Variations in Excision Repair of UVB-Induced Pyrimidine Dimers in DNA of Human Skin In Situ

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The excision repair kinetics of UVB (280–320 nm)*-induced pyrimidine dimers in DNA of human skin in situ was determined for seventeen volunteers using a dimer-specific endonuclease from Micrococcus luteus in conjunction with agarose gel electrophoresis. Removal of pyrimidine dimers from human skin could be detected within 6 h after irradiation and the average half-life for removal of pyrimidine dimers was 11.0 h (±4.3 h). However, there was significant inter-individual variability of repair as indicated by a half-life coefficient of variation of 38%. J Invest Dermatol 90:814–817, 1988

Ultraviolet radiation (UV) in sunlight is known to induce different types of damage to cellular DNA. One predominant UV-induced lesion is the cyclobutyl pyrimidine dimer formed between adjacent pyrimidines on the same DNA strand [1]. Cleaver [2] showed that cells from individuals with xeroderma pigmentosum (XP), a syndrome in which individuals are extremely prone to sunlight-induced skin cancer, were defective in unscheduled DNA synthesis (UDS). He therefore connected a defect in DNA repair with a high risk of cancer from an environmental agent. The relationship between UV-induced DNA damage and carcinogenesis was augmented further when it was shown that XP cells are defective in the excision of pyrimidine dimers [3]. Thus, these observations present direct experimental evidence that damage to DNA is potentially carcinogenic and that this potential depends strongly on DNA repair systems available to excise pyrimidine dimers.

Pyrimidine dimers alter the biologic function of DNA and are a major cause of lethal [4], tumorigenic [5], and transformational [6] events induced by UV exposure. Pyrimidine dimers in DNA can be detected by using a dimer-specific endonuclease from Micrococcus luteus [7] that quantitatively makes a single-strand break adjacent to each dimer [8,9]. Alkaline agarose gel electrophoresis has been used to detect [10] and quantitate [11,12] the number of single-strand breaks in DNA from UV-irradiated human skin [12,16]. This technique disperses single-stranded DNA according to molecular length [17], and not only measures directly the number of pyrimidine dimers in DNA, but can also be used to measure the number of pyrimidine dimers removed [17]. This report describes the kinetics of excision repair of UV-induced pyrimidine dimers in human skin in situ using agarose gel electrophoresis. It was determined that there was significant inter-individual variation in the ability of human skin to repair pyrimidine dimers.

MATERIALS AND METHODS

Irradiation of Human Skin Seventeen healthy volunteers between the ages of 23 and 69 years, from whom informed consent was obtained, were employed for the study. Untanned gluteal skin sites were exposed to ultraviolet radiation (UV) from two Westinghouse FS-40 fluorescent sunlamps at a distance of 5.5 cm. The sunlamps emit wavelengths between 280 and 400 nm with a peak emission at 313 nm and with relative emissions of 0.04, 0.27, 0.69, 1.0, and 0.09 at 280, 290, 300, 313, and 360 nm, respectively [19]. Therefore, the greatest amount of energy delivered from the lamps was UVB (280–320 nm). Dose rate from the FS-40 sunlamps was 6 W/m² between 280–400 nm as determined with an Optronic Model 742 spectroradiometer (Optronics Laboratories, Inc. Orlando, FL). This scanning spectroradiometer measures the spectral emissions at 1 nm intervals and the emitted energies are summed over the range of 280–400 nm.

The minimal erythema dose (MED) of UVB irradiation for each volunteer was determined by exposure of nine (1.5 × 1.5 cm) skin sites to graduated exposures of UVB, increasing by 25% increments. Twenty-four hours after the lowest exposure that induced uniform pinkness filling the exposure site with well-defined margins was identified as the MED. Separate untanned gluteal skin sites (1.5 × 1.5 cm) were then exposed to at least two different exposures of UVB in multiples of the MED (1/4, 1/2, 1, or 1 1/2 MED) to induce similar levels of dimers in each individual [14]. After intradermal injection of 0.1 ml of 1% lidocaine, superficial shave biopsies (4 mm in diameter) were excised either immediately after or 6–24 h after UVB irradiation, using a number 11 sterile surgical scalpel. The room was illuminated with dim red lights to prevent photoreactivation following...
irradiation \([20,21]\). Individual biopsies were immediately immersed in 1.0 ml of cold 0.25% trypsin (Difco) in phosphate-buffered saline (0.15 M NaCl, 0.01 M sodium phosphate buffer, pH 7.3) and incubated on ice in the dark for 12–24 h.

**DNA Preparation** The epidermis was separated from the underlying dermis by gentle scraping and homogenized in a glass/glass micro-tissue grinder. The epidermal cells were then resuspended in a Tris buffer (0.05 M Tris pH 8.0, 0.01 M EDTA, 0.04 M NaCl) and the cells were lysed by the addition of 75 ml of a 10% (w/v) solution of sodium dodecyl sulfate. The cells were incubated for 5 min at 55°C, then 25 ml of protease K (10 mg/ml) was added, and incubation continued for 30 min at 37°C. The DNA was extracted [13] and aliquots of the DNA (40–60 ng) were treated with enough pyrimidine dimer-specific *Micrococcus luteus* UV-endonuclease [7] to give stoichiometric cleavage at dimer sites. The DNA was denatured with an alkaline stop buffer [0.13% (w/v) bromoresol green, 25% (v/v) glycerol, 0.5 N NaOH] and 15–30 ng of DNA was added to a well of a 0.4% alkaline agarose gel in 2 mM EDTA, with 30 mM NaOH as electrophoresis solution. The gel containing the treated DNA, along with DNA controls not treated with UV-endonuclease and DNA molecular length standards (bacteriophage DNA from T4, T7 and a HindIII digest of lambda DNA) was subjected to electrophoresis in a BioRad minigel apparatus for 2 h at 40 V. The gel was neutralized (0.1 M Tris, pH 8.0, 30 min), stained with ethidium bromide (1 μg/ml) in distilled water, destained, and photographed using Polaroid Type 55 positive/negative film.

**Pyrimidine Dimer Assay** The DNA distribution along each lane was determined by scanning with a Hoefer GS 300 Scanning Densitometer and the scans analyzed. In brief, the digital information on disc was transferred to a VAX microcomputer (Digital Equipment Corporation) for analysis [22,23]. A calibration curve was constructed from the migration distances of the DNA molecular length standards and the number-average molecular length (\(L_n\)) of each experimental DNA distribution was determined as described by Freeman et al [11]. The frequency of UV-endonuclease sensitive sites per 1000 bases (ESS/kb) was then calculated from the equation

\[
ESS/kb = 1/L_n(+ \text{end}) - 1/L_n(- \text{end}),
\]

where \(L_n(+ \text{end})\) and \(L_n(- \text{end})\) are the number average molecular lengths of the same DNA samples with and without treatment with UV endonuclease, respectively.

**Data Analysis** If it is assumed that there are no pyrimidine dimers in unirradiated skin then the number of pyrimidine dimers can be related to UV exposure in the following way:

\[
PD_b = m_b \cdot D,
\]

\[
PD_s = m_s \cdot D,
\]

where \(PD_b\) and \(PD_s\) are the number of dimers at time 0 and time \(t\), \(m_b\) and \(m_s\) are the slopes of the dose response curves at 0 and \(t\) respectively, and \(D\) is the UV exposure. If it is also assumed that excision repair of pyrimidine dimers follows first-order kinetics, then the number of dimers remaining after \(t\) (PD) can be determined from the equation

\[
\ln(PD/PD_0) = -kt,
\]

where \(k\) is the first-order rate constant \(\ln\) is the natural logarithm. Substituting from Eqs. 2 and 3 for \(PD_b\) and \(PD_s\), and solving for \(k\)

\[
k = -(\ln(m_b/m_s)/t).
\]

The time at which 50% of the dimers would be removed \((t_{1/2})\) can thus be determined from the equation

\[
t_{1/2} = -0.693/k.
\]

**RESULTS**

The number of UV-endonuclease sensitive sites (pyrimidine dimers) in the DNA of irradiated skin was first determined for a volunteer at 0 and 6 h after irradiation. Untanned gluteal skin sites were irradiated with UVB and biopsies taken immediately and 6 h after irradiation. The DNA was then extracted from the epithelial cells, treated with UV-endonuclease, and subjected to electrophoresis in a 0.4% alkaline agarose gel. After neutralization and staining, the gels were photographed, the negatives scanned, and the number of UV-endonuclease sensitive sites per 1000 bases (ESS/kb) determined. A dose response curve of ESS/kb at 0 and 6 h after irradiation was obtained for the volunteer in Fig 1. Each point represents the averaged ESS/kb as determined from independent gels. The number of background DNA breaks induced by the UV endonuclease has been subtracted from each average. The lines were generated by the method of least squares.

To estimate the rate constant \((k)\) for repair of pyrimidine dimers, the slopes of the dose response curves, i.e., \(m_b\) and \(m_s\) (see Data Analysis) were determined by the method of least squares and substituted into Eq. (5) (Table I, Volunteer 1). The value for \(t_{1/2}\) was determined from \(k\) using Eq. (6) (Table I, Volunteer 1).

Intra-individual variability in repair of pyrimidine dimers was tested by making two independent assessments of DNA repair in the same individual. First, two volunteers were irradiated with multiples of their MED from the FS-40 sunlamp, biopsies obtained at 0 and 6 h, and the number of pyrimidine dimers determined. The values for \(k\) and \(t_{1/2}\) were \(-0.0783\) and 8.8 h, and \(-0.0471\) and 14.7 h, respectively (Table I, volunteers 2 and 3). Then, these two volunteers were irradiated two months later with 1/4 MED from the FS-40 sunlamp and biopsies were obtained 6 and 24 h later. The number of pyrimidine dimers were determined and \(k\) was calculated from the slope of the least-squares line of a plot of \(\ln(PD/PD_0)\) versus \(t\) [See Eq. (4)] (Table II). The values for \(k\) and \(t_{1/2}\) were \(-0.0862\) and 8.0, and \(-0.0414\) and 16.7 h, respectively. Thus, there was very little intra-individual variability seen in these two volunteers as determined from the similarity of their \(k\) and \(t_{1/2}\) values. The removal of pyrimidine dimers in the skin of volunteer 3 (Fig 2, closed circles) apparently followed first-order kinetics. However, removal of pyrimidine dimers in skin of volunteer 2 (Fig 2, closed squares) was faster in the 0–6 h interval following irradiation than the 6–24 h interval. Thus, removal of pyrimidine dimers in the skin of this volunteer may be biphasic.

The rate constants and \(t_{1/2}\) were determined for 15 additional volunteers (Table I). The average half-life for removal of pyrimidine dimers was 11.0 ± 4.3 h. There was significant inter-individual variability as determined from the 38% coefficient of variation.

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*Figure 1. The number of UV-endonuclease sensitive sites (pyrimidine dimers) in DNA from the skin of volunteer 1 at 0 and 6 h after UVB exposure. DNA was extracted from skin biopsies taken 0 and 6 h after irradiation with 0.25, 0.5, or 1 MED UVB from an FS-40 sunlamp, treated with UV-endonuclease, and subjected to gel electrophoresis. The gels were photographed, negatives scanned, and the number of UV-endonuclease sensitive sites per 1000 bases determined for each dose. The MED for this volunteer was 2384 J m\(^{-2}\). Each point is the averaged determination at 0 (square) and 6 (triangle) h after irradiation. The lines were generated by the method of least squares. The error estimates are one standard error of the mean.*
Table I. Kinetics of repair of pyrimidine dimers in human skin

<table>
<thead>
<tr>
<th>Volunteer</th>
<th>Age</th>
<th>Sex</th>
<th>MED*</th>
<th>PD/MED*</th>
<th>k</th>
<th>t₀*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>63</td>
<td>F</td>
<td>2384</td>
<td>0.0329</td>
<td>-0.0712(0.0070)</td>
<td>9.7(1.0)</td>
</tr>
<tr>
<td>2</td>
<td>34</td>
<td>M</td>
<td>2980</td>
<td>0.0238</td>
<td>-0.0783(0.0480)</td>
<td>8.8(5.4)</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-0.0862(0.0077)</td>
<td>8.0(0.9)</td>
</tr>
<tr>
<td>3</td>
<td>26</td>
<td>F</td>
<td>1907</td>
<td>0.0638</td>
<td>-0.0471(0.0085)</td>
<td>14.7(2.7)</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-0.0414(0.0017)</td>
<td>16.7(1.1)</td>
</tr>
<tr>
<td>4</td>
<td>31</td>
<td>F</td>
<td>2980</td>
<td>0.0694</td>
<td>-0.1025(0.0160)</td>
<td>6.8(1.1)</td>
</tr>
<tr>
<td>5</td>
<td>68</td>
<td>M</td>
<td>2384</td>
<td>0.0415</td>
<td>-0.0398(0.0297)</td>
<td>17.4(1.3)</td>
</tr>
<tr>
<td>6</td>
<td>26</td>
<td>F</td>
<td>2980</td>
<td>0.0447</td>
<td>-0.0457(0.0155)</td>
<td>15.2(5.1)</td>
</tr>
<tr>
<td>7</td>
<td>27</td>
<td>M</td>
<td>2843</td>
<td>0.0718</td>
<td>-0.0726(0.0366)</td>
<td>9.5(4.8)</td>
</tr>
<tr>
<td>8</td>
<td>31</td>
<td>M</td>
<td>4656</td>
<td>0.0480</td>
<td>-0.0620(0.0266)</td>
<td>11.2(4.8)</td>
</tr>
<tr>
<td>9</td>
<td>23</td>
<td>M</td>
<td>2384</td>
<td>0.0710</td>
<td>-0.0859(0.0220)</td>
<td>8.1(2.1)</td>
</tr>
<tr>
<td>10</td>
<td>27</td>
<td>M</td>
<td>3725</td>
<td>0.0544</td>
<td>-0.0614(0.0090)</td>
<td>11.3(1.2)</td>
</tr>
<tr>
<td>11</td>
<td>33</td>
<td>F</td>
<td>2980</td>
<td>0.0480</td>
<td>-0.0462(0.0140)</td>
<td>15.0(4.5)</td>
</tr>
<tr>
<td>12</td>
<td>24</td>
<td>F</td>
<td>2384</td>
<td>0.0570</td>
<td>-0.0989(0.0251)</td>
<td>7.0(1.8)</td>
</tr>
<tr>
<td>13</td>
<td>29</td>
<td>M</td>
<td>3725</td>
<td>0.0436</td>
<td>-0.0592(0.0244)</td>
<td>11.7(4.4)</td>
</tr>
<tr>
<td>14</td>
<td>28</td>
<td>F</td>
<td>3725</td>
<td>0.0555</td>
<td>-0.1259(0.0191)</td>
<td>5.5(0.8)</td>
</tr>
<tr>
<td>15</td>
<td>27</td>
<td>F</td>
<td>3725</td>
<td>0.0428</td>
<td>-0.0977(0.0166)</td>
<td>7.1(1.2)</td>
</tr>
<tr>
<td>16</td>
<td>69</td>
<td>M</td>
<td>2980</td>
<td>0.0545</td>
<td>-0.0327(0.0171)</td>
<td>21.1(11.2)</td>
</tr>
<tr>
<td>17</td>
<td>53</td>
<td>F</td>
<td>2980</td>
<td>0.0346</td>
<td>-0.0915(0.0285)</td>
<td>7.6(2.3)</td>
</tr>
</tbody>
</table>

* Minimal erythema dose of UVB of J·m⁻².
* The number of pyrimidine dimers per 1000 bases in DNA at an individuals MED. Extrapolated from the MED using the least squares slope of the dose response curve at 0 h.
* The rate constant for excision repair (h⁻¹) as determined from the slopes of the dose response curves at 0 and 6 h after irradiation.
* Root mean square error in k. The value was calculated by the differential method using the standard error of the slopes of the dose response curves at 0 and 6 h.
* The time in hours required to remove one half the original number of dimers. The value was determined from k using Eq. (6).
* Root mean square error in t₀. The value was calculated by the differential method using the standard error of k.
* Repeat determination of this volunteer two months later. Skin sites were irradiated with 1/4 MED and biopsies taken at 0, 6, and 24 h after irradiation. The value of k was determined by the slope of the line from a plot of 1n (PD/PD₀) versus t [See Eq. 4].
* Average PD/MED.
* Average t₀. Repeat determination on Volunteers 2 and 3 not included in the average.
* Standard deviation.
* Coefficient of variation.

The number of pyrimidine dimers induced at an individual's MED (PD/MED) has been shown to be comparable among different individuals (0.0430 dimers per 1000 bases) [14]. From the slope of the least-squares line for the dose response curve at 0 h and the MED, the PD/MEDs were extrapolated for each volunteer (Table I). The average PD/MED for the 17 volunteers of 0.050 ± 0.0140 dimers per 1000 bases (Table I) is consistent with reported values [15].

DISCUSSION

The data presented here demonstrate that, for the volunteers used in this study, the average half-life for pyrimidine dimer removal was 11 h. Although the extent of variation among individuals was significant, the rate of repair of pyrimidine dimers was not as fast as in any of the volunteers as previously reported values for human skin in situ [18,24]. One study using alkaline sucrose gradient sedimentation of DNA showed that 50% of dimers in skin were removed in approximately 58 min [24]. However, the measurement of dimer yields at variable times for the different volunteers and the 50% time point was extrapolated from an idealized curve. Other data [18] using gel electrophoresis indicated that approximately 40% of dimers were removed after 20 min in the dark. However, these determinations were made in a limited number of volunteers.

Data shown in one in vitro study that 50% of UV-induced dimers were repaired in 1 h after irradiation [25]. However, our results are consistent with the many in vitro studies that suggest that 50% of pyrimidine dimers are excised in mammalian cells in approximately 12–24 h [26–31].

There was very little difference in the values for k as determined from two volunteers (2 and 3), both irradiated at two different times. These results indicate, at least for these two volunteers, that there was very little intra-individual variability. In one of the volunteers, removal of pyrimidine dimers apparently followed first-order kinetics, while in the other volunteer (2) the kinetics were biphasic. In order to determine the true nature of the kinetics of repair of pyrimidine dimers in human skin in situ, experiments in which biospies are obtained at additional time points will be necessary.

The results presented here also show that there is substantial inter-individual variability in repair of UV-induced pyrimidine dimers in human skin. Lambert et al [32] and Madden et al [33] found large inter-individual differences in the ability of human leukocytes from different donors to perform UV-induced unscheduled DNA synthesis (UDS). A number of investigations have attempted to correlate variations in DNA repair with susceptibility to different premalignant and malignant skin tumors. There was a decrease in UDS in peripheral blood lymphocytes from patients with the premalignant skin disorder actinic keratosis [34–36] and for patients with the nevoid basal cell carcinoma syndrome [37]. Patients with both squamous cell and basal cell carcinomas had very high UDS values when compared with patients with basal cell carcinoma only [38]. Five patients with multiple basal cell carcinomas showed no deviation from controls regarding UDS in lymphocytes [37]. It remains to be determined whether a correlation can be made between variability in repair of UV-induced pyrimidine dimers in human skin in situ and susceptibility to UV-induced skin cancer.

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