Kinetics of Formation and Persistence of Ethylguanines in DNA of Rats and Hamsters Treated with Diethylnitrosamine

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ABSTRACT

The kinetics of formation and persistence of 7-ethylguanine (e7Gua) and O6-ethylguanine (O6eGua) were determined in rat liver and kidney DNA following i.p. injection with 12.5, 50, 100, or 200 mg DENA per kg body weight. The rate of ethylguanine formation in hepatic DNA was independent of carcinogen dose; however, the maximum level of DNA ethylation reached was linearly related to DENA dose. Persistence of O6eGua but not e7Gua in rat liver DNA appeared to be dose-dependent; the rate of decline in O6eGua concentration slowed as the dose of DENA increased. Ethylation of rat kidney DNA was quantifiable only following treatment with 200 mg DENA per kg body weight, and maximum concentrations of e7Gua and O6eGua were approximately ten times less than those in hepatic DNA of these animals. Nevertheless, elimination of e7Gua and O6eGua from DNA occurred at similar rates in these tissues. Whereas lung DNA from DENA-treated rats contained no detectable ethylguanines, both e7Gua and O6eGua were detected in lung DNA from treated hamsters. The half-life of e7Gua in hamster lung DNA was 28 h, while O6eGua persisted longer, exhibiting a half-life of 91 h. Only trace quantities of e7Gua and O6eGua were detected in hamster kidney DNA, precluding an accurate estimation of the kinetics of DNA alkylation in this tissue. The rate of formation of ethylguanines in hepatic DNA was faster in hamster than in rat, while maximum levels of e7Gua and O6eGua were similar in these two species. Persistence of both e7Gua and O6eGua was markedly different in hepatic DNA of rats and hamsters. e7Gua was eliminated at a faster rate in the hamster (half-life of 20 h), as compared to the rat (half-life of 35 h). Conversely, O6eGua persisted longer in hamster than in rat liver DNA; a half-life of 34 h was found for the hamster, compared to a half-life of 14 h for the rat. The half-lives of e7Gua and O6eGua in hepatic DNA of DENA-treated rats and hamsters were similar to those reported previously for m7Gua and O6mGua in these species, suggesting that the same enzymatic DNA repair systems act upon these structurally related DNA adducts. The formation and prolonged persistence of O6eGua in lung DNA of DENA-treated hamsters may be related to the sensitivity of this species to the induction of respiratory tract neoplasms following exposure to DENA.

INTRODUCTION

DENA is carcinogenic in at least 17 species (50). While the exact mechanisms of action of chemical carcinogens remain to be elucidated, investigations have implicated as a possible precursor to cancer induction the metabolic conversion of these compounds to electrophiles which covalently bind to cellular macromolecules, including DNA (27, 30). The tissue-specific enzymatic N-dealkylation of DEMA (4, 27) to an electrophilic intermediate which is capable of ethylating DNA (23, 38, 48, 53) is thought to be responsible for the toxic, mutagenic, and carcinogenic properties of this chemical (see Refs. 29 and 32). Replication of such damaged DNA may lead to somatic mutation and cancer development.

Recently, much research has focused upon identification of critical lesions in DNA which may be related to carcinogenesis by alkylating agents (see Ref. 36). Initially, attention centered upon the production of 7-alkylguanine in target-organ DNA, since this is quantitatively the major adduct found in DNA following treatment with DMNA or DEMA (28, 52, 53). However, the significance of this DNA adduct to carcinogenesis has been repeatedly questioned, since synthetic polynucleotidetemplates containing m7Gua do not miscode in vitro replication assays (26), and the correlation between m7Gua formation in DNA and organotropy of specific alkylating carcinogens can be poor (53). Although alkylation of the O6-atom of DNA guanine occurs to a lesser extent than alkylation at the N-7 position, O6Gua is believed to be promutagenic, since its presence in synthetic polynucleotide templates leads to miscoding during in vitro replication (2, 16). Alkylation of DNA at other base-pairing sites is also likely to be important to cancer initiation (1, 51); Swenberg et al. (55) have shown that O4-ethyldeoxythymidine accumulates in target cell DNA to concentrations at least 50 times greater than those for O6-ethyldeoxyguanosine in rats exposed to DEMA in a carcinogenic regimen. In the case of monkey liver DNA methylated by methyltrisourea, the repair of O4-methyldeoxythymidine was found to be 30 to 50 times slower than the repair of O6-methyldeoxyguanosine (5).

Cell replication appears to be a prerequisite to cancer initiation. Presumably, failure to correctly repair carcinogen-induced DNA lesions prior to DNA replication leads to somatic mutation. Thus, tissue and cell differences in the rates of repair of critical DNA lesions may play a central role in organ and cell specificity in chemical carcinogenesis (17). Evidence suggests the rate of repair of O6mGua in rat liver may be dependent upon its concentration.

The abbreviations used are: DEMA, diethylnitrosamine; DMNA, dimethylnitrosamine; m7Gua, 7-methylguanine; e7Gua, 7-ethylguanine; O6mGua, O6-methylguanine; O6eGua, O6-ethylguanine; O6aGua, O6-alkyllguanine; HPLC, high-performance liquid chromatography.
neutral hydroxylates and O\textsubscript{6}eGua and guanine in mid acid hydroxylates was achieved by using electronic integration and/or peak height analysis by comparison to calibration curves generated daily with standard solutions of authentic purines. Radiolabeled hydroxylates were similarly fractionated and quantitated and, in addition, 5-m fractions of column eluate were collected and assayed for radioactivity by liquid scintillation spectroscopy following the addition of 15 ml Aquasol II. Efficiency was determined by the internal standard method. Standard deviations about the means were calculated where three or more individual DNA samples were analyzed. First-order curves for the elimination of ethylguanines from DNA were estimated by curve fitting using regression analysis (least squares) for the expression \( a = \ln b - kt \), where \( a \) denotes alkylguanine content at time \( t \), \( b \) denotes the intercept of the ordinate axis, and \( k \) is the first-order rate constant of elimination. The half-times of e\textsuperscript{7}Gua and O\textsuperscript{6}eGua in DNA were computed from the first-order rate constant.

RESULTS

Measurement of e\textsuperscript{7}Gua and O\textsuperscript{6}eGua in DNA Hydroxylates.

Adaptation of an optical HPLC technique reported previously (18) proved to be feasible for quantitation of e\textsuperscript{7}Gua and O\textsuperscript{6}eGua in DNA hydroxylates from DENA-treated animals. To verify this method of analysis, liver DNA hydroxylates from a rat killed 24 h after receiving 200 mg \([1-\textsuperscript{14}C]\)DENA per kg body weight were fractionated by HPLC, and ethylguanine concentrations were estimated by both optical and isotopic procedures. Assuming that the specific activity of DNA ethylguanines was one-half that of the adenylated DNA, the radiotracer technique estimated 672 \( \mu \)mol e\textsuperscript{7}Gua and 416 \( \mu \)mol O\textsuperscript{6}eGua per mol guanine. Optical quantitation of these DNA hydroxylates estimated 574 \( \mu \)mol e\textsuperscript{7}Gua and 404 \( \mu \)mol O\textsuperscript{6}eGua per mol guanine. Thus, the two methods of analysis appear comparable, agreeing closely upon O\textsuperscript{6}eGua concentration, and within 15% for e\textsuperscript{7}Gua content. Maximum sensitivity using the optical technique allowed detection of as little as 2 \( \mu \)mol O\textsuperscript{6}eGua and 20 \( \mu \)mol e\textsuperscript{7}Gua per mol DNA guanine (15 pmol O\textsuperscript{6}eGua and 150 pmol e\textsuperscript{7}Gua applied to the analytical column). The optical HPLC method provided a rapid and sensitive means for determining e\textsuperscript{7}Gua and O\textsuperscript{6}eGua concentrations in DNA.

Formation and Persistence of e\textsuperscript{7}Gua and O\textsuperscript{6}eGua in DNA from DENA-Treated Rats.

The concentration of DNA hydroxylates and persistence of e\textsuperscript{7}Gua and O\textsuperscript{6}eGua in DNA from rats treated with 0, 12.5, 50, 100, or 200 mg DENA per kg body weight were determined. Ethylguanines were not detected in colon, lung, or brain DNA at any time following treatment with 200 mg DENA per kg body weight; therefore, subsequent studies in rats were restricted to analysis of liver and kidney DNA. The concentration of e\textsuperscript{7}Gua and O\textsuperscript{6}eGua in rat liver and kidney DNA are plotted as a function of time after carcinogen treatment (Charts 1 and 2). The formation of e\textsuperscript{7}Gua and O\textsuperscript{6}eGua in DNA was rapid, with both ethylguanines apparently formed simultaneously. The time required to reach maximum hepatic DNA alkylation seemed to be concentration-dependent, with maxima being reached from 2 to 18 h following DENA exposure. Trace levels of e\textsuperscript{7}Gua and O\textsuperscript{6}eGua were detected in kidney DNA from rats given 100 mg DENA per kg body weight; these data are not shown, since accurate quantitation was not feasible. No ethylated bases were detected in kidney DNA isolated from rats given 0, 12.5, or 50 mg DENA per kg body weight.

To obtain estimates of the time dependency of hepatic DNA ethylation as a function of DENA dose, total DNA ethylation was

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Chart 1. Levels of e'Gua and O'eGua in rat liver DNA at various times after a single dose of DENA. Rats were given injections i.p. with DENA at doses of 12.5, 50, 100, or 200 mg per kg body weight and were killed 1 to 96 h later. Liver DNA was isolated and analyzed optically for e'Gua and O'eGua concentrations. Standard deviation bars are included where 3 or more separate DNA samples were analyzed.

estimated by summation of e'Gua and O'eGua concentrations at each time interval for each carcinogen dose. Such data were plotted as a function of time after DENA treatment (not shown), and the time corresponding to 50% maximum DNA ethylation was determined graphically. As summarized in Table 1, the time following DENA exposure required to reach 50% maximum ethylation of rat liver DNA increased as the dose of DENA increased.

The dose-response relationship between DENA and ethylation of hepatic DNA guanine in the rat is shown in Chart 3. The logarithm of the maximum level of DNA ethylation for each dose of DENA is plotted as a function of the logarithm of DENA dose. Levels of maximum alkylation were chosen graphically, independent of time, since the time required to achieve maximum
alkylation was found to be dose-dependent. A linear dose-response relationship is obtained when these kinetics are taken into account. Similar dose-response curves were obtained for both $e^7$Gua and $O^6$eGua individually (not shown), as would be expected if ethylation at both guanine sites occurred concurrently from the same reactive intermediate.

Comparable comparative kinetic analyses were not possible for DENA-induced ethylation of rat kidney DNA, since a complete kinetic profile was obtained for only one dose of DENA. Chart 2 illustrates rapid and simultaneous formation of $e^7$Gua and $O^6$eGua kidney DNA following exposure to 200 mg DENA per kg body weight. Half-maximum alklyation occurred within 6 h after treatment, and maximum levels of $e^7$Gua and $O^6$eGua were found approximately 24 h after carcinogen exposure. Levels of $e^7$Gua and $O^6$eGua in kidney DNA were approximately 10 times lower than those in liver DNA in these animals.

The rates of decline in $e^7$Gua and $O^6$eGua concentrations in liver DNA were estimated by linear regression analysis, assuming first-order kinetics; i.e., the decline in alkylguanine content in DNA was analyzed as a function of time, assuming that a constant fraction of alkylguanines were removed from DNA in each equal time interval. The data are summarized in Table 1.

### Table 1

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Dose (mg/kg)</th>
<th>$e^7$Gua Half-life (h)</th>
<th>Coefficient</th>
<th>$O^6$eGua Half-life (h)</th>
<th>Coefficient</th>
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<tr>
<td>Rat liver</td>
<td>12.5</td>
<td>1.2</td>
<td>38</td>
<td>0.81</td>
<td>8</td>
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<tr>
<td></td>
<td>50</td>
<td>1.6</td>
<td>36</td>
<td>0.87</td>
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<td></td>
<td>100</td>
<td>5.3</td>
<td>29</td>
<td>0.93</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>200</td>
<td>8.0</td>
<td>35</td>
<td>0.93</td>
<td>14</td>
</tr>
<tr>
<td>Rat kidney</td>
<td>200</td>
<td>6.0</td>
<td>44</td>
<td>0.99</td>
<td>16</td>
</tr>
<tr>
<td>Hamster liver</td>
<td>200</td>
<td>2.2</td>
<td>20</td>
<td>0.99</td>
<td>34</td>
</tr>
<tr>
<td>Hamster lung</td>
<td>200</td>
<td>2.0</td>
<td>28</td>
<td>0.99</td>
<td>91</td>
</tr>
</tbody>
</table>

Chart 3. Dose-response relationship for DENA ethylation of rat liver DNA guanine. Total alklyation of DNA guanine was estimated for each dose at the time of maximal alklyation by summation of $e^7$Gua and $O^6$eGua concentrations. Since the time to maximum alklyation varied with DENA dose, levels of maximum alklyation were chosen independently of time. Note log scale on both ordinate and abscissa.

Similar analysis of ethylguanine persistence in rat kidney DNA revealed that both $e^7$Gua and $O^6$eGua were eliminated from DNA of this organ at slightly slower rates than from liver DNA. $e^7$Gua had a half-life of 44 h, while $O^6$eGua exhibited a half-life of 16 h in rat kidney DNA following treatment with 200 mg DENA per kg body weight (Table 1).

### Table 2

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Time (h) to 50% maxima</th>
<th>$e^7$Gua</th>
<th>$O^6$eGua</th>
<th>Coefficient</th>
<th>Coefficient</th>
</tr>
</thead>
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<td></td>
<td>50</td>
<td>1.6</td>
<td>36</td>
<td>0.87</td>
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<tr>
<td>Rat liver</td>
<td>200</td>
<td>6.0</td>
<td>44</td>
<td>0.99</td>
<td>16</td>
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<td></td>
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<tr>
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<td>28</td>
<td>0.99</td>
<td>91</td>
</tr>
</tbody>
</table>

Kinetic analysis of the formation of $e^7$Gua and $O^6$eGua dem-
**DISCUSSION**

Despite extensive studies of DENA carcinogenesis (see Ref. 20) and numerous investigations concerning DNA alkylation following exposure to methylating carcinogens (36), surprisingly few experiments have focused upon in vivo ethylation of DNA by DENA. In the present investigation, the rates of formation and the persistence of ethylguanines in DNA of rats and hamsters treated with a single dose of DENA were determined. These experiments were undertaken to determine whether the rate of DNA ethylation was dose-dependent in rats and whether rats and hamsters differed with respect to formation or persistence of ethylguanines in DNA of various tissues.

The observed dose independence of rates of formation of ethylguanines in rat liver DNA is consistent with a zero-order process of DENA bioactivation; that is, regardless of DENA dose, a constant quantity of ethylguanines is produced in liver DNA per unit time. Such kinetics of DENA activation would predict that the time-to-maximum DNA alkylation would occur at later times following progressively larger doses of the carcinogen (35). Indeed, this was observed, utilizing the time-to-50% maximum alkylation to avoid the greater inherent error in determining the time of maximum alkylation. Although such data cannot be interpreted as unequivocal proof of zero-order kinetics of DENA bioactivation, the consistency of the data with the kinetic model is evident.

Accurate determination of the dose-response curve for DNA ethylation by DENA in rat liver required consideration of the kinetics of formation. With this consideration, the dose-response curve for ethylation of liver DNA was linearly related to DENA dose. This finding confirms the results of an earlier study of Scherer et al. (48), in which ethylation of liver DNA (at the N-7 position of guanine and N-3 atom of adenine) were found to be
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Chart 5. Levels of e7Gua and O'eGua in hamster liver and lung DNA at various times after i.p. injection with 200 mg DENA per kg body weight. Each time point in the upper panel represents the mean of 3 determinations of separate DNA samples; standard deviation bars are shown. Each time point in the lower panel represents an individual determination of DNA isolated from lungs pooled from 7 hamsters.

nearly related to the dose of DENA. In other studies using DMNA, when m'Ogu was measured in rat liver DNA at the same time interval regardless of the administered dose of dimethylnitrosamine, a linear relationship between dose and m'Ogu content was demonstrated independently in 2 rat strains (12, 37). Those results were interpreted as an indication of nonsaturation of the oxidative enzyme systems responsible for DMNA activation; our findings indicate this is not the case with DENA. DENA metabolism in the rat is slower than DMNA metabolism (27), and the apparent zero-order kinetics of DENA alkylation of rat liver DNA reported here suggests saturation of the metabolic pathway leading to formation of ethylating electrophiles at all doses of DENA investigated. Differences in metabolism of DENA and DMNA in vivo may account for the apparent differences in kinetics obtained in the present investigation and the previous reports (12, 37).

An inherent problem with experiments designed to measure formation of DNA adducts in vivo following exposure to nitrosamines is that metabolism of these compounds requires a significant period of time, during which DNA repair systems may be active. The maximum level of O6mGua in rat liver DNA following treatment with low doses of DMNA was only 36 to 44% of that expected based upon the amount of m'Ogu found, indicating concomitant formation and repair of O6mGua (41). Similar results were not obtained in the present investigation; this may reflect our use of relatively large doses of DENA and the slightly slower rate of repair of O6eGua as compared to O6mGua (43). Our findings that the half-life of O6eGua decreased as the dose of DENA decreased suggest that at lower doses of DENA concomitant alkylation and repair could lead to less than the expected

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amount of O6eGua at the time of maximum DNA alkylation. Pegg et al. (42) estimated the maximum levels of O6eGua formation in liver DNA of rats treated with 0.1 to 2 mg DENA/kg body weight by back extrapolation of data plotted similarly to that in Chart 4. Using the same technique of back extrapolation on the data in Chart 4 to estimate maximum levels of O6eGua for the doses of 12.5 to 200 mg DENA/kg body weight (y-intercepts) and combining these results with those of Pegg and coworkers in a plot similar to Chart 3, we estimate by extrapolation from the high dose data that the maximum level of O6eGua in liver DNA of rats treated with 0.1 mg DENA/kg body weight would be approximately 0.55 μmol/mol guanine rather than the 0.2 μmol/mol guanine estimated by Pegg by extrapolation from low-dose data. Hence, it appears that concomitant alkylation and repair can lead to less than the expected amount of O6eGua at the time of maximum DNA alkylation.

The current investigation confirms and extends the findings of Pegg and Balog (39) that the time of maximum O6eGua concentration in liver DNA of DENA-treated rats is dose-dependent. Previously, large doses of DENA were reported to facilitate O6eGua formation in rat liver DNA (48). Interpolation from our study suggests it is likely that the times chosen by Scherer et al. (48) to measure O6eGua in liver DNA following low doses of DENA were well beyond the respective times of maximum hepatic DNA alkylation. Thus, the amounts of O6eGua measured previously after low doses of DENA (48) may not have reflected only O6eGua formation but were, in all likelihood, influenced by the rapid rate of repair of this DNA adduct in rat liver (see Table 1).

The preceding discussion illustrates the need to consider dose and time dependence of DNA alkylation in animals treated with alkylating agents so that possible dose or pretreatment differences in the formation or persistence of DNA adducts truly reflect the biology of the system.

Organotropy for DENA carcinogenesis is species-specific. The respiratory tract is the most sensitive tissue in the hamster whereas, in the rat, liver and kidneys are affected most often (20). Following treatment with DENA, ethylation of DNA was quantifiable in liver and lung of hamsters. Initially, lung DNA was ethylated approximately one-fifth as much as liver DNA. However, lung contains as many as 40 cell types (10), while liver contains only 4 (24). The distribution of bound radioactivity in lungs from hamsters given radiolabeled DENA coincided with the distribution of nonciliated bronchiolar epithelial (Clara) cells (47). Moreover, such cells have been implicated as one origin of DENA-induced respiratory tract tumors in hamster (46). If Clara cells are the only cell type within the lung which metabolize DENA to an appreciable extent, then the total amount of DENA-induced ethylation of Clara cell DNA may be comparable to or greater in extent than ethylation of hamster liver cell DNA, since Clara cells comprise only 5 to 10% of the total number of lung cells (44).

A single dose of DENA given to neonatal hamsters induces both respiratory tract and liver tumors (34), yet adolescent hamsters treated with DENA primarily develop upper respiratory tract neoplasms (25). In the present experiment, the half-life of eGua was only slightly longer in lung DNA than in liver DNA, whereas the half-life of O6eGua in lung DNA was approximately 3 times longer than in liver DNA. The persistence of eGua and O6eGua in hamster liver in lung DNA following DENA treatment
has been independently determined* and found to closely agree with our measurements. Thus, persistence of O6eGua in hamster lung DNA appears to be correlated with the sensitivity of this organ to DENA-induced carcinogenesis.

The relationship between formation and persistence of O6eGua in DNA and chemical carcinogenesis remains to be elucidated. For a number of organs, including brain, bladder, and kidney, persistence of O6eGua in DNA appears to correlate with organotropy (see Ref. 36). However, a single dose of DENA induces primarily kidney tumors and, to a lesser extent, liver tumors in rats (13, 15, 20, 31), yet the present experiments demonstrated approximately 10 times less O6eGua in kidney DNA than in liver DNA following a single dose of 200 mg DENA per kg body weight, while the decline in O6eGua concentrations in DNA of these 2 tissues did not markedly differ.

The importance of differences in alkylation kinetics in single-dose and multiple-dose studies is recognized but difficult to quantitate. Bosan and Shank (9) showed that O6mGua accumulated in liver DNA of hamsters exposed daily for 9 weeks to hydrazine, a compound which has failed to induce liver cancer in the hamster in 3 independent bioassays (7, 58); however, after 6 months of exposure, O6mGua no longer accumulated in liver DNA and was undetectable in another 6 months, in spite of the continuous exposure to the carcinogen. In this chronic study of Bosan and Shank, DMNA was used as a positive control and, in these hamsters, which began to die with liver tumors at 6 months, sufficient accumulation of O6mGua occurred in liver DNA after 6 months of exposure to yield a O6mGua:m7Gua ratio of 1.8. These results were difficult to predict from single-dose studies. Certainly other factors, in addition to persistence of O6mGua in total organ DNA, are related to induction of tumors in nitrosamine- and hydrazine-treated animals. These include other alkylation sites within the DNA molecule, target cell replication rate, and endogenous and exogenous promoting factors.

O-Ethylpyrimidines have been shown to persist longer than eGua in rat liver DNA following treatment with DENA or ethyl-nitrosourea (49, 51), and the relevance of the more stable DNA lesions to liver carcinogenesis should be taken into account. Another important factor may be the formation and persistence of alkylated bases in target cell populations. O6mGua was shown to persist longer in nonparenchymal liver cells of rats given 1,2-dimethylhydrazine, apparently correlated with induction of endothelial neoplasms in livers of these animals (24); rat liver hepatocytes were about 10 times more active than nonparenchymal cells in removing O6eGua from DNA in DENA-treated rats (54). However, 1,2-dimethylhydrazine and DENA produce hepatocellular carcinomas in rats, even though removal of O6eGua was apparently induced in hepatocytes of these animals (6, 54).

Recently, several laboratories (8, 11, 21, 57) have demonstrated that alkylation of DNA by methylating and ethylating carcinogens leads to a reduced level of 5-methylcytosine, the only normal methylated base in mammalian DNA. Because 5-methylcytosine is thought to have a significant role in the regulation of differentiation and cell expression (45), this intriguing effect of DNA adduct formation on 5-methylcytosine levels in DNA deserves further investigation.

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