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Apurinic/apyrimidinic endonucleases in repair of pyrimidine dimers and other lesions in DNA

(DNA repair/nick translation)

HUBER R. WARNER*, BRUCE F. DEMPLE, WALTER A. DEUTSCH†, CAROLINE M. KANE, AND STUART LINN

Department of Biochemistry, University of California, Berkeley, California 94720

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ABSTRACT **The characteristics of the nicks (single-strand breaks) introduced into damaged DNA by *Escherichia coli* endonucleases III, IV, and VI and by phage T4 UV endonuclease have been investigated with *E. coli* DNA polymerase I (DNA nucleotidyltransferase). Nicks introduced into depurinated DNA by endonuclease IV or VI provide good primer termini for the polymerase, whereas nicks introduced into depurinated DNA by endonuclease III or into irradiated DNA by T4 UV endonuclease do not. This result suggests that endonuclease IV nicks depurinated DNA on the 5′ side of the apurinic site, as does endonuclease VI, whereas endonuclease III has a different incision mechanism. T4 UV endonuclease also possesses apurinic endonuclease activity that generates nicks in depurinated DNA with low priming activity for the polymerase. The priming activity of DNA nicked with endonuclease III or T4 UV endonuclease can be enhanced by an additional incubation with endonuclease VI and, to a lesser extent, by incubation with endonuclease IV. These results indicate that endonuclease III and T4 UV endonuclease (acting upon depurinated and irradiated DNA, respectively) generate nicks containing apurinic/apyrimidinic sites at their 3′ termini and that such sites are not rapidly excised by the 3′ → 5′ activity of DNA polymerase I. However, endonuclease IV or VI apparently can remove such terminal apurinic/apyrimidinic sites as well as cleave on the 5′ side of the unnicked sites. These results suggest roles for endonucleases III, IV, and VI in the repair of apurinic/apyrimidinic sites as well as pyrimidine dimer sites in DNA. Our results with T4 UV endonuclease suggest that the incision of irradiated DNA by T4 UV endonuclease involves both cleavage of the glycosylic bond at the 5′ half of the pyrimidine dimer and cleavage of the phosphodiester bond originally linking the two nucleotides of the dimer. They also imply that the glycosylic bond is cleaved before the phosphodiester bond.**

It has been generally assumed that repair of pyrimidine dimers introduced into DNA by UV irradiation occurs by a nucleotide excision mechanism initiated by a specific endonuclease (1). Such endonucleases are known as UV endonucleases, and have been found in various organisms, including *Escherichia coli* (2, 3), *Micrococcus luteus* (4), and bacteriophage T4 (5). The specific incision generates a nick (single-strand break) consisting of a 3′-hydroxyl terminus and a 5′-phosphoryl terminus (6, 7), but the exact nature and location of this nick have not been elucidated. If it is located near the 5′ side of the dimer, the dimer could then be removed by an exonuclease activity such as *E. coli* exonuclease VII (8) or the 5′ → 3′ exonuclease of DNA polymerase I (DNA nucleotidyltransferase) (9), and repair could be completed by DNA polymerase and DNA ligase activities.

The repair of DNA containing apyrimidinic or apurinic (AP) sites is also initiated by incision of the DNA by a specific endonuclease (10). Such AP sites may be generated either by DNA glycosylases (11) or by spontaneous depurination (12). In *E. coli*, at least three AP site-specific endonucleases have been discovered. The best studied of these is the endonuclease activity associated with exonuclease III (13), which is also known as endonuclease VI (14). The others are endonuclease IV, which is present in much smaller amounts than endonuclease VI (15), and endonuclease III, which attacks DNA containing AP sites as well as DNA damaged by a variety of agents (16, 17). Neither of the latter two activities is associated with exonucleases.

Evidence indicates that the incision made by endonuclease VI occurs on the 5′ side of the AP site and generates 3′-hydroxyl and 5′-phosphoryl termini (see Fig. 7). This mode of attack has been elucidated by studying the action of various enzymes on the termini generated (14, 18, 19). The nick produced by endonuclease III has not been so well characterized; studies with alkaline phosphatase and polynucleotide kinase suggest that endonuclease III nicks on the 3′ side of the AP site (17), but the 3′ terminus generated by endonuclease III has not directly been shown to contain the AP site. The nick generated by endonuclease IV has apparently not been studied.

E. coli DNA polymerase I catalyzes strand elongation and either nick translation or strand displacement when presented with an appropriately nicked primer-template (20). The priming activity of these nicks requires a 3′-hydroxyl primer terminus, whereas the nature of the 5′ terminus is relatively unimportant. In this paper we have used the specificity of *E. coli* DNA polymerase I for an appropriate primer terminus to characterize the nature of the nicks generated by the various *E. coli* AP endonucleases and by the T4-induced UV endonuclease.

EXPERIMENTAL PROCEDURES

Materials. *E. coli* DNA polymerase I (6000 units/mg) was purchased from New England BioLabs; 1 unit of activity is the amount of enzyme necessary to convert 10 nmol of total deoxyribonucleotides to an acid-insoluble form in 30 min at 37°C. *E. coli* endonucleases III and VI, T4 UV endonuclease, and *Neurospora crassa* endonuclease were purified as described (17, 21–23). Endonuclease IV was a gift from Tomas Lindahl (University of Göteborg, Sweden). One unit of activity for all of the endonucleases is defined as 1 fmol of nicks produced per min at 37°C. [^{3}H]dATP (9 Ci/mmol; 1 Ci = 3.7×10^{10} becquerels) was obtained from Schwarz/Mann (Orangeburg, NY), and unlabeled deoxyribonucleoside 5′-triphosphates were from Sigma. Phage PM2 DNA labeled with [*methyl*-^{3}H]thymidine was prepared as described (24), with a specific activity of 20–30 cpm per fmol of duplex circles.

Preparation of Damaged DNAs. PM2 DNA (0.2 mM in nucleotide) was partially depurinated by heating at 70°C at pH 5.2 for 10 or 15 min (17) to produce up to two AP sites per DNA circle. PM2 DNA (0.2 mM) was irradiated with UV light at an average dose of up to 25 J/m^2 to produce up to two pyrimidine dimers per DNA circle. PM2 DNA was treated with 10 μg of osmium tetroxide per ml for 30 min as described (17).

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Abbreviation: AP, apurinic.

* Permanent address: Department of Biochemistry, University of Minnesota, St. Paul, MN 55108.
† Present address: Department of Biochemistry, Louisiana State University, Baton Rouge, LA 70803.

Incision of DNA by AP and UV Endonucleases. Depurinated PM2 DNA was incubated at a final concentration of 0.04 mM nucleotide with AP endonuclease in 10 mM $MgCl_2$/25 mM Tris·HCl, pH 7.5, at 37°C to nick the DNA at the AP sites. Irradiated PM2 DNA was incubated at a final concentration of 0.04 mM nucleotide with T4 UV endonuclease in 25 mM potassium phosphate buffer (pH 7.5) containing 0.2 M NaCl and 0.08 mg of bovine serum albumin per ml to nick the DNA at dimer sites. In the DNA synthesis experiments, sufficient AP endonuclease or UV endonuclease was added to nick the DNA at all of the AP or dimer sites, respectively. Endonucleases were then inactivated by heating the mixture for 3 min at 70°C before portions were assayed for nicks (24) or DNA synthesis with *E. coli* DNA polymerase I.

DNA Synthesis. Reaction mixtures (225 μl) contained 70 mM potassium phosphate buffer (pH 7.5), 7 mM $MgCl_2$, 90 μM each of dTTP, dGTP, and dCTP, 1.12 μCi of dATP (9 Ci/mmol), 60–75 fmol of PM2 DNA circles, and 0.68 unit of *E. coli* DNA polymerase I. After incubation at 37°C for various times, 50-μl portions were removed and assayed for acid-insoluble radioactivity.

Assay for DNA Nicks. The number of nicks introduced into closed circular PM2 DNA was determined from the amount of DNA retained on a nitrocellulose filter after a short alkaline treatment (24). Unnicked circular DNA renatures and passes through the filter, whereas single-stranded DNA from nicked circles binds to the filter. The absolute number of nicks in the DNA population (n) was then calculated from the number of nicked circles (N_n), by using the equation $n = -N \ln[(N - N_n)/N]$, in which N is the total number of circles present.

RESULTS

Priming Activity of AP Endonuclease Products. Initially we compared the priming activity of *E. coli* DNA polymerase I at the 3′-hydroxyl termini generated by *N. crassa* endonuclease and *E. coli* endonuclease VI. The *Neurospora* enzyme was used as a standard because it generates 3′-hydroxyl and 5′-phosphoryl termini and nicks supercoiled DNA only once, whereas it does not nick circular DNA that is not supercoiled (25, 26). The priming activity of these nicks was similar to that of the nicks generated by *E. coli* endonuclease VI (Fig. 1). This result indicates that the presence of a deoxyribose 5′-phosphate at the 5′ terminus of the nick formed by endonuclease VI has little, if any, effect on the priming activity with *E. coli* DNA polymerase I.

The priming activity of nicks generated by *E. coli* endonuclease IV was also high and comparable to that observed with endonuclease VI in the same experiment (Fig. 2*A*). In contrast, the priming activity of DNA nicked by *E. coli* endonuclease III was only slightly better than that observed with AP DNA that had not been treated with endonuclease (Fig. 2*A*). A 3′-phosphoryl terminus would not be a good primer for DNA synthesis, but previous studies with polynucleotide kinase have indicated that the phosphomonoester group is on the 5′ terminus in a nick generated by endonuclease III (17). These results suggest that the nick generated by endonuclease IV is similar to that generated by endonuclease VI, whereas the 3′ terminus generated by endonuclease III is probably an AP deoxyribose moiety, which has low priming activity with *E. coli* DNA polymerase I. None of these AP endonuclease preparations was able to significantly nick DNA or generate priming sites in DNA that had not first been depurinated (Fig. 2 *B* and *C*).

Priming Activity of T4 UV Endonuclease Products. The properties of the nick generated by T4 UV endonuclease were also investigated; preliminary results of Grossman *et al.* (27) have suggested that incision by *M. luteus* UV endonuclease may involve the combined action of a glycosylase activity and an AP endonuclease activity. Whereas nicks generated by T4 UV endonuclease had some priming activity with DNA polymerase I, the activity was much less than that observed with nicks generated by endonuclease IV or VI, but was comparable to that observed with endonuclease III (Fig. 2). The T4 UV endonuclease was inactive on untreated DNA, and the AP endonucleases were inactive on irradiated DNA. These results indicate that the T4 UV endonuclease specifically nicks sites in irradiated DNA, but these sites have low priming activity with DNA polymerase I. This suggests that T4 UV endonuclease may be generating nicks with AP sites at their 3′ termini.

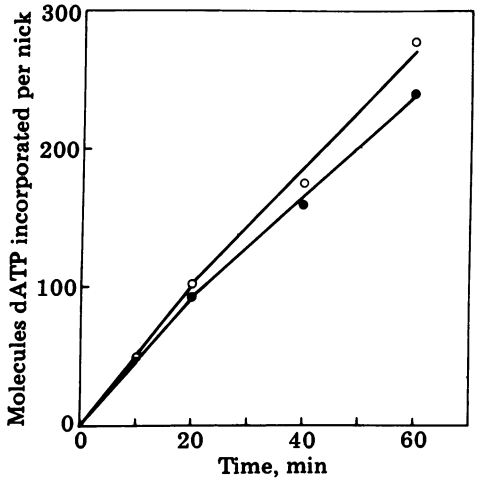

FIG. 1. Priming activity of nicks generated by *N. crassa* endonuclease (○) or *E. coli* endonuclease VI (●). Supercoiled PM2 DNA (150 fmol of circles) was incubated with *N. crassa* endonuclease (7 units) for 10 min at 37°C or it was partially depurinated and incubated with endonuclease VI (12 units) for 10 min at 37°C, then processed. The average number of nicks per molecule of DNA after treatment with *N. crassa* endonuclease was 0.5; after treatment with *E. coli* endonuclease VI, the average number was 0.8.

Enhancement of Priming Activity by Endonucleases IV and VI. When AP sites were first incised with endonuclease III and then this nicked DNA was incubated with endonuclease IV or VI, the priming activity was greatly stimulated (Fig. 3*A*). This indicates that endonucleases IV and VI are able to incise on the 5′ side of an AP site whether it is covalently attached within the interior of a DNA strand or located at the 3′ terminus of a nick.

A similar experiment was carried out with irradiated DNA nicked by T4 UV endonuclease. The priming activity was greatly enhanced by subsequent incubation of the incised DNA with endonuclease VI and enhanced to a lesser extent by endonuclease IV; it was not similarly stimulated by incubation with endonuclease III (Fig. 3*B*). Because treatment of irradiated DNA with endonuclease III, IV, or VI without prior incubation with the T4 UV endonuclease neither nicked the DNA nor increased the priming activity of the DNA (Fig. 2*C*), we interpret these results to indicate that the T4 UV endonuclease does generate AP sites, presumably at the 3′ terminus of the nick.

AP Endonuclease Activity of T4 UV Endonuclease. In experiments in which levels of T4 UV endonuclease were used such that the DNA was not incised at all pyrimidine dimers, we observed that the DNA contained sites that could be incised by endonuclease III, IV, or VI. This observation suggested that under these conditions the T4 UV endonuclease preparation might be generating AP sites that, at least transiently, were remaining unnicked. To confirm this, we compared the rate of nicking of irradiated DNA by T4 UV endonuclease to the rate of nicking by endonuclease III and by T4 UV endonuclease and endonuclease III together (Fig. 4). Endonuclease III alone failed to nick the irradiated DNA, whereas the combination of

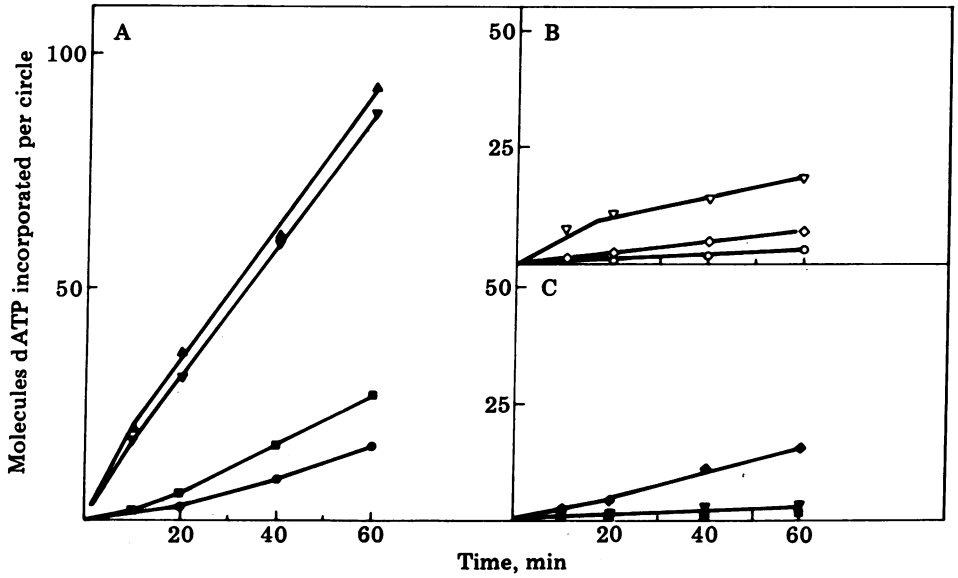

FIG. 2. Priming activity of nicks generated by T4 UV endonuclease and various *E. coli* AP endonucleases. (*A*) Partially depurinated DNA (150 fmol of circles) was incubated with no enzyme (●) or with endonuclease III (■, 55 units) for 30 min or with endonuclease IV (▼, 16 units) or VI (▲, 25 units) for 10 min. (*B*) Untreated DNA (160 fmol of circles) was incubated with no enzyme (○) or with T4 UV endonuclease (◇, 8 units) for 20 min or with endonuclease III (30 units), IV (▽, 20 units), or VI (13 units) for 10 min. The data for endonucleases III and VI overlap or lie between those for T4 UV endonuclease and no enzyme. (*C*) Irradiated DNA (160 fmol of circles) was incubated with no enzyme or with T4 UV endonuclease (◆, 8 units) for 20 min or with endonuclease III (■, 30 units), IV (▼, 20 units), or VI (13 units) for 10 min. The data for endonuclease VI and no enzyme overlap or lie between those for endonucleases IV and III. All incubations were performed at 37°C. The average number of nicks per molecule of DNA after endonuclease treatment was as follows. (*A*) No enzyme, 0.1; endonuclease III, 0.7; endonuclease IV, 0.5; and endonuclease VI, 0.4. (*B*) No enzyme, 0.1; endonuclease III, 0.3; endonuclease IV, 0.2; endonuclease VI, 0.2; and T4 UV endonuclease, 0.3. (*C*) No enzyme, 0.1; endonuclease III, 0.3; endonuclease IV, 0.2; endonuclease VI, 0.1; and T4 UV endonuclease, 1.1.

endonuclease III and T4 UV endonuclease nicked the DNA twice as fast during the first 20 min of the incubation as did the UV endonuclease alone. This confirmed that the T4 UV endonuclease generates internal AP sites which subsequently can be incised either by the T4 UV endonuclease or by the added AP endonuclease.

The presence of unnicked AP sites in irradiated DNA treated with T4 UV endonuclease suggests the possiblity that the T4 *v* gene product acts only as a DNA glycosylase and that the preparations generally used are contaminated with an *E. coli* AP endonuclease. (Such contamination would, in fact, be mandated by the purification of "endonuclease" activity.) The

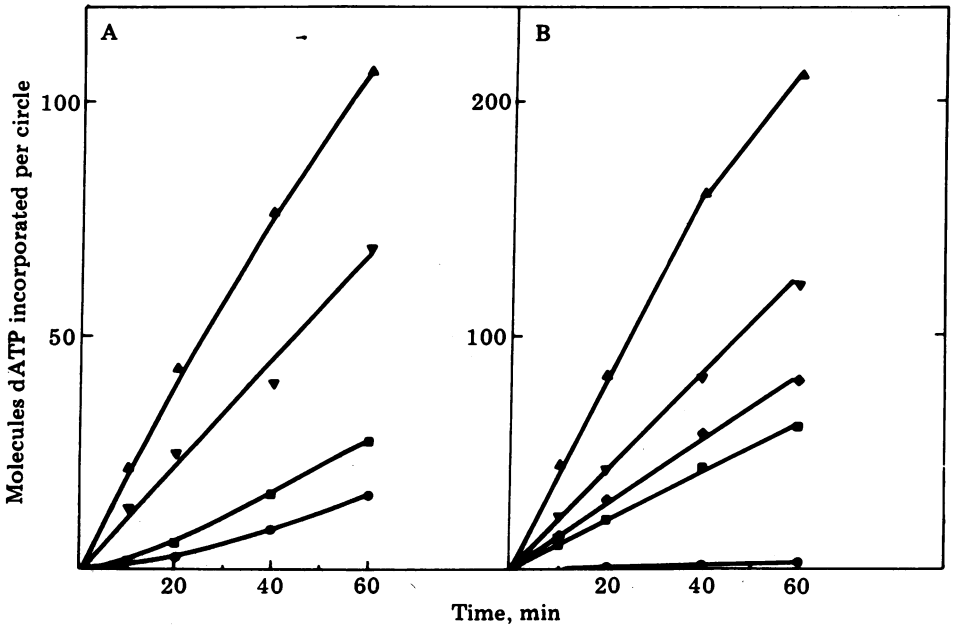

FIG. 3. Enhancement of priming activity by endonucleases IV and VI. (*A*) Partially depurinated DNA (150 fmol of circles) was incubated with no enzyme (●) or with endonuclease III (55 units) for 20 min. Then endonuclease IV (▼, 16 units) or VI (▲, 25 units) or no enzyme (■) was added to the samples containing endonuclease III and the incubation was continued for 10 min. (*B*) Irradiated DNA (180 fmol of circles) was incubated with no enzyme (●) or with T4 UV endonuclease (18 units) for 20 min. Then no enzyme (◆) or endonuclease III (■, 27 units), IV (▼, 24 units), or VI (▲, 37 units) was added to the samples containing T4 UV endonuclease and the incubation was continued for 10 min. All incubations were performed at 37°C. The average number of nicks per molecule of DNA after endonuclease treatment was as follows. (*A*) No enzyme, 0.1; endonuclease III alone, 0.7; endonucleases III and IV, 0.8; and endonucleases III and VI, 0.8. (*B*) No enzyme, 0.1; T4 UV endonuclease alone, 1.6; UV endonuclease and endonuclease III, 1.6; UV endonuclease and endonuclease IV, 1.6; and UV endonuclease and endonuclease VI, 1.5.

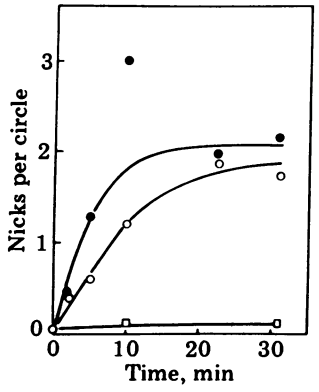

FIG. 4. Production of sites sensitive to *E. coli* endonuclease III during incubation of irradiated DNA with T4 UV endonuclease. Irradiated DNA (88 fmol of circles) was incubated at 37°C with T4 UV endonuclease (○, 10 units), or endonuclease III (□, 30 units), or both (●) for various lengths of time and then assayed for nicks.

most likely candidate for such contamination would be *E. coli* endonuclease III because the low priming activity of irradiated DNA incised with the T4 UV endonuclease preparation suggests that the AP site is at the 3′ terminus. To investigate this possibility, we compared the activities of the UV endonuclease preparation on untreated DNA, AP DNA, and DNA treated with osmium tetroxide with similar activities of endonuclease III because endonuclease III nicks osmium tetroxide-treated DNA (17). These experiments were done in the presence of EDTA and the absence of Mg^{2+} to avoid interference from endonuclease V, a possible contaminant that requires Mg^{2+} (17). Whereas the T4 UV endonuclease preparation had considerable AP endonuclease activity, it had very low activity on DNA treated with osmium tetroxide, in contrast to endonuclease III (Fig. 5). Neither preparation was active on untreated DNA. Thus, whereas endonuclease III could have been present in the T4 UV endonuclease preparation, the bulk of the AP endonuclease activity was not due to contamination by endonuclease III. However, the nick generated when the AP endonuclease activity of the T4 UV endonuclease incises at AP sites probably does have an AP site at the 3′ terminus because the priming activity of these sites was much less than that observed with endonuclease VI (Fig. 6). The UV endonuclease of *M. luteus* has also been reported to be able to incise unirradiated, depurinated DNA (28).

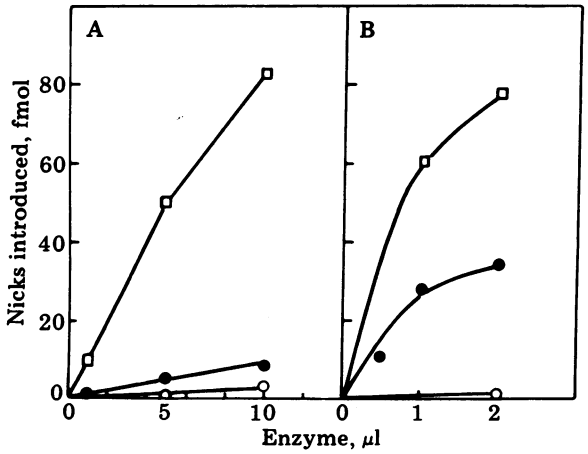

FIG. 5. Activity of T4 UV endonuclease on depurinated DNA and DNA treated with osmium tetroxide. Untreated and damaged DNAs were incubated for 10 min at 37°C with various amounts of T4 UV endonuclease (2 units/μl) (*A*) or endonuclease III (6 units/μl) (*B*) in the presence of 10 mM Tris·HCl, pH 7.5/4 mM EDTA. The DNA was then assayed for nicks. □, Partially depurinated DNA (64 fmol of circles per assay); ●, osmium tetroxide-treated DNA (60 fmol of circles per assay); ○, untreated DNA (70 fmol of circles per assay).

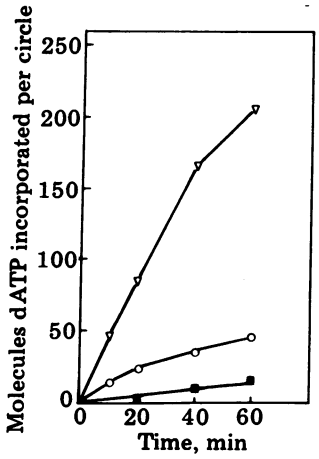

FIG. 6. Priming activity of depurinated DNA after incubation with T4 UV endonuclease or endonuclease VI. Partially depurinated DNA (137 fmol of circles) was incubated with T4 UV endonuclease (○, 8 units) or endonuclease VI (▽, 13 units) for 10 min at 37°C to nick the DNA. ■, No enzyme. The average number of nicks per molecule of DNA after endonuclease treatment was as follows: no enzyme, 0.2; T4 UV endonuclease, 0.6; endonuclease VI, 0.8.

DISCUSSION

The ability of *E. coli* DNA polymerase I to catalyze DNA synthesis at nicks produced by *M. luteus*, *E. coli*, and T4 UV endonucleases has been previously reported (6–8). In all cases stimulation was observed compared to unincised DNA, but the rates were not compared to a system known to be efficient for DNA synthesis. We also have observed a stimulation after incubation of irradiated DNA with T4 UV endonuclease, but this stimulation is much less than that observed when DNA is incised with *N. crassa* endonuclease or when AP DNA is incised with endonuclease IV or VI. Furthermore, the ability of *E. coli* AP endonuclease IV or VI to enhance the priming activity of irradiated DNA incised by the T4 UV endonuclease indicates that the 3′ terminus at nicks generated by T4 UV endonuclease probably contains an AP deoxyribose and that endonuclease IV or VI can remove deoxyribose 5-phosphate from this 3′ terminus (Fig. 7).

The model shown for T4 UV endonuclease in Fig. 7 is similar to that proposed by Grossman *et al.* (27) for *M. luteus* UV endonuclease. Incision of irradiated DNA by the *M. luteus* enzyme may involve two distinct enzymatic activities, one a glycosylase and the other an AP endonuclease. The model predicts that the T4 UV endonuclease has AP endonuclease activity and that the nicks generated by incision at such AP sites would not be efficient priming sites. These predictions were fulfilled, although it remains to be demonstrated unequivocally that the AP endonuclease activity in the T4 UV endonuclease preparation is an integral part of the T4 UV endonuclease enzyme. Nevertheless, it appears that the cleavage of the glycosylic bond between the pyrimidine dimer and the deoxyribose precedes the cleavage of the phosphodiester bond. There is no evidence to indicate that the *E. coli* UV endonuclease complex (29) has the same incision mechanism as the T4 and *M. luteus* enzymes.

Our results confirm that the action of endonuclease III on AP DNA is distinct from that of endonuclease IV or VI. Thus, *E. coli* contains at least three AP endonuclease activities with at least two mechanisms of incision. Whereas the significance of these three separate activities was not explicitly determined, hypothetical roles for these enzymes are suggested in an integrative scheme for repair of *E. coli* and phage DNA containing damaged bases (Fig. 7). Endonucleases IV and VI could play a role in repair of phage DNA incised by T4 UV endonuclease as well as in repair of AP sites in *E. coli* DNA. The role of endonuclease III in DNA repair is more obscure. Because the nick generated by this enzyme may not be efficiently repaired by DNA polymerase I and DNA ligase, its role is somewhat analogous to that of T4 UV endonuclease; it produces an intermediate that must be acted upon by endonuclease IV or VI or by a 3′-exonuclease before repair synthesis can occur. Perhaps it

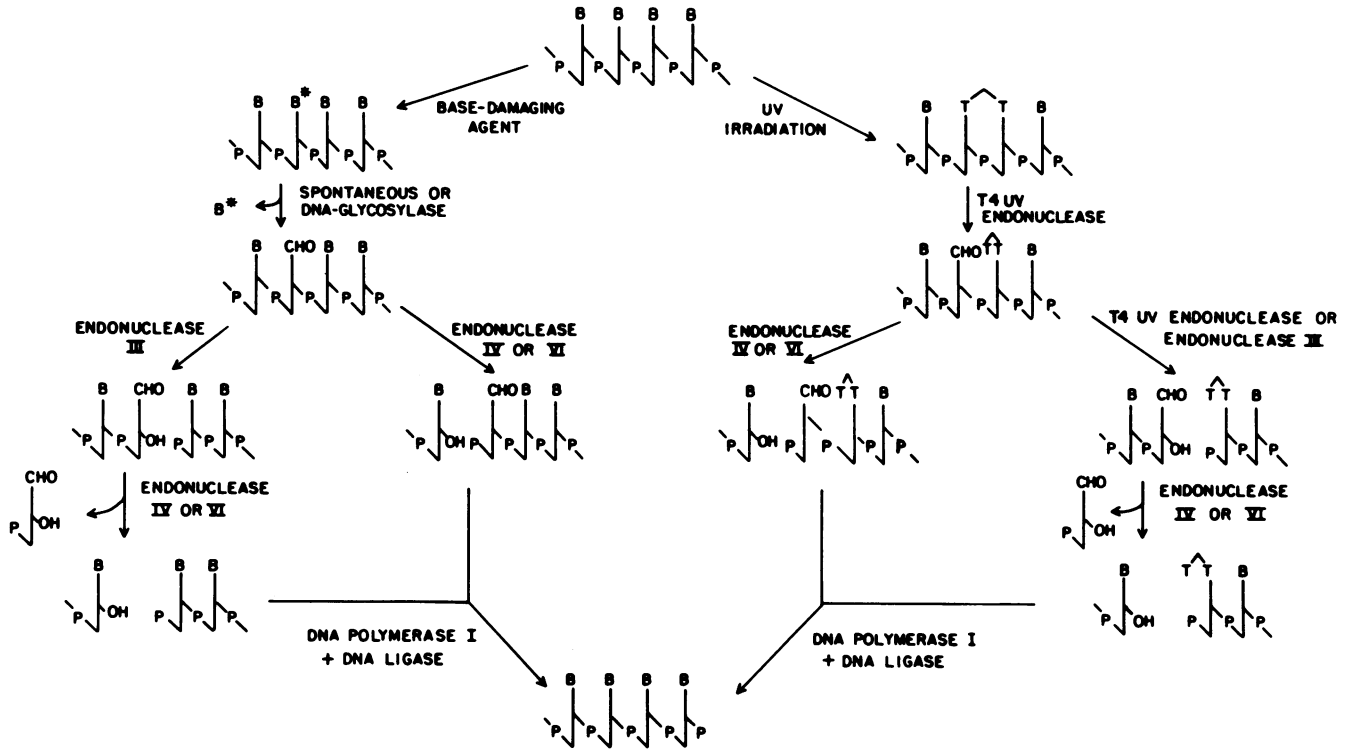

FIG. 7. Proposed integrative scheme for repairing damaged DNA in *E. coli*. Only one strand of the duplex is shown.

acts both as a "back-up" nicking system for the UV endonuclease of *E. coli* (if that enzyme has the same mechanism as the T4 enzyme) and in conjunction with endonuclease IV or VI for removal of AP lesions.

One general pattern that would then emerge is that DNA containing damaged bases is first acted upon by a DNA glycosylase, then incised by an AP endonuclease activity that leaves an AP deoxyribose on the 3′ terminus of the nick; the AP site can then be removed by endonuclease VI, or possibly endonuclease IV, whereupon the 5′ → 3′ exonuclease of DNA polymerase I excises any remaining nucleotides containing damaged bases near the 5′ terminus, and the polymerase activity fills the gap generated by this excision (other sequences of enzyme action would obviously also lead to the same result). The possiblity of AP site excision by the combined action of endonuclease III with either endonuclease IV or endonuclease VI is noteworthy; no specific excision exonuclease is required.

The mechanism of *in vitro* DNA synthesis at nicks containing an AP site at the 3′ terminus but not removed by endonuclease IV or VI has not been elucidated by these experiments. Preliminary experiments have indicated that the 3′ → 5′ exonuclease of *E. coli* DNA polymerase I does not efficiently excise AP sites from the 3′ terminus (data not shown). Although it is most likely that the AP sites are slowly excised, the possibilities of elongation from the 3′-AP deoxyribose terminus itself or of spontaneous hydrolysis at the 3′-AP structure were not ruled out.

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