediment at 70 S. The shaded area represents the tubes which were pooled for the studies of rat liver mitochondria.

Fig. 4. Inhibition of polyphenylalanine synthesis in a cell-free system by erythromycin, carbomycin, or chloramphenicol. Ribosomes isolated from rat liver (●—●) or yeast (O--O) mitochondria were incubated as described in the legend to Table II with different concentrations of the inhibitors. Control value for ribosomes from rat liver mitochondria was 356 pmoles per mg of RNA and that from yeast mitochondria was 302 pmoles per mg of RNA.

The inhibitory effects of different concentrations of erythromycin, carbomycin, and chloramphenicol were tested in the cell-free system with both rat liver and yeast mitoribosomes. As seen in Fig. 4, polyphenylalanine synthesis on the two different ribosomes was inhibited to the same degree by all concentrations of the three inhibitors. The one slight exception is carbomycin which at low concentrations was a more effective inhibitor of protein synthesis on the liver mitoribosomes than on the yeast mitoribosomes.

The binding of radioactive chloramphenicol to the purified ribosomes obtained from both liver and yeast mitochondrial ribosomes was compared to that obtained with E. coli ribosomes. As seen in Table III, the amount of chloramphenicol quantitatively bound to each type of ribosome varied over a 2.5-fold range but was in the same order of magnitude. Addition of either erythromycin or carbomycin almost completely prevented the binding of chloramphenicol to the ribosomes from E. coli or yeast mitochondria. Lincomycin blocked by 75% the binding of chloramphenicol to the yeast mitochondrial ribosomes, but only by 43% that to the E. coli ribosomes. The effect of the different macrolides on the binding of chloramphenicol to rat liver mitoribosomes indicated that these ribosomes do differ from yeast mitoribosomes. Carbomycin was the only antibiotic which effectively prevented the binding of chloramphenicol to the ribosomes isolated from rat liver mitochondria. The effects of lincomycin were similar to those observed with E. coli ribosomes; however, erythromycin was a very ineffective inhibitor of chloramphenicol binding to liver mitochondrial ribosomes.

**DISCUSSION**

The present study was undertaken to determine whether protein synthesis on rat liver mitochondrial ribosomes is sensitive to
the macrolides, erythromycin, and lincomycin, as is protein synthesis on yeast mitochondrial ribosomes. Initially, the inhibitors were tested both in intact rat liver mitochondria and in an inner membrane-matrix fraction prepared by the use of digitonin. The latter fraction had been shown previously (23) to catalyze amino acid incorporation at rates similar to those obtained with intact liver mitochondria provided that ATP and a regenerating system were used as a source of energy. An exogenous energy source also has advantages in inhibitor studies, as an interference of the drug with ATP synthesis by oxidative phosphorylation can be ruled out. Both erythromycin and lincomycin inhibited amino acid incorporation only in the inner membrane-matrix fraction, while carbomycin inhibited incorporation equally well in the intact mitochondria. These results are in essential agreement with those of Kroon and DeVries (13) but in direct contrast to those reported by Towers et al. (10, 11) with rat liver mitochondrial ribosomes. Both of these groups used mitochondria presumably made permeable to the drugs by treatment with hypotonic solutions and observed no inhibition by erythromycin or lincomycin. We have observed that mitochondria treated by incubation in hypotonic sucrose have been damaged so that the incorporation rates are only 25% of those obtained with the digitonin inner membrane fraction. For meaningful inhibition studies, it is essential to study amino acid incorporation under optimal conditions.

Inhibitor studies with isolated yeast mitochondria revealed that the amount of erythromycin necessary to inhibit the incorporation rate was almost one-half that needed for comparable inhibitions of incorporation by the inner membrane fraction. Furthermore, the maximum inhibition of incorporation in this fraction was approximately 70% even when the concentration of erythromycin was increased significantly. This differential sensitivity might result because of a change in the mitochondrial ribosome so that erythromycin is not bound as tightly to the ribosome and is hence a less effective inhibitor; alternatively, the inner membrane may still be somewhat impermeable to these drugs.

The isolation of mitochondrial ribosomes highly active in protein synthesis in a cell-free system has demonstrated clearly that there is no difference in the response of rat liver and yeast mitochondrial ribosomes to the inhibitors, chloramphenicol, carbomycin, and erythromycin. Polyphenylalanine synthesis by both ribosomes was inhibited to the same extent over a wide range of inhibitor concentrations. Lincomycin, however, was not an effective inhibitor of protein synthesis in the cell-free system with either ribosome. Hence, we can conclude that the decreased sensitivity of amino acid incorporation by the inner membrane fraction to erythromycin results from a permeability barrier to the drug in the inner membrane as the isolated ribosomes respond identically to all three inhibitors.

The activity of rat liver mitochondrial ribosomes in the cell-free system varied somewhat in different preparations. When the synthetic activity of a preparation was less than 200 pmoles per mg of RNA, erythromycin, carbomycin, and chloramphenicol were all much less effective inhibitors of protein synthesis. In order to ensure maximum rates of protein synthesis, ribosomes were frozen at -70° immediately after preparation and only thawed once prior to use. The source of supporting enzymes was also critical for maximum rates of protein synthesis. The supernatant factors obtained from E. coli supported protein synthesis on both rat liver and yeast mitochondrial ribosomes to a much greater extent than the corresponding supernatant factors obtained from either mitochondria. The E. coli S 100 fraction was also frozen at -70° immediately after preparation and only thawed once prior to use. Furthermore, it was imperative that at least 1 mg per ml of S-100 be added to each incubation tube.

The method we have used for the isolation of mitochondrial ribosomes active in protein synthesis differs significantly from that recently reported by Greco et al. (9). For example, they prefer mitochondria from the post-nuclear supernatant by centrifugation at 10,000 × g. We have observed that the isolation of mitochondria at centrifugal forces greater than 7,000 × g, while it increases the yield of mitochondria substantially, resulted in significant contaminating material sedimenting at 80 × g. Furthermore, the medium used in our studies to lyse the mitochondria as well as the sucrose gradient contained a 20 mM concentration of Mg++; while Greco et al. (9) use a final Mg++ concentration of 10 mM; however, O'Brien (25) had demonstrated previously that high concentrations of Mg++ prevent the dissociation of the mitochondrial monosome to its two subunits. Despite these differences, the 55 S mitochondrial ribosome isolated by Greco et al. (9) from the sucrose gradient possessed similar activity as our preparation of 55 S ribosomes in the cell-free system for protein synthesis.

One significant difference between the ribosomes isolated from liver and yeast mitochondria was observed when the effects of the different macrolides on the binding of chloramphenicol was tested. Both erythromycin and carbomycin almost completely prevented the binding of radioactive chloramphenicol to yeast mitochondrial ribosomes, while only carbomycin effectively blocked the binding of chloramphenicol to liver mitochondrial ribosomes. In addition, it should be noted that the inhibitory effects of carbomycin were significantly lower with the liver mitochondrial ribosomes than with the yeast mitochondrial ribosomes. Erythromycin, however, only blocked by 15% the binding of chloramphenicol, despite the fact that protein synthesis on the same preparation of ribosomes was inhibited 70% by erythromycin. Hence, the affinity of the 55 S rat liver mitochondrial ribosomes for erythromycin may be much lower than the affinity of yeast mitochondrial ribosomes. A similar conclusion was reached by DeVries et al. (26) who studied the peptidyltransferase reaction of isolated rat liver mitochondrial ribosomes. Very high concentrations of erythromycin were necessary to reverse the chloramphenicol inhibition of the reaction. Extensive studies (27) with E. coli ribosomes have indicated that
chloramphenicol, lincomycin, and erythromycin act at closely related sites on the 50 S subunit; however, significant differences in the binding sites for the three different antibiotics were observed. Perhaps the binding sites for these antibiotics to liver mitochondrial ribosomes also may have significant differences which may be responsible for the inability of the macrolides to prevent the binding of chloramphenicol to these ribosomes.

Another significant difference in the response of 55 S bovine mitochondrial ribosomes to the antibiotic lincomycin as compared to bacterial ribosomes was recently reported (28). Nearly 100-fold higher concentrations of lincomycin were necessary to inhibit partially the "fragment reaction" catalyzed by the 55 S ribosomes than were necessary to inhibit completely the reaction catalyzed by the 70 S bacterial ribosomes.

The results of this paper indicate that mitochondrial protein synthesis, especially when assayed in the inner membrane-matrix fraction, is sensitive to emetine confirming several previous reports (29-31). Originally, Grollman (32) had observed that emetine, a compound which is structurally similar to cycloheximide, also resembled cycloheximide in its mode of action on 80 S cytoplasmic ribosomes. Furthermore, he reported that emetine was not an inhibitor of protein synthesis on bacterial ribosomes. The inhibition of mitochondrial protein synthesis by emetine may suggest a similarity between cytoplasmic and mitochondrial ribosomes not shared by bacterial ribosomes. In addition, these results suggest that emetine should be used with some caution as a selective inhibitor of cytoplasmic protein synthesis in studies of mitochondrial biogenesis in whole cells (33).

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