Cordycepin

AN INHIBITOR OF NEWLY SYNTHESIZED GLOBIN MESSENGER RNA*

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The effect of cordycepin (3′-deoxyadenosine) on newly synthesized globin mRNA in cultured mouse fetal liver erythroid cells is investigated. At cordycepin concentrations that do not inhibit amino acid incorporation into acid-precipitable material, the quantity of pulse-labeled (radioactive) globin mRNA nucleotide sequences is reduced by 90%, as compared to adenosine-treated controls. The reduction of radioactivity in globin-specific RNA sequences is greater than the inhibition of total RNA synthesis in experiments in which the labeling times range from 6 to 60 min. Control experiments demonstrate that cordycepin does not reduce the recovery of total cell RNA or steady state (unlabeled) globin mRNA. The hybridization assay used to detect radioactive globin mRNA sequences is independent of the cellular location or the number of 3′-terminal adenylate residues in the mRNA-containing molecules. These data thus indicate that cordycepin inhibits newly synthesized mRNA as effectively as it inhibits ribosomal and transfer RNA synthesis.

Of the several classes of eukaryotic RNA (rRNA, hnRNA, mRNA, and tRNA), only hnRNA and mRNA contain 3′-terminal poly(A) sequences (Darnell et al., 1971b; Lee et al., 1971; Edmonds et al., 1971). Some hnRNA (LaTorre and Perry, 1973) and mRNA (Adesnik and Darnell, 1972; Nemer et al., 1974; Milcarek et al., 1974) molecules are not polyadenylated.

The role that poly(A) plays in mRNA function or metabolism has not been clearly defined. It may function in the cytoplasm since the mRNA of some viruses that replicate exclusively therein is polyadenylated (Johnston and Bose, 1972; Ehrenfeld, 1974), and adenylate residues are added onto maternal mRNA in the cytoplasm of sea urchin embryos (Slater et al., 1973; Wilt, 1973). It is unlikely that poly(A) is required for translation since the initial rates of translation of adenylated and nonadenylated mRNAs are similar (Fromson and Verma, 1976; Gedamu and Dixon, 1976; Sippel et al., 1974).

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The abbreviations used are: hnRNA, heterogeneous nuclear RNA, defined here as that portion of nuclear RNA that is distinct from rRNA and tRNA; MFL, mouse fetal liver.

Soreq et al., 1974; Nudel et al., 1976). The poly(A) might retard the degradation of polysomal mRNA (Sippel et al., 1974; Soreq et al., 1974; Nudel et al., 1976).

It has been suggested that poly(A) functions in the processing and/or transport of mRNA from the nucleus. Evidence supporting this hypothesis has come, in large part, from experiments with the adenosine analog cordycepin (3′-deoxyadenosine). Cordycepin was originally isolated from the liquid growth medium of the mold Cordyces militaris. It is triphosphorylated in animal cells (Kienow, 1963) and, at sufficient concentrations, inhibits rRNA, tRNA (Siev et al., 1969), and protein synthesis (LaTorre and Perry, 1973) in intact cells. The following data support the hypothesis that post-transcriptional polyadenylation is essential for complete processing and/or transport of nuclear mRNA-containing molecules. 1) Cordycepin blocks post-transcriptional polyadenylation in the nucleus (Darnell et al., 1971a; Mendecki et al., 1972; Nakazato et al., 1974). 2) Under conditions in which nuclear polyadenylation is inhibited 75% or more, synthesis of hnRNA is either unaffected or is inhibited to a lesser extent (Siev et al., 1969; Penman et al., 1970; Darnell et al., 1971a; Mendecki et al., 1972; Nakazato et al., 1974; Debrusiers et al., 1976). 3) The percentage of inhibition of newly synthesized (nucleus-derived) poly(A)-containing mRNA in polysomes is approximately the same as the inhibition of nuclear poly(A) (Mendecki et al., 1972; Adesnik et al., 1972; Nakazato et al., 1974; Milcarek et al., 1974); the accumulation of polysomal mRNA lacking poly(A) is also reduced, but to a lesser extent than is the poly(A)-containing mRNA (Milcarek et al., 1974).

One interpretation of these data is that cordycepin inhibits the accumulation of newly synthesized polysomal mRNA by blocking polyadenylation of nuclear mRNA molecules or their precursors. The nonpolyadenylated molecules are then unable to be processed or transported. This interpretation is supported by the fact that hnRNA synthesis is relatively resistant to cordycepin. However, this hypothesis makes the important, but unproved, assumption that cordycepin does not inhibit mRNA transcription, i.e. that the cordycepin-resistant hnRNA contains unprocessed mRNA molecules. Another interpretation is that total hnRNA consists of two distinct classes of RNA that respond differently to cordycepin: 1) mRNA molecules and their putative precursors; and 2) non-messenger RNA molecules. The nonmessenger fraction, representing the vast majority of the hnRNA, might be resistant to cordycepin, while only the minor portion of hnRNA that is related to mRNA is inhibited. This interpretation would...
account for the fact that cordycepin inhibits the accumulation of polysomal mRNA more so than hnRNA.

Globin mRNA is transcribed initially into a precursor molecule that is 2- to 3-fold larger than globin mRNA and is cleaved to generate the mature molecule (Curtis and Weissmann, 1976; Ross, 1976; Kwan et al., 1977). This precursor is polyadenylated. Since cordycepin inhibits polyadenylation, it seemed feasible to exploit this analog to investigate the role of poly(A) in the cleavage, processing, and transport of a specific mRNA precursor. The question was whether precursor molecules lacking poly(A) would undergo any or all of these posttranscriptional modifications. This experiment requires that cordycepin does not inhibit transcription of the heteropolymeric mRNA nucleotide sequences themselves. In order to investigate this question, the quantity of radioactive globin-specific RNA from cordycepin-treated or control erythroid cells was determined by hybridization with excess unlabelled globin cDNA. Since this assay detects radioactive globin mRNA sequences, whether or not they contain poly(A), it was possible to monitor directly the effect of cordycepin on the heteropolymeric portion of specific mRNA's. We find that cordycepin inhibits the transcription and/or accumulation of globin mRNA sequences.

**MATERIALS AND METHODS**

Details of the isolation and culture conditions for mouse fetal liver cells and the procedure for RNA isolation were as described (Ross, 1976). The liver of the 14-day-old mouse embryo consists primarily of erythroid precursor cells (Paul et al., 1969). As primary cultures, these cells mature and synthesize appreciable quantities of adult mouse hemoglobin and globin mRNA (Chui et al., 1971; Ramirez et al., 1975; Ross, 1976). For isolation of total cell RNA, whole cells were lysed and extracted with phenol plus chloroform/isoamyl alcohol. The nucleic acids were then centrifuged in an isopycnic cesium chloride gradient; the RNA pelleted to the bottom of the tube and the DNA remained in the gradient. The pellet was resuspended in buffer and concentrated by ethanol or trichloroacetic acid precipitation (see Ross, 1976 for details).

The hybridization methods for detecting labeled and unlabelled globin mRNA nucleotide sequences were as described (Ross, 1976). Briefly, to detect unlabelled (steady state) globin mRNA, cell RNA was incubated in solution with globin [3H]DNA. The reaction mix was then treated sequentially with S1 nuclease to hydrolyze nonanucleotide nucleotide sequences. The exogenous adenosine exerted no significant effect on globin mRNA synthesis since adenosine-treated cells had essentially the same with labeling times of 6 or 30 min. Incorporation into total RNA, measured by absorbance at 260 nm were the same. These control experiments indicated that the cordycepin effect was not due to decreased recovery of RNA.

The results (Table I) indicated that cordycepin either inhibited the transcription or accelerated the breakdown of newly synthesized globin mRNA sequences. In an effort to distinguish between these mechanisms, a similar experiment was performed, except that cells were labeled for shorter intervals. In preliminary experiments, cells were labeled for 10 min without cordycepin, and the RNA was analyzed by electrophoresis in a formamide-containing polyacrylamide gel; greater than 90% of the globin mRNA nucleotide sequences was in precursor molecules larger than 10 S. Based on these data, a labeling time of 6 min was chosen for some of the cordycepin experiments so that most of the radioactive globin mRNA sequences would be in precursor molecules. If cordycepin caused increased (but not instantaneous) breakdown of newly synthesized molecules, the percentage reduction of radioactive globin mRNA sequences should increase without labeling times. As shown in Table II, the per cent inhibition of radioactive, globin-specific sequences was greater than that of total RNA, confirming the results of Table I, and was essentially the same with labeling times of 6 or 30 min. This result strongly indicates, but does not prove, that cordycepin causes breakdown during or immediately after transcription. We are unable to speculate further on this matter since the rate of synthesis of the globin mRNA precursor is unknown. The important point
is that cordycepin inhibits newly synthesized globin mRNA nucleotide sequences even with relatively short labeling times.

To determine the effect of different cordycepin concentrations, MFL cells were preincubated with adenosine or cordycepin for 30 min and were then labeled with [3H]uridine for 60 min. Total RNA and radioactive globin mRNA nucleotide sequences were quantitated. As expected, increasing concentrations of cordycepin reduced incorporation into total RNA (Table III). At concentrations of 1 µg/ml or greater, cordycepin also reduced the percentage of newly synthesized globin mRNA sequences (Table III). With as little as 3 µg/ml, the percent hybridization was reduced approximately 2-fold, from 0.3 to 0.15%. Therefore, even at low concentrations, the synthesis (or accumulation) of globin mRNA nucleotide sequences is more sensitive to cordycepin than is total RNA synthesis.

One trivial explanation for these results was that cordycepin preferentially inhibited a specific size class of nuclear RNA. This seemed unlikely, based on sedimentation analysis of hnRNA from control versus cordycepin-treated mammalian tissue culture cells (e.g. see Penman et al., 1970). Nevertheless, to determine the effect of cordycepin with MFL cells, total cell pulse-labeled RNA from treated or untreated cultures was sedimented in a sucrose gradient. Although incorporation was reduced in all size classes of RNA from cordycepin-treated cells, there was no selective decrease in the 4 to 28 S RNA (Fig. 2). There was slightly greater inhibition of 30 to 50 S RNA. This result indicates that cordycepin does not selectively inhibit the 10 to 18 S portion of the hnRNA, which contains globin mRNA and its precursor.

**TABLE I**

| Effect of cordycepin on newly synthesized globin mRNA nucleotide sequences during 60-min labeling period |
|---|
| 3 x 10⁶ MFL cells (10⁵/ml) were incubated in growth medium (Ross, 1976) for 75 min, and adenosine or cordycepin was added to a final concentration of 20 µg/ml. Forty minutes later [3H]uridine was added to a final concentration of 400 µCi/ml. After 60 min of labeling, the cells were harvested, and total cell RNA was extracted and concentrated as previously described (Ross, 1976). |
| Treatment (20 µg/ml) | Total RNA | Inhibition of total RNA | Globin mRNA | Inhibition of globin mRNA |
|---|---|---|---|---|
| Adenosine | 10.8 | 2.2 | 69 | 0.2 | 91 |
| Cordycepin | 3.3 | 45.6 | 45.4 | 100 | 100 | 100 |

\[ a \] Cold trichloroacetic acid-precipitable disintegrations per min.

\[ b \] Determined by hybridization to unlabeled globin cDNA as previously described (Ross, 1976). These numbers are the total hybridized disintegrations per min per culture.

**TABLE II**

| Effect of cordycepin on newly synthesized globin mRNA nucleotide sequences |
|---|
| MFL cells were incubated at 3.3 x 10⁶ cells/ml; 5 x 10⁶ cells were used in the 30-min experiment and 10⁶ cells in the 6-min experiment. After 75 min in culture, cordycepin or adenosine was added to a final concentration of 20 µg/ml; 30 min later [3H]uridine, [3H]guanosine, and [3H]cytidine were added (see Materials and Methods), the final concentration of each being 400 µCi/ml for the 30-min experiment and 200 µCi/ml for the 6-min experiment. Cordycepin or adenosine concentrations were maintained at 20 µg/ml by adding an appropriate amount of the unlabeled nucleoside (adenosine or cordycepin) when the labeled nucleosides were added. Isolation of total cell RNA and determination of total RNA and of radioactive globin mRNA nucleotide sequences were made as in Table I. |
| **TABLE III**|

| Effect of cordycepin on newly synthesized total RNA and globin mRNA sequences |
|---|
| MFL cells (10⁶) were incubated in 1 ml of growth medium for 75 min, at which time cordycepin or adenosine was added. The cells were incubated an additional 30 min, and then [5,6-3H]uridine (200 µCi/ml) and [3H]amino acids (2 µCi/ml) were added. After 60 min of labeling, 0.1 ml of cells was removed and trichloroacetic acid-precipitated to determine the uridine and amino acid incorporation. The remainder of the cultures was used to isolate total cell RNA, which was hybridized to unlabeled globin cDNA as described (Ross, 1976). The RNase backgrounds (per cent RNase-resistant disintegrations per min in the absence of cDNA) ranged from 0.06 to 0.13 in this experiment. The background for each RNA sample has been subtracted to yield the percentages of hybridization. |
| **TABLE IV**|

| Treatment (20 µg/ml) | Amino acid incorporation | Total RNA | Globin mRNA |
|---|---|---|---|
| Cordycepin concentration | Acid precipitable | Per cent control | Acid precipitable | Per cent control | Total | Per cent control |
|---|---|---|---|---|---|---|
| 0 | 45.4 | 100 | 4.2 | 100 | 13.4 | 100 |
| 0.2 | 45.8 | 100 | 3.6 | 86 | 10.4 | 78 |
| 0.4 | 42.6 | 93 | 2.8 | 67 | 7.4 | 56 |
| 0.8 | 42.8 | 94 | 2.4 | 57 | 3.6 | 27 |
| 1 | 42.4 | 93 | 1.6 | 38 | 2.3 | 17 |
| 2 | 40.4 | 89 | 1.2 | 28 | 1.5 | 11 |

"Cold trichloroacetic acid-precipitable disintegrations per min.

Determined by hybridization to unlabeled globin cDNA as previously described (Ross, 1976). These numbers are the total hybridized disintegrations per min per culture.

**FIG. 1.** Effect of cordycepin on [3H]uridine and [14C]-amino acid incorporation by mouse fetal liver cells. 14-day MFL cells (10⁹/ml) were incubated for 75 minutes as described (Ross, 1976); at that time (time = 0 min) [3H]uridine and a [14C]-amino-acid mixture (Scharz/Mann) were added, each to a final concentration of 20 µCi/ml. Twenty minutes later unlabeled adenosine or cordycepin was added to a final concentration of 20 µg/ml. At each time point duplicate 0.1 ml aliquots were trichloroacetic acid-precipitated as described (Ross, 1976). O-O, adenosine; •-•, cordycepin. A, trichloroacetic acid-precipitable [3H] disintegrations per min; B, trichloroacetic acid-precipitable [14C] disintegrations per min.
markers (arrows), and the material was then counted directly after dropwise by gravity. The absorbance at 260 nm of each fraction was measured to determine the positions of the internal ribosomal RNA sequences. Although these results do not unequivocally distinguish between reduced synthesis or accelerated degradation of the mRNA sequences, the data strongly support the interpretation that cordycepin inhibits mRNA transcription. This conclusion is consistent with the fact that cordycepin triphosphate inhibits transcription in vitro by prokaryotic RNA polymerases (Shigeura and Boxer, 1964; Maale et al., 1975) and by mammalian cell RNA polymerase II, either with purified DNA as a template or in isolated nuclei (Maale et al., 1975; Desrosiers et al., 1976). Cordycepin also inhibits transcription from mitochondrial DNA in intact cells (Hirsch and Penman, 1974).

A major conclusion from these studies is that experiments with cordycepin in intact cells must be interpreted cautiously. Previous studies demonstrated that cordycepin inhibited both polyadenylation and the appearance of newly synthesized mRNA in polysomes, and it was concluded that polyadenylation was very likely required for mRNA processing and/or transport. This conclusion was strengthened by the observation that hRNA synthesis was either unaffected or only slightly reduced by cordycepin. The data presented here demonstrate that cordycepin inhibits globin mRNA transcription and/or accumulation when the labeling times are as brief as or briefer than those in the above cited experiments. Therefore, the inhibition of polysomal mRNA might be due to inhibition of mRNA transcription, rather than inhibition of polyadenylation.

Three additional factors relevant to this point should be mentioned. 1) Since it exerts multiple effects in mammalian cells, cordycepin might inhibit the accumulation of polysomal mRNA by a combination of effects. For example, when HeLa cells were pulse-labeled for 7.5 min and then incubated (chased) with either actinomycin or actinomycin plus cordycepin, the quantity of radioactive polysomal mRNA was reduced by 70% in the actinomycin plus cordycepin cells, as compared with actinomycin alone (Adesnik et al., 1972). When the labeling time was 20 min, so that a greater proportion of the nuclear mRNA sequences was more completely processed, there was little, if any, reduction of labeled polysomal mRNA with cordycepin (Penman et al., 1970). These experiments provide good evidence that cordycepin blocks transport of preformed (and, presumably, incompletely processed) nuclear mRNA sequences to the cytoplasm. 2) Our conclusions are based on the assumption that the effect of cordycepin on mRNA synthesis is a general one, i.e. that it inhibits most, if not all, mRNA's. A major asset of the cDNA hybridization assay is the ability to detect newly synthesized (radioactive) mRNA sequences by a specific method that is independent of general structural features, such as the poly(A) or the cap. However, only two mRNA's (for α- and β-globin) have been assayed so far, and there is no proof that total mRNA transcription is inhibited by cordycepin. Nevertheless, there are no known structural features of globin mRNA that would promote selective inhibition by cordycepin. In most respects the properties of globin mRNA are similar to those of other mRNA's (Gould and Hamlyn, 1973; Lim and Canellakis, 1970; Burr and Lingrel, 1971; Perry and Scherrer, 1975; see Dayhoff, 1972, for the primary structures of adult mouse globins). Therefore, there is no reason to suspect that the inhibition of globin mRNA synthesis by cordycepin is unique. The in vitro experiments support this assumption since cordycepin triphosphate is a potent inhibitor of transcription of total DNA by RNA polymerase II (Maale et al., 1975; Desrosiers et al., 1976). 3) We have not investigated the number of 3'-terminal adenylate residues or the binding to affinity columns (e.g. oligo(dT)-cellulose) of RNA from cordycepin-treated cells. Our experiments were concerned solely with the effect of cordycepin on the heteropolymeric portion of globin mRNA molecules and their precursors. Experiments are in progress to determine whether the globin-specific RNA transcribed in the presence of cordycepin contains poly(A) or oligo(A) (Mendecki et al., 1972).

**DISCUSSION**

Previous investigations revealed that cordycepin inhibited the appearance of newly synthesized, polyadenylated mRNA molecules. However, these studies did not exclude the possibility that the analog was blocking both polyadenylation and structural gene transcription because the cordycepin effect was evaluated in terms of the quantity of total polyadenylated RNA being made. The inhibitory effect might have resulted from the following: 1) inhibition of polyadenylation of mRNA; 2) inhibition of transcription of structural genes; or 3) a combination of the above. The novel aspect of our study is that we have directly determined the effect of cordycepin on the appearance of the heteropolymeric portions of specific mRNA's. This approach permitted us to monitor more directly the effect of cordycepin on gene transcription.

These experiments demonstrate that cordycepin inhibits the transcription and/or accumulation of globin mRNA nucleotide sequences under conditions in which amino acid incorporation is not appreciably reduced. This effect is observed with labeling times as short as 6 min, and the per cent inhibition of total RNA synthesis is less than that of the globin mRNA sequences. Although these results do not unequivocally distinguish between reduced synthesis or accelerated degradation of the mRNA sequences, the data strongly support the interpretation that cordycepin inhibits mRNA transcription. This conclusion is consistent with the fact that cordycepin triphosphate inhibits transcription in vitro by prokaryotic RNA polymerases (Shigeura and Boxer, 1964; Maale et al., 1975) and by mammalian cell RNA polymerase II, either with
The data of Table III indicate that some RNA continues to be synthesized in the presence of relatively large doses of cordycepin. Similar results are observed in a variety of cell types (Siev et al., 1969; Penman et al., 1970; Darnell et al., 1971a; Mendecki et al., 1972; Nakazato et al., 1974; Desrosiers et al., 1976; Fig. 2, closed circles; see also Glazer, 1976). This RNA might be transcribed by the three major RNA polymerases under conditions where they are not 100% inhibited. Alternatively, there might exist a fourth class of RNA polymerase that is sensitive to α-amanitin (Zylber and Penman, 1971; Jackson and Sugden, 1972; Reeder and Roeder, 1972; Price and Penman, 1972; Wallace and Kates, 1972; Schwartz et al., 1974; Weinmann and Roeder, 1974; Weinman et al., 1974; Ben-Zeev et al., 1976) and insensitive (or relatively insensitive) to cordycepin (Fig. 2). This hypothesis can be tested experimentally since it predicts the existence of a polymerase that will be sensitive to α-amanitin but resistant to cordycepin triphosphate when assayed in vitro.

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