Inhibitory Effect of Agents Altering the Structure of DNA on the Synthesis of Pyrimidine Deoxyribonucleotides in Bacteriophage T4 DNA Replication*

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(Received for publication, February 14, 1977)

Bacteriophage T4-infected cells exhibit a remarkable control over the synthesis of pyrimidine deoxyribonucleotides in vivo (1-8). In turn, the rate of deoxyribonucleotide synthesis is the limiting factor in DNA replication (5). The ratio of Thy/ HmCyto deoxyribonucleotides formed exactly mirrors the ratio of these nucleotides in T4 DNA, thus is 2:1 (1). This precise regulation is maintained even on infection by Dna− mutants until the accumulating deoxyribonucleotides reach exceedingly high levels. Therefore during T4 DNA replication in vivo, the regulation of deoxyribonucleotide biosynthesis does not appear to be primarily mediated by feedback control. Because of our earlier studies suggesting a direct role of the deoxyribonucleotide-synthesizing enzymes in DNA replication (6-8), comparable experiments from other laboratories (9-11), and new evidence of a channeled synthesis of deoxyribonucleotides (12), we have proposed that the regulation is intrinsic in the structure and activity of a complex of enzymes (1). Since the complex of enzymes carrying out polymerization reactions (13) and the complex-forming deoxyribonucleotides appear to be interacting systems (8), the DNA template itself might be an integral part of both. Because deoxyribonucleotide synthesis so accurately reflects the ratio of nucleotides found in the DNA template, the question may be posed whether or not the DNA itself has a role in this regulation. If so, altering its structure might affect not only DNA synthesis but the in vivo activities of the enzymes forming deoxyribonucleotides. To test such a possibility, we have used various agents known to alter DNA, using the in vivo assay described...
previously (1, 2, 5). The present study shows that such agents do, indeed, have a profound effect on the regulation of deoxyribo- nuclease biosynthesis, apparently without affecting the in vitro activities or the induction of the phage-induced early enzymes.

**EXPERIMENTAL PROCEDURES**

**Materials—Strains of Escherichia coli and mutants of bacterio- phage T4 used in this study were those described earlier (1, 4). Phage T4px, a segregant of T4x, was kindly provided by Dr. John Drake, University of Illinois, Urbana. Bacteriophage were propagated and purified as described (1). Mitomycin C and ethidium bromide were from Sigma Chemicals, methylethanesulfonate was from Eastman Kodak, and actinomycin D was a generous gift of Merck, Sharp and Dohme.

**Infection by Phage**—The host was E. coli strain GM201 (thyA deoB), a low thymine-requiring mutant of strain B from this laboratory (1). The conditions of infection were as described, with a multi- plicity of infection of 8 (1). In some experiments, the completeness of infection was verified by determining the activities of dCMP hydroxymethylase and dTMP synthetase as outlined earlier (5). L-Tryptophan was added to the adhesion medium (1) at 100 μg/ml in all experiments, as well as to the T4x" control.

**Ultraviolet Irradiation**—A 0.75-ml aliquot of a suspension of purified phage T4px (3 × 10⁹ plaque-forming particles/ml) in a 3-cm plastic Petri dish agitated on an eccentric rotary shaker was irradiated under a 15-watt mercury vapor germicidal lamp adjusted to a dose rate of 10 ergs/mm²/min with a shortwave ultraviolet dosimeter (Ultraviolet Products, model J225). After infection by ultraviolet-irradiated phage, the cultures were always manipulated and assayed in darkened rooms to prevent possible photoreactivation repair. However, control experiments testing for tritium release activity showed that such repair was always less than 5% in the presence of bright fluorescent lamps (2).

**Inactivation of Phage by Methyl Methanesulfonate**—Phage T4px suspended at about 10¹⁰ plaque-forming particles/ml of 50 mM Tris- HCl, pH 8, was treated at 37°C with 80 mM methyl methanesulfonate for 5 min (1). The treated phage suspension was diluted 10-fold into Fraser’s medium (1) and the phage collected by centrifugation. The pellet was taken up in Fraser’s medium and titered. Ninety-nine percent of the phage particles had been inactivated compared to a control carried through the same manipulations without the alkylat- ing reagent.

**Enzyme Assays**—Thymidylate synthetase (5, 15) and dCMP hydroxymethylase (5) were assayed in sonic extracts by following the release of tritium from [5-3H]UMP and [5-3H]CMP, respectively. Dihydrofolate reductase was assayed by a method similar to that described by Warner and Lewis (16).

**Tritium Release Assay, Thy/HmCyt Ratios, and DNA synthesis**—The release of tritium from 5-labeled pyrimidine precursors, the ratio of Thy/HmCyt deoxynucleotides synthesized via the de novo pathway, and DNA synthesis were measured as previously described (1, 5). The release of tritium from administered [5-3H]uridine begins at about 5 min, increases in rate exponentially until about 20 min, and then reaches a constant rate. For a discussion of the significance of these kinetic data see Refs. 5 and 8. The results in Fig. 3 show that proflavine added 10 min after infection by phage T4D inhibits not only DNA synthesis but also tritium release activity. At all concentrations, DNA synthesis was more sensitive than tritium release activity. At 20 μg/ml, the acridine dye gave almost total inhibition of both activities.

The inhibition of tritium release activity resulting from the addition of proflavine at 10 min after infection cannot result from an effect on protein synthesis. Thus, chloramphenicol added at 10 min to inhibit protein synthesis had little effect on the rate of tritium release or of DNA synthesis (5, 8, 17). The inhibition of tritium release also is not caused by a block of DNA synthesis per se since DNA-negative mutants show no inhibitory effect on tritium release activity (1, 5). Further- more, the results in Fig. 3 show that proflavine still inhibits tritium release in a culture infected by an amber mutant of gene 43, the structural gene for T4 DNA polymerase. That is, DNA synthesis is not related to the inhibitory effect of profla- vine on the synthesis of dTMP and HmCyt. It is conceivable that the inhibition of tritium release activity by proflavine could result from a direct interaction with the enzymes in the pyrimidine deoxyribonucleotide biosynthetic pathways. At 20 μg/ml, the agent had no effect on the activity of dCMP hydroxymethylase, thymidylate synthetase, or dihy- 

**RESULTS**

**Effect of Intercalating Agents on Release of Tritium from Administered [5-3H]Uridine in T4-infected Cultures**—The pathway of conversion of uridine to dTMP and HmCyt is shown in Fig. 1. In normal infection tritium release from administered [5-3H]uridine begins at about 5 min, increases in rate exponentially until about 20 min, and then reaches a constant rate. For a discussion of the significance of these kinetic data see Refs. 5 and 8. The results in Fig. 3 show that proflavine added 10 min after infection by phage T4D inhibits not only DNA synthesis but also tritium release activity. At all concentrations, DNA synthesis was more sensitive than tritium release activity. At 20 μg/ml, the acridine dye gave almost total inhibition of both activities.

**Fig. 1.** The pathways converting labeled uridine to HmCyt and dTMP and thence to DNA in T4-infected cultures. The reactions by Warner and Lewis (16) from position 5 of administered uracil compounds are indicated (from Ref. 1).
Structural Role of T4 DNA in Deoxyribonucleotide Synthesis

FIG. 3. The inhibitory effect of proflavine on tritium release activity after infection by a mutant in the structural gene for T4 DNA polymerase (amB22). The concentration of proflavine was 20 μg/ml. See legend to Fig. 2 for procedure.

drofolate reductase when assayed in vitro in sonic extracts of infected cells (data not presented).

In order to determine whether proflavine exerts a differential effect on the synthesis of dTMP and HmdCMP, the ratio of Thy/HmCyt deoxyribonucleotides synthesized de novo was measured in a culture treated at 10 min after infection by proflavine at a concentration which inhibited tritium release from administered [5-3H]uridine by 50%. At 15, 25, 35, and 45 min after infection the ratios were 2.0, 2.4, 2.8, and 4.4, respectively. Thus proflavine appeared to inhibit the synthesis of HmdCMP somewhat more effectively than dTMP (but see "Discussion").

Other intercalating agents also were shown to inhibit the release of tritium from administered [5-3H]uridine. Ethidium bromide at a final concentration of 50 μg/ml reduced tritium release activity by about 80% and completely inhibited DNA synthesis (Fig. 4). Actinomycin D was studied in sucrose-plasmolyzed cells (6) because of the relative impermeability of Escherichia coli to the drug. Low concentrations of actinomycin D inhibited both tritium release and DNA synthesis (Fig. 5). Preincubation of the plasmolyzed cells with the drug appeared to increase the inhibitory effect.

Effect of Mitomycin C on Deoxyribonucleotide Synthesis—The T4 gene x product has been considered to function in the repair of DNA damaged by ultraviolet light (18) and by alkylating agents (19). As shown by Shimizu and Sekiguchi (19) and as confirmed in Fig. 6, mitomycin C, at 3 μg/ml, profoundly inhibits DNA synthesis after infection with the T4x⁻ segregant, T4px. With T4x⁺ phage (T4D) however, this drug has only a comparatively small effect.

The results in Fig. 7 compare the effects of mitomycin C on DNA synthesis and tritium release after T4x⁻ infection. At concentrations that inhibit DNA synthesis greater than 90%, the rate of tritium release was inhibited by only about 35%. As stated in the previous section, the inhibition of DNA synthesis itself has no effect on tritium release (5). Nonspecific inhibition of enzymes in the pyrimidine deoxyribonucleotide-synthesizing pathway should be the same on infection by either T4x⁻ and T4x⁺. Several control experiments with wild type phage have shown that comparable concentrations of mitomycin C inhibit the rate of tritium release by less than 10% (not shown). Therefore, the additional inhibition of tritium release activity after T4x⁻ infection is considered to result from a specific effect of the drug on the DNA template. To rule out the
Fig. 7. Inhibition of DNA synthesis and tritium release activity by mitomycin C in a T4x- infected culture. Except where indicated the procedure was the same as given in Fig. 2. The temperature was 37°. The rates of DNA synthesis and tritium release between 30 and 40 min are given as percentages of the control rates. Note that higher concentrations of mitomycin C were required in this experiment than in the experiment shown in Fig. 6, apparently because of a lower potency of the particular batch. Other samples of mitomycin C (all from Sigma with different lot numbers) produced the same level of inhibition at about one-seventh the concentration.

Table I

| Phage     | Mitomycin C added | Thy/HmCyt ratios (min after infection) |
|-----------|-------------------|---------------------------------------|
|           |                   | 15 | 25 | 35 | 45 |
| T4x+      | -                 | 1.7 | 1.8 | 1.8 | 1.9 |
| T4x-      | +                 | 2.0 | 1.9 | 2.2 | 2.2 |
|           | +                 | 2.5 | 3.5 | 3.9 | 5.4 |

Fig. 8. Synthesis of dTMP and HmdCMP derivatives after the addition of mitomycin C to T4x- and T4x- infected cells. Mitomycin C was added at 10 min to yield 3 μg/ml. The ratio values and tritium release data obtained as described in Table I were used to calculate the quantities of deoxyribonucleotide synthesized.
modify the structure of the DNA template by a variety of means. Such techniques include irradiation with ultraviolet light, treatment with methyl methanesulfonate, and the addition of mitomycin C. These agents act by decreasing the efficiency of DNA synthesis, thus preventing the production of viral particles.

In addition to the decrease in tritium release activity, there was an increase in the ratio of Thy/HmCyt deoxyribonucleotides synthesized in infected cultures with irradiated or methyl methanesulfonate-treated phage. The synthesis of dTMP and HmdCMP derivatives in infected cells was inhibited (20, 21).

The results of this study clearly show that agents which modify the structure of the DNA template by a variety of mechanisms inhibit not only phage T4 DNA replication but also the de novo synthesis of the pyrimidine deoxyribonucleotides. Two types of effects have been observed. In the first (proflavine treatment or ultraviolet irradiation) both dTMP and HmdCMP synthesis were inhibited. In the second (mitomycin C) HmdCMP synthesis was immediately and specifically inhibited.

Since each of the agents tested inhibited DNA synthesis more effectively than the pyrimidine deoxyribonucleotide synthesis, the question might be raised as to whether or not the resulting accumulation of the pyrimidine deoxyribonucleoside triphosphates causes a secondary feedback inhibition of the de novo pathway. However, as shown earlier, blockage of DNA replication by Dnα− mutants has no effect on the combined rates of synthesis of dTMP and HmdCMP (1, 5; see the introduction). Finally, the inhibition of pyrimidine deoxyribonucleotide synthesis by proflavine occurred even with cells infected by a Dnα− mutant (Fig. 3).

A number of findings provide evidence that these agents act by altering the input T4 DNA and not by a direct action on the enzymes forming the deoxyribonucleotides. (a) None of the agents, as employed, decreased the induction or activities of dCMP hydroxymethylase and dTMP synthetase. (b) Addition of mitomycin C, proflavine, ethidium bromide, or actinomycin D after all of the proteins required for DNA synthesis had been formed, still inhibited tritium release from administered [5-3H]uridine. (c) That mitomycin C brings about its inhibitory action on tritium release specifically by interaction with DNA was shown by the susceptibility of T4x− but not T4x+ phage to this agent (Figs. 6 and 8). Inasmuch as mitomycin C damage of DNA is repaired by the action of the product of gene x (21, 22), (d) The wide range of the DNA agents employed and their application by treatment of the infected cells or by modification of the phage itself argues against an interaction on systems other than DNA.

Of the various agents tested, mitomycin C appeared to cause the most specific effect on deoxyribonucleotide synthesis. Mitomycin C causes an immediate decrease and an eventual cessation in the synthesis of HmdCMP in cells infected by T4x− (Fig. 8). The synthesis of dTMP derivatives is not decreased nor elevated. If the block were at dCMP hydroxymethylase, the accumulating dCMP would be diverted to dUMP by the action of dCMP deaminase and dTMP would be increased by the action of dCMP deaminase and dTMP synthetase. All experimental conditions are described in the legend to Fig. 9.

Fig. 11 (right). Synthesis of dTMP and HmdCMP derivatives after infection with ultraviolet irradiated T4x− phage. The phage were exposed to a dose of 300 ergs/mm2. Thy/HmCyt ratios and tritium release data obtained as described in Table I were used to calculate the amounts of deoxyribonucleotide synthesized.

**DISCUSSION**

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about 33%. This analysis is based on the conclusion made in a previous paper that on infection by T4 DNA- mutants product inhibition of dCMP deaminase occurs with time and the resulting dCMP is siphoned into dUMP synthesis by the deaminase so that dTMP synthesis decreases by 33% (1).

Therefore, we suggest that mitomycin C through its action on DNA causes a block prior to the formation of dCMP. The most reasonable site in the complex of enzymes synthesizing deoxyribonucleotides is at T4 ribonucleoside diphosphate reductase since this enzyme is involved in the synthesis of all four of the deoxyribonucleotides.

Treatment of infected cultures with proflavine or exposure of phage before infection to ultraviolet irradiation produces similar effects on the synthesis of thymine and HmCyt deoxyribonucleotides. That is, both agents show a prompt inhibition of tritium release from administered [5-3H]uridine. Both treatments ultimately bring about a greater inhibition of HmdCMP synthesis than of dTMP synthesis. Ultraviolet irradiation causes the Thy/HmCyt ratio to rise to about 3 by 25 min (Fig. 11), and proflavine produces an increase by 35 min. While the ratios increase in these cases, the overall rates of dTMP synthesis actually decrease as compared to an untreated, infected culture. Nevertheless, the increased ratio with proflavine appears to mimic the process occurring on infection by DNA mutants as outlined in the last paragraph. Again, these agents are likely to act at the level of ribonucleoside diphosphate reductase, but with less specificity in terms of UDP and CDP reduction than shown by mitomycin C.

It is relevant that the various agents inhibiting pyrimidine deoxyribonucleotide synthesis interact with DNA in different ways. Their actions may be reviewed briefly. Proflavine, ethidium bromide, and actinomycin D intercalate between the adjacent stacked base pairs of the DNA double helix (23–25). Mitomycin C, a bifunctional alkylating agent, forms interstrand cross-links between guanine residues (26, 27). Kersten and Kersten have reviewed the literature on the actions of mitomycin C (25). Methyl methanesulfonate has been shown to methylate double-stranded DNA primarily at position 7 of guanine residues (28). The main types of damage to the DNA induced by ultraviolet irradiation is the formation of cyclobutane dimers between adjacent pyrimidine residues, primarily thymine, in the same chain of the DNA double helix (29) (see Ref. 30 for other lesser changes).

Phage DNA might interact with the deoxyribonucleotide-synthesizing enzymes in several ways. A direct interaction between DNA and the enzymes themselves may occur. Since DNA agents inhibit the synthesis of dTMP and HmdCMP even with DNA- mutants, i.e., in the absence of replication, and since direct modification of the phage also causes inhibition, it is clear that this interaction is with the input template. Evidence has been presented earlier that the enzymes synthesizing deoxyribonucleotides for DNA replication function in vivo as components of a multi-enzyme complex (1, 5, 8), the products being channeled directly into the replication apparatus (12). The present study suggesting that the DNA template itself is a necessary component of this complex is in keeping with these earlier proposals. Alternatively, the DNA template may directly interact only with T4 DNA polymerase. Phage T4 DNA polymerase is required for maximal activity of the deoxyribonucleotide-synthesizing enzymes in vivo (5, 8). Structural changes in the DNA template could conceivably affect conformation of a bound polymerase which would in turn affect the activity of the other enzymes in the complex or might prevent normal complex formation.

The precise agreement between the ratio of dTMP/HmdCMP biosynthesis and the 2:1 Thy/HmCyt ratio in T4 DNA may suggest that the DNA sequence controls the process. However, this idea would seem to be untenable since regulation of the ratio still occurs in the absence of DNA synthesis (1) and presumably in the absence of movement of the DNA template in relation to the replication complex. Conceivably DNA could have an allosteric action on the enzyme complex, the synthesis of dTMP and HmdCMP (and the purine derivatives; see Ref. 1) being biased by the base sequences at the growing points, and an average value would be seen in a mixed population of infected cells.

An alternative role for DNA involving the integral membrane proteins formed by genes 59 and 52 (31, 32) also may be considered. In mutants (DNA delay) lacking these proteins T4 DNA synthesis is greatly decreased (33, 34). Huang and Buchanan have shown that these proteins are bound by DNA-cellulose columns (35), and the suggestion has been made (34, 35) that these products may link the replicating complex with the membrane (36). In this regard, McCarthy et al. have shown that DNA-delay mutants decrease the number of growing points (37). Should such a function be verified, an alteration of the DNA template structure by DNA agents might decrease the binding of the deoxyribonucleotide-synthesizing-replication complex by the membrane. Ultimately DNA could play roles both in linkage to the membrane and in maintenance of the precise structure of the complex of synthetic enzymes.

The concept of a structural role for DNA in an enzyme reaction is not novel. Thus, the recBC enzyme (exonuclease V) of E. coli is a DNA-dependent ATPase (38). Certainly DNA has been implicated as having a role in replication other than as the primer-template (39, 40). It is particularly pertinent that Alberts and co-workers have shown that the complex formed from the products of the T4 dna genes 44 and 62 stimulated by gene 45 protein, displays a DNA-dependent ATP → ADP + P, hydrolysis (41). Morris et al. also have reported that the dna gene 41 product catalyzes a GTP → GDP + P, reaction which is dependent on single-stranded DNA (13). The present study provides evidence that DNA plays an integral role in a system which on the surface would not appear to require so complex a molecule to maintain its structure or regulation.

The precise regulation of deoxyribonucleotide biosynthesis may be an important factor in insuring the fidelity of DNA replication (1). If so, then the biochemical basis for the mutagenic effect of certain agents which modify the structure of the DNA template should be explained in part by their effect on deoxyribonucleotide biosynthesis.

Acknowledgment—We are very grateful to Therese Ruettinger for carrying out some of the later experiments.

Note Added in Proof—Goodman and co-workers (42, 43) have described the inhibitory effects of DNA intercalating agents on the activities of T4 DNA polymerases. With wild type, mutator, and antimutator polymerases, these agents had little effect on the misincorporation frequencies of 2-aminopurine deoxyribonucleotide, the analogue of dAMP, and on
the editing efficiencies of the enzymes although they showed large differential effects on nucleotide incorporation rates.

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Inhibitory effect of agents altering the structure of DNA on the synthesis of pyrimidine deoxyribonucleotides in bacteriophage T4 DNA replication.
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J. Biol. Chem. 1977, 252:6031-6037.

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