JOURNAL OF BACTERIOLOGY, Feb. 1978, p. 769-774
0021-9193/78/0133-0769$02.00/0
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Vol. 133, No. 2
Printed in U.S.A.

Synergistic Killing of *Escherichia coli* by Near-UV Radiation and Hydrogen Peroxide: Distinction Between RecA-Repairable and RecA-Nonrepairable Damage

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Received for publication 21 July 1977

Wild-type cells and six DNA repair-deficient mutants (*lexA, recA, recB, recA recB, polA1,* and *uvrA*) of *Escherichia coli* K-12 were treated with near-ultraviolet radiation plus hydrogen peroxide (H_2O_2). At low H_2O_2 concentrations (6×10^{-6} to 6×10^{-4} M), synergistic killing occurred in all strains except those containing a mutation in *recA*. This RecA-repairable damage was absent from stationary-phase cells but increased in logarithmic cells as a function of growth rate. At higher H_2O_2 concentrations (above 6×10^{-4} M) plus near-ultraviolet radiation, all strains, including those with a mutation in *recA*, were synergistically killed; thus, at high H_2O_2 concentrations, the damage was not RecA repairable.

Exposure to one type of radiation is known to sensitize cells to damage by another (e.g., wild-type *Escherichia coli* cells are synergistically killed by 254-nm UV and X-radiation [12, 14]; preexposure to 365-nm radiation enhances lethal effects of both X- [21] and 254-nm radiation [24]; inactivation of transforming DNA by 365-nm radiation is considerably increased if simultaneously exposed to 313- or 334-nm radiation [17]).

The lethal effects of a tryptophan photoproduct (TP) resulting from near-UV (NUV) irradiation (300 to 410 nm) have been of particular interest in our laboratory. On the basis of spectrophotometric, chromatographic, chemical, and biological properties, the biologically active component of TP has been identified as hydrogen peroxide (H_2O_2) (15). TP is very toxic to recombination-deficient (*rec*) strains of *E. coli* and *Salmonella typhimurium* (25) as well as to mammalian cells in tissue culture (19). The importance of the H_2O_2 in TP is magnified by the observation that it can enhance the biological action of the same NUV used for the initial TP formation. Specifically, H_2O_2 (or TP) can act synergistically with NUV to yield an increased number of single-strand (SS) DNA breaks as well as enhanced lethality in both phage (2) and bacteria (24).

In this report we show that the damaging effects of simultaneous NUV and H_2O_2 treatment on *E. coli* may be separated into two types: damage that can be repaired in $recA^+$ cells, and damage that cannot be repaired, even in $recA^+$ cells.

MATERIALS AND METHODS

Bacterial strains. These are listed in Table 1.

Growth and harvesting. Overnight broth cultures were diluted into appropriate media and grown at 37°C with aeration. When exponential cell growth (monitored spectrophotometrically at 600 nm) reached ca. 5×10^7 cells per ml, the cells were transferred to M9 salts medium (4) followed by centrifugation, washing in M9, and recentrifugation. Resuspended cells were diluted appropriately in M9 medium and treated as indicated. Stationary-phase cultures were obtained by diluting an overnight culture in nutrient broth to ca. 5×10^7 cells per ml and were immediately harvested in a manner identical to that used for exponential cells. Antibiotic medium 3 (Penassay broth; Difco) and minimal medium (3) were also used.

Irradiation. Radiation was via four General Electric F15T8 BLB integral-filter black-light bulbs, with emission in the 300- to 420-nm range and with a peak at 365 nm (9). Exact irradiation procedures have been published previously (2).

Calculation of dose enhancement factor (DEF). A convenient measure of the degree of synergism is calculated at a cell survival of $1/e$ or 37% by the following formula: DEF = $cD_{37}/H_2O_2D_{37}$, where cD_{37} is the dose required to inactivate to 37% survival in the presence of NUV alone, and $H_2O_2D_{37}$ is the dose required to inactivate to 37% survival in the presence of NUV and 6×10^{-5} M H_2O_2. DEF values for strains are listed in Fig. 1.

Alkaline sucrose gradients. Specific procedures, such as labeling method, gradient preparation, time and speed of centrifugation, and calculation of number of SS breaks were reported previously (3).

RESULTS

In all experiments, treatment of the cells with 6×10^{-5} M H_2O_2 for 2 h inactivated less than

TABLE 1. *E. coli K-12 strains*[a]

Designation	Repair-related genotype[b]	Other genotypes	Reference or source	Surviving fraction (6×10^{-5} M H_2O_2 exposure)
W3110		*thy*	8	0.88
P3478	*polA1*	*thy*	8	0.76
AB1157		*thr-1 leu-6 thi-1 argE3 his-4 proA2 lacY1 galK2 mtl-1 xyl-5 ara-14 str-31 tsx-33* λ^- *supE44*	13	0.93
AB1886	*uvrA6*	*thr-1 leu-6 thi-1 argE3 his-4 proA2 lacY1 galK2 mtl-1 xyl-5 ara-14 str-31 tsx-33* λ^- *supE44*	13	0.85
JC5029		*thi-1 ilv-318 thr-300 rel-1 spc-300* λ^-	7	0.89
X9247	*recA56 recB21*	*thi-1 ilv-318 thr-300 spc-300* λ^-	Argonne National Laboratory	0.71
JC5088	*recA56*	*thi-1 ilv-318 thr-300 rel-1 spc-300* λ^-	7	0.52
KL168	*recB21*	*thi-1 drm-3 rel-1* λ^-	B. J. Bachmann	0.81
DM49	*lexA3*	*thr-1 leu-6 proA2 his-4 thi-1 argE3 lacY galK2 ara-14 xyl-5 mtl-1 tsx-33 strA31 sup-37* λ^-	David Mount	0.84

[a] Gene symbols are as described by Bachmann et al. (5).

[b] W3110 and P3478 are isogenic. JC5029, JC5088, and X9247 are isogenic. KLI68 is closely related to JC5029 and JC5088. AB1157 and AB1886 are isogenic. DM49 is closely related to AB1157 and AB1886.

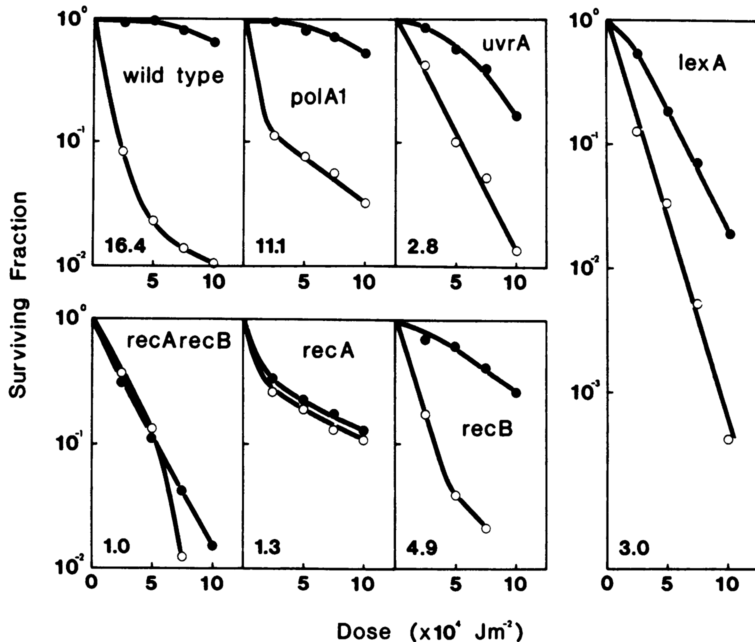

FIG. 1. *Survival of cells after NUV irradiation in the presence and absence of 6×10^{-5} M H_2O_2. Cells irradiated in M9 buffer (●) or in M9 buffer plus 6×10^{-5} M H_2O_2 (○). H_2O_2 at a concentration of 6×10^{-5} M had little or no killing action on cells. DEF values (see text) are listed for each strain. Data for strains JC5029 and AB1157 (not shown) were similar to data obtained for W3110.*

half the population; thus, under these conditions, killing by H_2O_2 alone was very small (Table 1).

Figure 1 summarizes the effects of NUV in the presence and absence of 6×10^{-5} M H_2O_2. The NUV plus H_2O_2 data have been corrected for the effects of H_2O_2 alone. NUV irradiation in the presence of H_2O_2 resulted in increased killing of wild type (W3110), *polA1, uvrA, lexA,* and *recB* strains, with synergism either very

small or absent in strains with *recA* mutations. Particularly in wild-type and *polA1* strains, synergistic action was lost after an initial exposure to NUV and H_2O_2, possibly due to H_2O_2 breakdown by cellular catalase (Fig. 1). Experiments on wild-type strains JC5029 and AB1157 were also performed, yielding DEFs of 15.5 and 17.2, respectively. In addition, the shapes of the survival curves for both NUV and NUV plus H_2O_2 were similar to those obtained for W3110 (data not shown).

The effects of the *recA* gene product on SS break induction after NUV, H_2O_2, and NUV plus H_2O_2 treatments were studied by sedimentation through linear alkaline sucrose gradients. Wild-type (W3110) and *recA* (JC5008) cells were treated with: (i) 6×10^{-4} M H_2O_2 for 7 min; (ii) 3.0×10^4 J/m^2 of NUV irradiation (time of exposure = 7 min); or (iii) both (i) and (ii). Inactivation curves yielded DEFs of 1.0 for the *recA* mutant and 9.0 for wild type under these conditions (data not shown).

In wild-type cells (Table 2), there was a 4.3-fold increase in SS breaks if NUV and H_2O_2 were administered simultaneously (68.8 breaks) as compared with the sum of separate exposures (1.4 + 14.5 = 15.9 breaks). This synergism was less in the *recA* mutant (Table 2), where the NUV plus H_2O_2 treatment yielded a 1.35-fold increase in SS breaks (53.5 breaks) when compared with the sum of separate treatments (9.8 + 29.7 = 39.5 breaks). These results suggest that the increased number of SS breaks observed for the NUV plus H_2O_2 treatment of wild-type cells was not due to an actual synergism in SS break formation but rather was a reflection of inhibition of RecA$^+$-dependent repair processes.

Experiments were conducted to determine the effect of varying concentrations of H_2O_2 plus a constant NUV dose of 2.5×10^4 J/m^2 applied to cells incubated in M9 salts with H_2O_2 (6×10^{-7} to 6×10^{-2} M). As a control, cells were incubated in the same concentrations of H_2O_2 but kept in the dark.

Levels of H_2O_2 below 6×10^{-5} M did not kill either wild-type (W3110) or *recA* (JC5088) cells (Fig. 2). Concentrations above 6×10^{-5} M decreased viability in both the strains, but with a

TABLE 2. *SS DNA break induction with NUV and/or H_2O_2 treatment of wild-type and recA cells*

Treatment[a]	No. of SS breaks per SS genome	
	recA	Wild type
NUV	9.8	1.4
N_2O_2	29.7	14.5
NUV plus H_2O_2	53.5	68.8

[a] See text for detailed description of treatments.

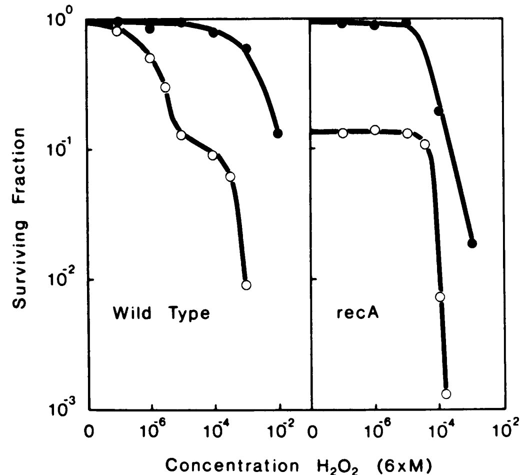

FIG. 2. *Survival of wild-type and recA cells at different concentrations of H_2O_2 in the presence and absence of 2.5×10^4 J/m^2 irradiation of NUV. H_2O_2 alone (●); H_2O_2 plus NUV (○).*

more pronounced effect in the *recA* mutant.

The response of wild type was quite different than that of the *recA* mutant (Fig. 2). The curve for wild type was biphasic, indicating two distinct types of synergistic interactions between H_2O_2 and NUV. One type of synergism occurred at concentrations between 6×10^{-6} to 6×10^{-4} M and corresponded to the RecA-dependent synergism presented in Fig. 1; a second and more intense interaction took place at concentrations above 6×10^{-4} M. In contrast, at H_2O_2 concentrations below 6×10^{-4} M, *recA* cells were killed only by the NUV.

Wild-type cells (W3110) in stationary and exponential phase were used to test NUV plus H_2O_2 sensitivities in a variety of growth media (Fig. 3). Again, cells were subjected to 2.5×10^{-4} J/m^2 of NUV irradiation in the presence of varying concentrations of H_2O_2. As a control, cells were incubated in H_2O_2 alone (data not shown). In all cases there was more than 10% survival with H_2O_2 concentrations of 6×10^{-3} M or below.

The data (Fig. 3) suggest the following: (i) the RecA-independent synergism (H_2O_2 above 6×10^{-4} M) is the same in both stationary- and exponential-phase cells; (ii) the RecA-dependent synergism (H_2O_2 below 6×10^{-4} M) is highly growth-phase dependent. Wild-type cells in stationary phase failed to exhibit RecA-dependent synergism and showed a response similar to that of stationary-phase *recA* cells (data not shown); and (iii) the extent of cell death without RecA repair is relative to growth rates. Penassay broth, nutrient broth, and minimal medium var-

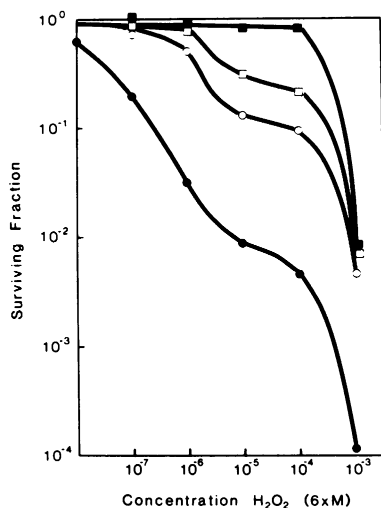

FIG. 3. *Survival of wild-type cells at different concentrations of H_2O_2 in the presence of 2.5×10^4 J/m^2 irradiation as a function of growth conditions. Stationary-phase cells (■); exponential cells grown in minimal medium (□), nutrient broth (○), Penassay broth (●).*

ied in both capacity to support maximum growth rates (doubling times for wild types equaled 28, 36, and 63, respectively) and capacity to repair this type of damage (Penassay broth > nutrient broth > minimal medium).

Inactivation experiments were also performed with far-UV (254-nm) radiation in the presence and absence of H_2O_2. There was no H_2O_2 enhancement of far-UV kill under any condition (data not shown); thus the synergism was specific for NUV. In addition, sequential experiments showed that NUV and H_2O_2 must be present simultaneously to elicit maximal response (data not shown).

Upon testing the relative NUV sensitivities of *recA* (JC5088) and wild-type (W3110) cells in both exponential and stationary phase (Fig. 4), exponential-phase *recA* showed the greatest sensitivity, followed by stationary-phase *recA*, exponential-phase wild type, and stationary-phase wild type. While exponential-phase wild-type cells were still more resistant than stationary-phase *recA*, it is important to note the difference in relative shift of sensitivity within each strain. DEF can again be employed to compare relative sensitivities; in this case the dose required to inactivate to 37% survival of stationary-phase cells is divided by the dose required to inactivate to 37% survival of exponential-phase cells. The DEF for wild type is 1.1, whereas the DEF for the *recA* mutant is 5.8. Thus the relative shift in NUV sensitivity in exponential- versus stationary-phase cells is ca. five times greater in the *recA* mutant than for wild type.

Exponential-phase *recA* cells showed a decrease in NUV sensitivity between the ranges of 2.5 to 10×10^4 J/m^2. This shoulder reflects that the *recA* population may be heterogeneous with respect to growth phase.

DISCUSSION

Several lines of evidence indicate that at low H_2O_2 concentrations (6×10^{-6} to 6×10^{-4} M), NUV irradiation in the presence of H_2O_2 disrupts RecA-dependent repair. (i) NUV and H_2O_2 synergism was absent in *recA* strains (Fig. 1). (ii) TP was shown previously to inhibit Rec-dependent type III repair processes (26). (iii) TP decreases the frequency of genetic recombination (A. Eisenstark, manuscript in preparation), a process highly dependent on the RecA gene product. (iv) Wild type, *polA1, uvrA, lexA,* and *recB,* when synergistically treated with NUV plus H_2O_2, exhibited approximately the same sensitivity as the *recA* and *recA recB* cells irradiated only with NUV. If the *recA* function was absent, either through mutation or inhibition by H_2O_2, NUV sensitivity was the same. This was particularly striking in wild-type and *polA1* cells, where the shoulders typical of NUV inactivation curves were lost with the addition of 6×10^{-5} M H_2O_2. (v) The inactivation curve for wild type was biphasic (Fig. 2 and 3). If the repair processes were already inhibited by a low concentration of H_2O_2, an increase in concentration should have resulted in little or no addi-

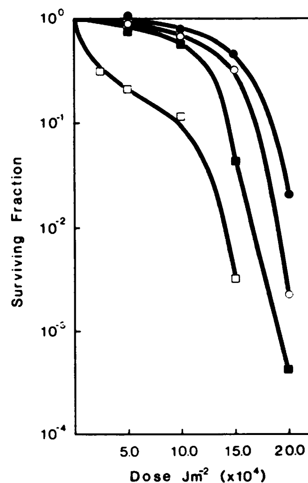

FIG. 4. *Survival of wild-type and recA cells after NUV irradiation as a function of growth conditions. Wild-type stationary (●) and exponential (○) phase; recA stationary (■) and exponential (□) phase.*

tional lethality. Such a shoulder is present in the curve at concentrations of 6×10^{-5} to 6×10^{-4} M H_2O_2. (vi) The increased number of SS breaks seen with NUV plus H_2O_2 treatment in wild type (Table 2) reflects an inhibition of RecA-dependent repair processes rather than a synergism in SS break induction.

The following distinguished between two types of synergistic damage, RecA repairable and RecA nonrepairable. (i) While 6×10^{-5} M H_2O_2 enhanced NUV inactivation in only *recA*$^+$ strains (Fig. 1), higher H_2O_2 concentrations resulted in enhanced killing of all the strains tested, including *recA*. (ii) Wild-type cells showed a biphasic inactivation curve (Fig. 2 and 3), suggesting two distinct types of synergism. (iii) The two types of killing differed with respect to growth-phase dependency (Fig. 3).

The variance in DEF values between wild type (16.4), *polA1* (11.1), and *uvrA* (2.8) may be a reflection of the increasing importance of excisable lethal photoproducts (wild type < *polA1* < *uvrA*) as a lethal event in these strains. The UvrA gene product, which codes for a specific endonuclease (6), and the PolA gene product, which codes for DNA polymerase I (8), both play a vital role in excision repair. Since NUV radiation induces significant numbers of pyrimidine dimers (20), if the lethality mediated by pyrimidine dimers (or other excisable photoproducts) is increased via this lack of excision repair, the nondimer lethal damage of NUV radiation will be less pronounced; thus, the DEF will be smaller.

If H_2O_2 does inhibit RecA functions, *uvrA* and *polA1* strains would be expected to exhibit the greatest sensitivity in the presence of both H_2O_2 and NUV irradiation when compared with the other strains, since under these conditions they would perform neither RecA repair (due to inhibition by H_2O_2) nor excision repair (due to absence of gene product). While the results (Fig. 1) do not support this argument, it is possible that, with respect to the lesion(s), either both the *polA1* and *uvrA* mutants possess other excisional repair capacities, or excision repair is ineffective in repairing this particular lethal lesion.

Recent data (27) suggest that post-replicational (*recA*$^+$) repair can be subdivided into at least five separate branches, of which two involve the RecB gene product and two the LexA gene product. In light of this information, the decreased DEF value for *recB* (4.9) and *lexA* (3.0) can be explained as follows: since post-replicational (RecA) repair was already diminished by either the *recB* or *lexA* mutation, the addition of H_2O_2 to these cells resulted in a smaller relative loss in total DNA repair capacity than if post-replicational repair was fully functional (as is the case in wild-type cells before the addition of H_2O_2).

It is possible that NUV might inactivate bacterial catalase, thus allowing the lethal action of H_2O_2. If so, the *recA* gene product could be exercising one of its pleiotropic regulatory functions (10, 18). However, the catalase levels in the extracts of *recA* and wild-type cells have been shown to be the same (3). In addition, the complete absence of RecA-repairable damage in wild-type cells in stationary phase (Fig. 3) argues against RecA-mediated control of catalase production. Finally, three strains of *E. coli* B have been shown to possess H_2O_2 sensitivities independent of catalase activity (1).

The *recA* mutant showed greater NUV sensitivity in exponential phase than in stationary phase (DEF = 5.8), unlike wild-type cells (Fig. 4). Wild-type strains, but not *uvrA* strains, of *E. coli* are more sensitive to far-UV in exponential phase (23), suggesting that sensitivity fluctuates with excision-repair enzyme levels throughout the growth cycle. Repair-proficient strains of *E. coli* are also more sensitive to NUV in exponential than in stationary growth phase (11, 16), thus explaining the fivefold increase in NUV sensitivity in *recA* over that of wild-type exponential cells (Fig. 4). Since *recA* cells lack post-replication repair, any variation in excision-repair enzyme levels would be more pronounced in the *recA*, with variation of sensitivity in wild type partially masked due to post-replication repair.

The growth-phase dependence of the RecA-repairable NUV plus H_2O_2 synergism (Fig. 3) supports the alternate hypothesis that this damage may be related to the number of DNA replication forks. Perhaps a specific lesion, either at or near the replication fork, was rapidly fixed as a lethal event unless affected by post-replication repair.

The observation that the double mutant *recA uvrA* is not growth-phase dependent in NUV sensitivity (23) does not fit the hypothesis presented in this paper. However, the double mutant is much more sensitive than the *recA* mutant as measured in exponential-phase cells. The extreme sensitivity of the double mutant would then obscure detection of damage at the growing forks, since the cells would be rapidly killed by damage at other positions on the chromosome.

These arguments do not refute the supposition that variation in excision-repair enzyme levels accounts for differential NUV sensitivity dependent on growth phase. The absence of such a difference in *uvrA* mutants is evidence in support of such an explanation. However, perhaps the increased NUV sensitivity of exponential-

phase as compared with stationary-phase *recA* cells (as opposed to wild-type cells) might also reflect a role of RecA repair of a DNA damage unique to exponential-phase cells (i.e., the presence of chromosomal growing forks).

ACKNOWLEDGMENTS

The authors thank H. N. Ananthaswamy and Shamim Ahmad for many helpful discussions and encouragement and Cathy Huckins for assistance in preparation of figures.

This work was supported by Public Health Service grant 2 R01 FD00658-05.

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