The possibility that *Escherichia coli* MutT and human MTH1 (hMTH1) hydrolyze oxidized DNA precursors other than 8-hydroxy-dGTP (8-OH-dGTP) was investigated. We report here that hMTH1 hydrolyzed 2-hydroxy-dATP (2-OH-dATP) and 8-hydroxy-dATP (8-OH-dATP), oxidized forms of dATP, but not (R)-8,5'-cyclo-dATP, 5-hydroxy-dCTP, and 5-formyl-dUTP. The kinetic parameters indicated that 2-OH-dATP was hydrolyzed more efficiently and with higher affinity than 8-OH-dGTP. 8-OH-dATP was hydrolyzed as efficiently as 8-OH-dGTP. The preferential hydrolysis of 2-OH-dATP over 8-OH-dGTP was observed at all of the pH values tested (pH 7.2 to pH 8.8). In particular, a 5-fold difference in the hydrolysis efficiencies for 2-OH-dATP over 8-OH-dGTP was found at pH 7.2. However, *E. coli* MutT had no hydrolysis activity for either 2-OH-dATP or 8-OH-dATP. Thus, *E. coli* MutT is an imperfect counterpart for hMTH1. Furthermore, we found that 2-hydroxy-dADP and 8-hydroxy-dGDP competitively inhibited both the 2-OH-dATP hydrolase and 8-OH-dGDP hydrolase activities of hMTH1. The inhibitory effects of 2-hydroxy-dADP were 3-fold stronger than those of 8-hydroxy-dGDP. These results suggest that the three damaged nucleotides share the same recognition site of hMTH1 and that it is a more important sanitization enzyme than expected thus far.

Endogenous oxidation of DNA and DNA precursors by reactive oxygen species appears to induce spontaneous mutations, aging, and various diseases, including cancer and neurodegeneration (1, 2). 8-OH-dGTP\(^1\) is an oxidized form of dGTP and induces A:T to C:G transversions because it can pair with adenine as well as cytosine (3–6). It is known that the *Escherichia coli* MutT protein hydrolyzes 8-OH-dGTP to 8-hydroxy-dGMP (4). Because the mutation rate in a *mutT*-deficient strain increases up to 1000-fold as compared with the wild type (7), 8-OH-dGTP is considered to be a major source of spontaneous mutations caused by endogenous reactive oxygen species, and MutT appears to efficiently prevent the spontaneous occurrence of A:T to C:G transversion mutations. In human cells, the hMTH1 protein is considered to be a functional homologue of the *E. coli* MutT because the hMTH1 protein hydrolyzes 8-OH-dGTP in vitro and suppresses the mutator phenotype of *E. coli mutT*-deficient cells (8, 9).

Recently, we found that 2-hydroxy-dAdo and 2-OH-dATP are produced efficiently by reactive oxygen species treatment of dAdo and dATP, respectively (10, 11). 2-OH-dATP specifically induces G:C to T:A transversion mutations and is more mutagenic than 8-OH-dGTP in vivo (5). Thus, 2-OH-dATP is thought to act as an endogenous mutagen in cells. However, the presence of a hydrolyzing activity for 2-OH-dATP has not been described. We supposed that the MutT and hMTH1 proteins may act on this mutagenic nucleotide, 2-OH-dATP. We report here that the hMTH1 protein, which is known as an 8-OH-dGTPase, hydrolyzes 2-OH-dATP more efficiently than 8-OH-dGTP. In addition, hMTH1 also hydrolyzed 8-OH-dATP, another oxidized form of dATP, as efficiently as 8-OH-dGTP. On the other hand, the MutT protein hydrolyzed neither 2-OH-dATP nor 8-OH-dATP. This is the first demonstration that various oxidized nucleotides are hydrolyzed by a nucleotide sanitization enzyme, hMTH1.

**EXPERIMENTAL PROCEDURES**

**Materials**—The hMTH1 protein and the *E. coli* MutT protein were purified from an *E. coli* overexpression system (12, 13). 2-OH-dATP, 8-OH-dGTP, 5-formyl-dUTP, and 5-hydroxy-dCTP were prepared by the oxidation of dATP, dGTP, dTTP, and dCTP (Sigma), respectively, and purified by reverse-phase HPLC as described previously (6, 10, 14). Similarly, 2-OH-dAdP, 2-hydroxy-dAMP, 8-OH-dGDP, and 8-hydroxy-dGMP were obtained by the oxidation of dAdP, dAMP, dGDP, and dGMP, respectively. 8-OH-dATP and (R)-8,5'-cyclo-dATP were prepared by subjecting a 1 mg/ml dATP (Sigma) solution to 1400 Gy of γ-irradiation and purified by reverse-phase HPLC using a YMC-Pack ODS-AM 5-5 column (4.6 × 250 mm; YMC) with isocratic elution by buffer A (12.5 mM citric acid, 25 mM sodium acetate, 10 mM acetic acid, 45 mM sodium hydroxide, and 4% methanol) at a flow rate of 1 ml/min and by monitoring of the UV spectra. The 8-OH-dATP and (R)-8,5'-cyclo-dATP fractions were re-injected into a YMC-Pack ODS-AM column with isocratic elution by buffer B at a flow rate of 1 ml/min. The 8-OH-dATP and (R)-8,5'-cyclo-dATP were finally desalted by reverse-phase HPLC using an Ultra-sphere ODS column (4.6 × 250 mm; 5 μm; Beckman) at a flow rate of 1 ml/min. Detection was performed with a Hewlett Packard 1040 M HPLC Detection System. 8-OH-dAdP and 8-hydroxy-dAMP were obtained by similar procedures.

**Analysis of MutT Pyrophosphatase Activity**—The MutT activities were assayed in a reaction mixture (5 μl) containing 20 mM Tris-HCl (pH 7.5), 8 mM MgCl\(_2\), 80 μg/ml bovine serum albumin, 5 mM dithio-

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threitol, 4% glycerol, and various amounts of deoxynucleotide substrates. After a preincubation at 30 °C for 2 min, the mixtures were incubated at 30 °C for 10 min with various amounts of the MutT protein. Reactions were terminated by adding 200 μl f2 mM EDTA. All samples were injected into a TSK-GEL DEAE-2SW column, with an isocratic elution by 75 mM phosphate buffer (pH 7.0) and 20% acetonitrile at a flow rate of 1 ml/min. The nucleoside triphosphates and their hydrolyzed products were quantified by measuring the area of UV absorbance.

Analysis of hMTH1 Pyrophosphatase Activity—The hMTH1 activities were assayed in a reaction mixture (200 μl) containing 20 mM Tris-HCl (unless otherwise noted, pH 8.0), 4 mM MgCl2, 40 μM NaCl, 80 μg/ml bovine serum albumin, 8 mM dithiothreitol, 10% glycerol, and various amounts of the deoxynucleotide substrates. After a preincubation at 30 °C for 2 min, the mixtures were incubated at 30 °C for 5 min with 1 nM hMTH1 protein. Reactions were terminated by adding 50 μl of 40 mM EDTA. The nucleoside triphosphates and their hydrolyzed products were quantified as described above.

RESULTS

Substrate Specificities of E. coli MutT—The MutT activities for 8-OH-dGTP, undamaged dGTP, and 2-OH-dATP were measured. A fixed amount (400 μM) of each substrate was mixed with various amounts of the MutT protein and incubated at 30 °C for 10 min. The hydrolyzed products were separated and quantified by anion exchange HPLC. Under our conditions, the nucleoside triphosphates and their cognate di- and monophosphates were clearly separated (Fig. 1A; data not shown). As expected, the hydrolyses of 8-OH-dGTP and undamaged dGTP were confirmed by the use of our procedure (Fig. 1, B–D). The reaction rate of the 8-OH-dGTPase activity of MutT was 8-fold higher than the deoxyguanosine triphosphatase activity (Fig. 2). This result was expected, based on the kinetic parameters determined previously by the use of radiolabeled substrates (4). However, 2-OH-dATPase activity was not found, even under conditions in which deoxyguanosine triphosphatase activity was detectable (Fig. 1E). No 2-OH-dATPase activity was detected at substrate concentrations ranging from 2 to 400 μM and at extensions of the incubation time up to 3 h. Similarly, 8-OH-dATP and (R)-8,9-cyclo-dATP, other forms of oxidized dATP, and 5-hydroxy-dCTP and 5-formyl-dUTP, the major oxidative products of pyrimidine nucleotides (11), were not hydrolyzed by the MutT enzyme (data not shown). Thus, MutT appears to be a sanitization enzyme specific for 8-OH-dGTP.

Preferential Hydrolysis of 2-OH-dATP by the Human MutT Homologue, hMTH1—Various amounts of 2-OH-dATP and 8-OH-dGTP were incubated with the hMTH1 protein, and the reaction mixtures were analyzed by anion exchange HPLC. When 2-OH-dATP was incubated with hMTH1, it was hydrolyzed to the cognate monophosphate as 8-OH-dGTP (Fig. 2). Surprisingly, 2-OH-dATP was hydrolyzed more rapidly than 8-OH-dGTP (Fig. 3). Undamaged dGTP was slightly hydrolyzed, whereas no hydrolysis of undamaged dATP was detected (data not shown).

The Michaelis constant (Km) and the catalytic constant (kcat) of the reactions catalyzed by the hMTH1 protein at pH 8.0 were calculated (Table I). 8-OH-dGTP was hydrolyzed with 14-fold greater efficiency as compared with the undamaged dGTP, as described previously (8). The (kcat/Km) value, representing the catalytic efficiency, for 2-OH-dATP was 2-fold higher than that for 8-OH-dGTP. This kinetic difference for 2-OH-dATP over 8-OH-dGTP contributed fully to the Km values, and the kcat values for the two nucleotides were similar. Thus, hMTH1

\[ \text{FIG. 1. Hydrolysis of nucleotides by MutT, monitored by anion exchange HPLC. A, separation of standard nucleotides 2-OH-dATP, 2-OH-dADP, and 2-hydroxy-dAMP. B and C, 400 μM 8-OH-dGTP incubated with 128 nM MutT at 30 °C for 0 and 10 min, respectively. D and E, 400 μM dGTP and 400 μM 2-OH-dATP, respectively, incubated with 128 nM MutT at 30 °C for 10 min. The arrowhead in E indicates the position where 2-hydroxy-dAMP is eluted.} \]

\[ \text{FIG. 2. Hydrolysis of 2-OH-dATP by hMTH1, monitored by anion exchange HPLC. A, separation of standard nucleotides 2-OH-dATP, 2-OH-dADP, and 2-hydroxy-dAMP. B and C, 5 μM 2-OH-dATP incubated with 1 nM hMTH1 at 30 °C for 0 and 5 min, respectively. D, 5 μM 8-OH-dGTP incubated with 1 nM hMTH1 at 30 °C for 5 min.} \]
recognized 2-OH-dATP with a 2-fold higher affinity and consequently hydrolyzed 2-OH-dATP twice as efficiently as 8-OH-dGTP. In addition to the normal form of hMTH1 (valine 83) described above, the variant form of the protein (methionine 83) (12) also hydrolyzed 2-OH-dATP more efficiently than 8-OH-dGTP (data not shown).

pH Effects on the hMTH1 Activities—The effects of pH on the 2-OH-dATPase and 8-OH-dGTPase activities of hMTH1 were analyzed (Fig. 4). The hMTH1 protein hydrolyzed 2-OH-dATP more efficiently than 8-OH-dGTP at all of the pH values tested (pH 7.2 to pH 8.8). In particular, the reaction rates (s⁻¹) for 2-OH-dATP and 8-OH-dGTP were quite different at pH 7.2 and pH 8.8, as compared with those at pH 8.0. With the change from pH 8.0 to pH 7.2, the predominance of the catalytic efficiency (kcat/Km) for 2-OH-dATP over 8-OH-dGTP increased up to 5-fold with the major contribution to the kcat values (Table I).

These results imply that 2-OH-dATP is a better substrate for hMTH1 than 8-OH-dGTP in cells.

Inhibition of the hMTH1 Activities by Damaged Nucleoside Diphosphates—During the course of this study, we found that 2-OH-dADP inhibited the 2-OH-dATPase activity of the hMTH1 protein. Previously, it was shown that 8-OH-dGDP is an inhibitor of the 8-OH-dGTPase activity of the hamster MTH1 protein (15). We then studied whether 2-OH-dADP and 8-OH-dGDP inhibit the 8-OH-dGTPase and the 2-OH-dATPase activities, respectively, of the hMTH1 protein. Various amounts of the diphosphate and triphosphate derivatives of 2-hydroxy-dAdo and 8-hydroxy-dGuo were mixed and incubated with hMTH1. 8-OH-dGDP competitively inhibited the 2-OH-dATPase activity in addition to the 8-OH-dGTPase activity (data not shown). Similarly, 2-OH-dADP inhibited both the 2-OH-dATPase and 8-OH-dGTPase activities. The inhibition constants (Ki) indicated that the inhibitory effects of 2-OH-dADP were 3-fold stronger than those of 8-OH-dGDP (Table II). These results are in agreement with our finding that 2-OH-dATP is recognized with higher affinity than 8-OH-dGTP. It is noteworthy that 2-OH-dADP and 8-OH-dGDP are the strongest hMTH1 inhibitors that have been found. In addition, 8-OH-dGTP and 2-OH-dATP were also inhibitors of the 2-OH-dATPase activity and the 8-OH-dGTPase activity, respectively (Table II).

8-OH-dATP Is Another Substrate for hMTH1—The preferential hydrolysis of 2-OH-dATP over 8-OH-dGTP by hMTH1 prompted us to study whether other damaged purine nucleotides are substrates. 8-OH-dATP and (R)-8,5'-cyclo-dATP were incubated with the hMTH1 protein, and their hydrolyses were analyzed by HPLC. As shown in Fig. 5, 8-OH-dATP was hydrolyzed to 8-hydroxy-dAMP by the hMTH1 protein. We found that the Km and kcat values of this reaction were similar to those for 8-OH-dGTP (Fig. 3; Table I). Thus, the hydrolysis of 8-OH-dATP was as efficient as that of 8-OH-dGTP. On the other hand, no hydrolyzing activity of hMTH1 for (R)-8,5'-cyclo-dATP was detected (data not shown). The damaged pyrimidine nucleotides, 5-hydroxy-dCTP and 5-formyl-dUTP, were also not hydrolyzed (data not shown). Therefore, the hMTH1 protein hydrolyzed the three oxidized purine nucleotides, 8-OH-dGTP, 2-OH-dATP, and 8-OH-dATP.

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**TABLE I**

**Substrate specificity of hMTH1**

| Substrate | Km (µM) | kcat (s⁻¹) | kcat/Km (µM⁻¹·s⁻¹) |
|-----------|---------|------------|----------------------|
| pH 8.0    |         |            |                      |
| 2-OH-dATP | 8.3     | 13.9       | 1.68                 |
| 8-OH-dGTP | 15.2    | 12.3       | 0.81                 |
| 8-OH-dATP | 13.9    | 10.8       | 0.78                 |
| dGTP      | 258     | 15.7       | 0.06                 |
| pH 7.2    |         |            |                      |
| 2-OH-dATP | 5.7     | 4.7        | 0.83                 |
| 8-OH-dGTP | 12.8    | 2.1        | 0.16                 |

**FIG. 3.** (A) Reaction rate versus substrate concentration plots and (B) Lineweaver-Burk plots for the hMTH1 activities. The data for 2-OH-dATP (●), 8-OH-dGTP (○), 8-OH-dATP (■), and dGTP (□) were obtained from the HPLC assay, as described under “Experimental Procedures.” Curves were fitted to the Michaelis-Menten equation, based on the kinetic parameters calculated in Table I.

**FIG. 4.** The effects of pH on the hMTH1 activity for 2-OH-dATP and 8-OH-dGTP. The reaction mixture (pH 7.2 to pH 8.8) containing 2 µM 8-OH-dGTP (○) or 2 µM 2-OH-dATP (●) was incubated with 1 nM hMTH1 for 5 min at 30 °C. The reaction rate was calculated as molecules of product formed per molecule of hMTH1 per second.
The reaction mixtures, containing various amounts of substrates (1–10 μM for 2-OH-dATP and 8-OH-dGTP) and inhibitors (0–0.5 μM for 2-OH-dADP and 8-OH-dGDP), were incubated with the hMTH1 protein for 5 min at 30 °C. The inhibition constants, $K_i$ (μM), were obtained by performing linear least-squares fitting to the Dixon plots.

| Activity          | $K_i$ (μM) |
|-------------------|------------|
| 8-OH-dGTPase      | 0.51       |
| 2-OH-dATPase      | 0.72       |
| 8-OH-dATP         | 0.20       |
| 2-OH-dADP         | 0.22       |
| 8-OH-dGTP         | 0.51       |
| 2-OH-dATP         | 0.72       |
| 8-OH-dATP         | 0.20       |
| 2-OH-dADP         | 0.22       |

**FIG. 5. Hydrolysis of 8-OH-dATP by hMTH1, monitored by anion exchange HPLC.** A, separation of standard nucleotides 8-OH-dATP, 8-OH-dADP, and 8-hydroxy-dAMP. B, 5 μM 8-OH-dATP incubated with 1 nM hMTH1 at 30 °C for 5 min. Half of the amount of the 8-OH-dATP reaction mixture was analyzed by HPLC.

**TABLE II**

Inhibition parameters of various nucleotides on the hMTH1 activities

The most striking feature of this study is that hMTH1 hydrolyzed 2-OH-dATP more efficiently and with higher affinity than 8-OH-dGTP (Table I). In particular, a 5-fold difference in the hydrolysis efficiencies for 2-OH-dATP over 8-OH-dGTP was observed at pH 7.2. These results imply that 2-OH-dATP is an intrinsic substrate for hMTH1. In agreement with these findings, it was observed that the 2-OH-dATPase and the 8-OH-dGTPase activities of hMTH1 were competitively inhibited by both 2-OH-dADP and 8-OH-dGDP and that the inhibitory effect of 2-OH-dADP is 3-fold stronger than that of 8-OH-dGDP (Table II). These results indicate that the two damaged bases of these nucleotides share the same recognition site of hMTH1. In addition, hMTH1 also hydrolyzed 8-OH-dATP (Fig. 5). The hMTH1 protein recognizes and hydrolyzes at least three oxidized purine nucleotides.

In contrast to hMTH1, E. coli MutT hydrolyzed neither 2-OH-dATP nor 8-OH-dATP. It has been reported that MutT hydrolyzes 8-OH-dGTP and prevents the mutations caused by this damaged nucleotide (4). The hMTH1 protein also hydrolyzes 8-OH-dGTP and suppresses the mutator phenotype of E. coli mutT-deficient cells (8). Thus, hMTH1 has been proposed to be a functional homologue of E. coli MutT. However, our results indicate that MutT is an imperfect functional counterpart for hMTH1. In addition, the 8-OH-dGTPase activity of MutT, as compared with its undamaged deoxyguanosine triphosphatase activity, was more specific (2000-fold) (4) than that of hMTH1 (14-fold; this study). Moreover, the MutT protein has higher activity for 8-hydroxy-rcTP than hMTH1 (16, 17). Consistent with these findings, the amino acid sequence of MutT has little identity to that of hMTH1, except for the conserved region, which is thought to be a catalytic domain (from the 36th to the 60th amino acid of hMTH1) (8, 18). The MutT protein may also differ from the hMTH1 protein in the structure of its base recognition site, although the predicted secondary structure of hMTH1 resembles that of MutT (12).

It is possible that the MutT protein interacts with some of the nucleotide functional groups, such as the 7-NH and 8-oxo groups. Another possibility is that the MutT protein recognizes specific conformations of oxidized nucleotides. For example, the conformations of the MutT-bound AMP derivative and dGMP are high anti (19), which are part of a syn conformation near the syn-anti boundary (20). 8-OH-dGTP appears to favor a syn conformation (21, 22) and may adopt a high anti conformation in the binding site of MutT. In addition, 8-bromo-dGTP, which also favors a syn conformation, is hydrolyzed with 66-fold higher efficiency as compared with the unmodified dGTP (19). However, the MutT protein did not hydrolyze 8-OH-dATP, which also has 7-NH and 8-oxo groups and adopts a syn conformation (21, 23). Lin et al. (24) reported that the 6-NH$_2$ group of an ATP analogue bound to MutT is located close to Asn-119, and they suggested the existence of electrostatic repulsion between these NH$_2$ groups. They speculated that this unfavorable interaction may determine the preferential binding with dGTP rather than with dATP. The observation that the MutT protein hydrolyzed 8-OH-dGTP but not 8-OH-dATP may be explained by this interaction, at least in part.

It is very interesting how 2-OH-dATP and 8-OH-dATP, in addition to 8-OH-dGTP, are bound to the hMTH1 protein. The kinetic parameters indicate that the affinities to hMTH1 are in the order of 2-OH-dATP > 8-OH-dATP > 8-OH-dGTP. The hMTH1 protein specifically recognized these oxidized purine bases and seemed not to distinguish between damaged adenine and guanine bases. These are critical differences between the hMTH1 activity and the MutT activity. The hMTH1 protein may interact with the 1-NH and/or 2-oxo groups of the 1,2-dihydrouracil or the 2-oxo group of the 2-hydroxy tautomer (25, 26) in addition to the 7-NH and/or 8-oxo groups of 8-OH-dGTP and 8-OH-dATP. However, it is more interesting to speculate that the hMTH1 protein also recognizes the specific conformations of oxidized nucleotides, because 2-hydroxy-dAdo, 8-hydroxy-dAdo, and 8-hydroxy-dGuo all favor the syn conformation (21–23, 27). This speculation agrees with the result that hMTH1 has no activity for (R)-8,5′-cyclo-adenine nucleotide.

On the other hand, no hMTH1 hydrolyase activities for 5-hydroxy-dCTP and 5-formyl-dUTP were detectable. The hMTH1 protein recognizes the three damaged purine bases specifically. The overall shape of the purine base may be required for recognition by hMTH1. The tertiary structures of the hMTH1 protein complexed with 8-OH-dGTP, 2-OH-dATP, and 8-OH-dATP would resolve these modes of substrate recognition.

Recently, it has been shown that two or three proteins other than the p18 hMTH1 protein, which we studied here, are generated by alternative splicing and that these proteins have different NH$_2$ termini (28). The possibility that other forms of hMTH1 may have substrate specificities different from those of the p18 protein should be noted.

We have shown that the hMTH1 protein has three functions: the 2-OH-dATPase, 8-hydroxydeoxyadenosine triphosphatase, and 8-OH-dGTPase activities. Our new findings highlight the possibility that a loss or decrease in the hMTH1 activity is more deeply involved in mutagenesis, carcinogenesis, aging, and other diseases with multiple mechanisms than expected thus far from only its 8-OH-dGTPase activity. Studies with

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2 H. Kamiya and H. Kasai, unpublished results.
3 H. Oda, A. Taketomi, R. Maruyama, R. Itoh, K. Nishio, H. Yakushiji, T. Suzuki, M. Sekiguchi, and Y. Nakabeppe, unpublished results.
4 W. Kamiya and H. Kasai, unpublished results.
MTH1-null mutant mice will provide more insight into the role of this sanitizing enzyme and are in progress.

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