Biochemical and Cytotoxic Actions of 3,6-Dihydroxy-4,5-dimethylphthalaldehyde in Sarcoma 180 Cells

Edward M. Newman and Alan C. Sartorelli

Department of Pharmacology and Developmental Therapeutics Program, Comprehensive Cancer Center, Yale University School of Medicine, New Haven, Connecticut 06510

ABSTRACT

The replication of Sarcoma 180 cells in culture was inhibited by 3,6-dihydroxy-4,5-dimethylphthalaldehyde (HMPA). The inhibition of growth caused by HMPA was evident after treatment of cells with drug for only 15 min. This exposure period caused decreases in (a) cloning efficiency, (b) transport and/or phosphorylation of \([^{3}H]\)thymidine and \([^{3}H]\)uridine, (c) incorporation of radioactive nucleosides into acid-insoluble material, and (d) incorporation of \([^{3}H]\)leucine into protein. Examination of the cytotoxicities of the model compounds 2,3,5,6-tetramethyl-1,4-dihydroquinone (durohydroquinone) and o-phthalaldehyde indicated that the dialdehyde portion of the molecule was responsible for the cytoidal effects of HMPA. The ratio of adenosine triphosphate to adenosine diphosphate in the acid-insoluble fraction of Sarcoma 180 cells incubated in vitro with HMPA for 45 min was reduced in a concentration-dependent manner. The reduction in the ATP pool size produced by HMPA contrasts with the action of the periodate oxidation product of cytidine dialdehyde, which has been reported to increase the intracellular concentration of adenosine triphosphate.

INTRODUCTION

Several \(\alpha,\beta\)-unsaturated aldehydes (4, 16, 17), \(\alpha\)-ketoaldehydes (1, 8, 9), and periodate oxidation products of ribonucleosides (2, 6) have been shown to have antineoplastic activity against transplanted animal tumors. One such compound, inosine dialdehyde (NSC 118994), has been shown to produce objective responses in human cancer (10). Aromatic aldehydes, particularly bifunctional phthalaldehydes, also appeared to be worthy of investigation because they contain reactive aldehyde groups on a molecule which differs structurally from those available previously. Agents of this type were considered to have the potential to create biochemical lesions that were different from those caused by aliphatic aldehydes and periodate oxidation products of nucleosides. In support of the potential of aromatic aldehydes, benzaldehyde, the simplest of the compounds of this class, has recently been reported to be of value in the treatment of a variety of human neoplasms (12).

For these reasons, we synthesized a variety of hydroquinone dialdehydes and structurally related compounds. One of these agents, HMPA (Chart 1), was found to inhibit the replication of Sarcoma 180 cells in culture and to prolong the survival time of mice bearing this neoplasm in ascites cell form (13). DQ, a model for the hydroquinone part of HMPA, and OPA, a model for the aldehyde portion, were cytotoxic at lower concentrations than HMPA, and OPA produced a maximum increase in the survival time of tumor-bearing mice essentially equivalent to that of HMPA but at lower dosage level. In contrast, DQ did not increase the life span of tumor-bearing animals, even at more than 4 times an effective dosage level of HMPA. Despite the difference in the absolute potencies of OPA and HMPA, the therapeutic indices of these compounds were similar.2 We have chosen to study HMPA more extensively, because it appeared to be more amenable to structural modification and to eventual clinical formulation.

This report describes experiments designed to elucidate the biochemical changes associated with the cytotoxicity of HMPA and the structural features necessary to exert these actions. The results demonstrate that HMPA decreases the pool of ATP in Sarcoma 180 cells and the incorporation of \([^{3}H]\)thymidine, \([^{3}H]\)uridine, and \([^{3}H]\)leucine into acid-insoluble material.

MATERIALS AND METHODS

Cytotoxic Activity in Vitro. Sarcoma 180 cells grown in suspension culture in Fischer’s medium supplemented with 10% horse serum, 100 units penicillin per ml, and 100 \(\mu\)g streptomycin per ml were diluted with medium to give a density of 10\(^6\) cells/ml at the initiation of experiments. Drugs were dissolved at 10 times their final concentration in 10% DMSO in PBS and brought to volume with cell suspension. Control cultures contained all components except drug (i.e., 90% medium-containing cells, 9% PBS, and 1% DMSO). Cell numbers were determined in triplicate 24, 48, and 72 hr later with a Coulter Model ZBI particle counter. In some experiments, cells were exposed to drug for 15 min at a density of 10\(^6\) cells/ml. Cells were then resuspended in culture medium at a dilution of 10\(^6\) cells/ml, and incubated at 37\(^\circ\), and cell numbers were determined in triplicate 48 and 72 hr later.

Cloning Efficiency. Cell viability was determined by the ability of cells to form visible clones in soft agar. The method of Chu and Fischer (3) was modified such that the final agar concentration was increased to 0.18%. This allowed the soft agar suspensions to be incubated in 6-well tissue culture plates rather than in culture tubes.

Measurement of DNA, RNA, and Protein Synthesis In Vitro. Sarcoma 180 cells were grown in culture to a density of 10\(^5\) cells/ml and exposed to drugs as described above. Triplicate 1-ml samples were incubated at 37\(^\circ\) with various concentra-

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1 This research was supported in part by USPHS Grants CA-02817 and CA-16359 from the National Cancer Institute.

2 The abbreviations used are: HMPA, 3,6-dihydroxy-4,5-dimethylphthalaldehyde; DQ, durohydroquinone (2,3,5,6-tetramethyl-1,4-dihydroquinone); OPA, o-phthalaldehyde; DMSO, dimethyl sulfoxide; PBS, phosphate-buffered saline (NaCl (0.9 g/liter)-KCl (0.2 g/liter)-Na\(_2\)HPO\(_4\) (1.15 g/liter)-KH\(_2\)PO\(_4\) (0.2 g/liter)); PCA, perchloric acid.

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2 E. M. Newman and A. C. Sartorelli, unpublished observations.
thymidine (6.7 Ci/mmol), [3H]uridine (7.3 Ci/mmol), or [L-3H]leucine (84 Ci/mmol) (New England Nuclear, Boston, Mass.) in 20 μl of aqueous solution were added to each ml of cell suspension. Following incubation for an additional 30 min, cells were collected by centrifugation in an Eppendorf 3200 centrifuge, the supernatant solution was aspirated, and cold 0.2 N PCA was added. Fifty μl of a solution of bovine serum albumin (20 mg/ml) were added, and the precipitate was washed 4 times with 0.2 N PCA. When labeled thymidine or uridine was used as the radioactive precursor, the final pellet was dissolved by heating at 95° for 30 min in 1.2 N PCA and then centrifuged, and a portion of the supernatant solution was taken for scintillation spectrometry. When radioactive leucine was used, the pellet was dissolved by warming at 55° for 15 min in 0.1 N NaOH and neutralized with 0.1 N HCl, and the radioactivity therein was determined by scintillation spectrometry.

**Determination of Nucleotide Pool Sizes.** Packed Sarcoma 180 ascites cells from mice bearing 7-day-old tumors were diluted 10-fold with PBS. One ml of HMPA in 10% DMSO (1 ml of 10% DMSO in PBS for the control suspension) and 1 ml of the cell suspension were added to 8 ml of PBS; flasks were stoppered and gently shaken at 37° for 45 min. The suspensions were transferred to conical tubes and centrifuged for 5 min at 4°. The supernatant solution was aspirated, 0.2 N PCA was added, and the cold acid-insoluble material was separated by centrifugation. The cold acid-soluble supernatant fraction was neutralized with KOH, and, after chilling on ice, potassium perchlorate was removed by centrifugation. An aliquot of the supernatant solution was chromatographed on a Whatman Partisil SAX 10-μm column, using as the eluent a linear gradient of from 0.02 to 0.75 M sodium phosphate buffer, pH 3.3. The gradient, formed with an LKB Ultragrad mixer, reached the final buffer concentration of 0.75 M in 30 min, and this final concentration was maintained until GTP was eluted. A constant flow of 1.8 ml/min was provided by an Altex 100 pump, while the effluent was monitored at 254 and 280 nm.

**Comparison of Cell Growth, Viability, and Radioactive Precursor Utilization in Vitro.** Cultured Sarcoma 180 cells were grown to a density of 10⁵ cells/ml, and cells were exposed to the various agents for 15 min at 37°, collected by centrifugation, and then washed twice in fresh medium. A portion of each culture was diluted with Fischer’s medium containing 10% horse serum to give 10⁵ cells/ml and cultured at 37° for 24, 48, and 72 hr, at which times cell numbers were determined. A second portion of each culture was diluted with Fischer’s medium containing 15% horse serum at densities of 6250, 625, and 62 cells/ml; these cells were cloned as described above. The remainder of each culture was used at its original density (approximately 9 × 10⁴ cells/ml) for radioisotopic incorporation studies as described above, except that drug was not present in the medium during incubation with the radioactive materials, and the cells were washed once with ice-cold 0.9% NaCl solution before the addition of 0.2 N PCA. The cold acid-soluble fraction was neutralized with KOH, and the potassium perchlorate was separated by centrifugation. One portion of the neutralized supernatant fraction was taken directly for scintillation spectrometry. When [3H]thymidine or [3H]uridine was used, one portion was analyzed by anion-exchange high-performance liquid chromatography to determine the distribution of radioactivity in nucleosides and nucleotides. Determination of nucleotide pool sizes was conducted by high-performance liquid chromatography as described above, with the flow rate reduced to 1 ml/min and the initial and final phosphate concentrations being 0.01 and 1 M, respectively. The effluent was collected as 1-min fractions. The identity of the radioactive material in each fraction was determined by comparison of the retention times to those of nonradioactive standards.

**RESULTS**

A comparison of the cytotoxicities of HMPA and the structurally related compounds DQ and OPA to Sarcoma 180 cells in culture following either continuous exposure to these agents or limited treatment for 15 min was carried out, and the results that were obtained are shown in Table 1. Under conditions of continuous exposure, DQ was the most cytotoxic of the agents studied, causing complete inhibition of cellular replication at a concentration of 25 μM. However, the cytotoxicity of DQ was reduced greatly by decreasing the exposure time to only 15 min. In contrast, the toxic effects of HMPA and OPA were essentially the same whether the cells were exposed continuously to these dialdehydes or treated for only 15 min, implying that a rapidly occurring initial event dependent upon the aldehyde moieties was responsible for the cytotoxicity of these agents. That HMPA was cytocidal within the 15-min exposure period was shown by measurement of the efficiency with which

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**Table 1**

*Effects of drug exposure time on the inhibition of Sarcoma 180 cell replication by HMPA, DQ, and OPA*

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Concentration (μM)</th>
<th>Continuous exposure</th>
<th>Limited exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMPA</td>
<td>25</td>
<td>31</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>89</td>
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<tr>
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<td>100</td>
<td>100</td>
<td>99</td>
</tr>
<tr>
<td>DQ</td>
<td>25</td>
<td>100</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>100</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>100</td>
<td>61</td>
</tr>
<tr>
<td>OPA</td>
<td>10</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>73</td>
<td>76</td>
</tr>
</tbody>
</table>

* Cultures at an initial density of 10⁵ cells/ml were incubated for 72 hr in the presence of various concentrations of inhibitor; at 72 hr, the number of cells in untreated control culture tubes was 2.1 × 10⁵ cells/ml.

* After 15 min of incubation in the presence of various concentrations of inhibitors, cells were collected by centrifugation, resuspended in fresh medium at a concentration of 10⁵ cells/ml, and reincubated for 72 hr; the number of cells in untreated control culture tubes at 72 hr was 2.7 × 10⁵ cells/ml.
Sarcoma 180 cells were able to form clones in soft agar after such treatment (Table 2). Thus, the reduction in the number of cells in suspension culture after 72 hr corresponded roughly to the decrease in the surviving fraction, as determined by measurement of cloning efficiency for the various concentrations of HMPA used.

To gain information on the biochemical mechanism of action of HMPA, the effects of this agent were compared with those of OPA and DQ on DNA, RNA, and protein synthesis in vitro. The results from separate experiments with [3H]thymidine, [3H]uridine, and [3H]leucine incorporation into acid-insoluble material as measures of macromolecular synthesis are summarized in Table 3. In agreement with cytotoxicity data, OPA was the most potent of these agents, causing 68 to 79% inhibition of DNA, RNA, and protein synthesis at 25 μM and essentially complete inhibition of these processes at a concentration of 100 μM. HMPA was significantly less inhibitory, particularly at the lower concentration of 25 μM, but caused substantial blockage of these metabolic processes (i.e., 75 to 95%) at the highest concentration tested (100 μM). DQ was the least efficacious of the agents as an inhibitor of macromolecular processes.

Since the effect of a given concentration of HMPA varied somewhat from experiment to experiment, data from individual experiments, each using a single radiolabeled precursor, could not be compared precisely. For this reason, a comparison was made of the effects of HMPA on cellular growth and viability and on metabolic processes in the same experiment. This was accomplished by the exposure of cultured Sarcoma 180 cells to this agent for 15 min followed by resuspension in fresh medium and dilution to a cell concentration appropriate for each portion of the experiment. The ability to replicate, cloning efficiency in soft agar, and the incorporation of [3H]thymidine and [3H]uridine into acid-insoluble and acid-soluble fractions were measured (Tables 4 and 5). In such experiments, HMPA caused slightly less inhibition of [3H]leucine incorporation into protein (Table 6) than of [3H]thymidine or [3H]uridine incorporation into DNA and RNA, respectively. Cell viability was also determined by growth in culture medium and by cloning efficiency in soft agar. These parameters correlated better with the inhibition by HMPA of [3H]thymidine and [3H]uridine incorporation than of [3H]leucine incorporation.

### Table 2

**Effects of HMPA on the cloning efficiency of Sarcoma 180 cells in culture**

<table>
<thead>
<tr>
<th>Concentration (μM)</th>
<th>Efficiency (clones/100 cells)</th>
<th>Surviving fraction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>65 ± 10a</td>
<td>100</td>
</tr>
<tr>
<td>25</td>
<td>29 ± 3</td>
<td>45</td>
</tr>
<tr>
<td>50</td>
<td>1.5 ± 0.3</td>
<td>2</td>
</tr>
<tr>
<td>100</td>
<td>&lt;0.01</td>
<td>&lt;0.02</td>
</tr>
</tbody>
</table>

Mean ± S.E.

### Table 3

**Effects of HMPA, DQ, and OPA on macromolecular synthesis**

Cultured Sarcoma 180 cells in exponential growth (10⁵ cells/ml) were exposed to various concentrations of HMPA for 15 min, washed, and resuspended in fresh medium containing 15% horse serum. Cells were then cloned in soft agar, as described in "Materials and Methods."

### Table 4

**Effects of HMPA on the metabolism of [3H]thymidine by Sarcoma 180 cells in culture**

Cultured Sarcoma 180 cells in exponential growth (10⁵ cells/ml) were exposed to HMPA for 15 min, washed, and incubated for 30 min at 37°C with [3H]thymidine, as described in “Materials and Methods.” The quantity of radioactivity incorporated into acid-soluble and acid-insoluble materials and the distribution of acid-soluble radioactivity in nucleoside and nucleotide fractions were measured. The radioactivity present in the acid-insoluble and acid-soluble fractions of control untreated cells was 7400 cpm/10⁵ cells and 2800 cpm/10⁵ cells, respectively. The cloning efficiency of these cells under the conditions used was 59 ± 3% for control cells; 25, 50, and 100 μM HMPA produced 72 ± 4, 97 ± 1, and 100% inhibition of cloning efficiency, respectively. These levels and conditions produced 25 ± 5, 74 ± 2, and 94 ± 1% inhibition of cellular replication, respectively.

### Table 5

**Effects of HMPA on the metabolism of [3H]uridine by Sarcoma 180 cells in culture**

Conditions were identical to those used in Table 4, except that [3H]uridine was used as the radioactive tracer. The radioactivity present in the acid-insoluble and acid-soluble fractions of control untreated cells was 4400 cpm/10⁵ cells and 6100 cpm/10⁵ cells, respectively.

### Table 6

**Effects of HMPA on the incorporation of [3H]leucine by Sarcoma 180 cells in culture**

Conditions were identical to those utilized in Table 4, except that [3H]leucine was used as the radioactive tracer. The radioactivity present in the acid-insoluble fraction of control untreated cells was 3300 cpm/10⁵ cells.
poration into acid-insoluble material than with its interference with $[^3H]$leucine incorporation into protein (Tables 4 to 6). Interference with the biosynthesis of DNA and RNA by HMPA did not appear to be caused solely by the inhibition of the formation of the nucleotide precursors of these macromolecules. Thus, the radioactivity present as dTTP, the major component of the acid-soluble fraction from labeled thymidine, was reduced only 46% by treatment with 50 μM HMPA; whereas, incorporation in acid-insoluble material was decreased by 88%. An increase in the level of HMPA to 100 μM, however, resulted in a major lowering of the intracellular pool of radioactive dTTP. In an analogous manner, following a 30-min incubation of cells with $[^3H]$uridine, the majority of the acid-soluble radioactive material was present as pyrimidine nucleoside triphosphates (Table 5, 67% of the total radioactivity in the control sample). In contrast to the acid-soluble material derived from $[^3H]$thymidine, a substantial amount of radioactivity (10% of the total) derived from $[^3H]$uridine appeared as pyrimidine nucleoside monophosphate, and another peak of radioactivity indicated the incorporation of $[^3H]$UTP into UDP sugars. Smaller amounts of radioactivity eluted with uridine and UDP.

Treatment of cells with HMPA for 15 min prior to the addition of $[^3H]$uridine caused a concentration-related decrease in the total amount of acid-soluble radioactivity. However, only at the highest level tested (100 μM HMPA) was there a substantial change in the relative proportions of the radioactive peaks. At this drug concentration, nucleoside triphosphate accounted for considerably less of the total radioactivity (30% of the total) than did that of the control cell samples (67% of the total), whereas the proportion of nucleoside and nucleoside mono- and diphosphates accounted for more radiolabel than in control cells. In a manner analogous to that obtained with $[^3H]$thymidine, at each concentration of HMPA, the activation of $[^3H]$-uridine to the level of nucleoside triphosphate was inhibited to a lesser extent than was the incorporation of radioactivity into acid-insoluble material.

The differences in the degree of inhibition by HMPA, shown in various experiments, are due largely to the variability from experiment to experiment experienced with this reactive material and not to differences in experimental design. The results presented in Tables 4 to 6 were obtained from one experiment by triplicate determinations of each of the parameters measured; thus, they can be directly compared.

The effects of HMPA on adenine nucleotide profiles of Sarcoma 180 ascites cells were determined by high-pressure liquid chromatography of cold acid-soluble extracts (Table 7). Cells treated with 25 and 50 μM, HMPA showed decreases in the size of the ATP peak, slight increases in the size of the ADP peak, and substantial increases in the amount of material which cochromatographed with AMP. In contrast, however, cells treated with 100 μM HMPA had a decrease in the size of all of the adenine nucleotide pools.

**DISCUSSION**

The mechanism by which the dihydroxydicarboxaldehyde HMPA exerts its cytotoxicity to Sarcoma 180 cells was compared with DQ, a model compound for the hydroquinone portion of HMPA, and OPA, which was used as a model for the o-dicarboxaldehyde part of the structure. We found that OPA and HMPA inhibited cellular proliferation whether they were present continuously or for only the first 15 min of incubation, whereas the cytotoxicity of DQ was reversed by replacing the culture medium with drug-free medium after 15 min of exposure to this agent, indicating that a relatively rapid event dependent upon the dialdehyde group was largely responsible for the cytotoxicity of HMPA. Furthermore, the fact that DQ was not rapidly cytocidal may explain at least, in part, the ineffectiveness of the hydroquinone as an anticancer agent in vivo (13).

The effects of aldehydes on DNA, RNA, and protein synthesis have not been examined carefully for all of these agents reported to have antineoplastic activity, but in those instances where such effects have been studied, the formation of one or more of these macromolecules has been shown to be affected. Not all of the aldehydes have identical actions. Although the periodate oxidation products of inosine and 6-methylthiopurine ribonucleoside inhibited all 3 biosynthetic pathways to approximately the same extent (2, 15), methylglyoxal was reported to decrease the rate of formation of protein to a greater degree than that of either RNA or DNA (6, 14). OPA and HMPA reduced the incorporation of $[^3H]$thymidine, $[^3H]$uridine, and $[^3H]$leucine into macromolecular material, with OPA being the more potent inhibitor of each of these processes. The interpretation of the results obtained with $[^3H]$leucine as a tracer is ambiguous, since OPA is known to react chemically with amines (5). HMPA should be similar in its degree of reactivity, but the finding that HMPA inhibits $[^3H]$leucine incorporation into protein of cells pretreated with this agent in drug-free medium argues against the possibility that inhibition results from a direct chemical reaction. Moreover, the chemical reaction of these compounds is not specific for leucine, and the total concentration of amino acids in the medium is in vast excess over the trace amount of $[^3H]$leucine added. DQ also interfered with the biosynthesis of DNA, RNA, and protein but to a lesser degree than did OPA and HMPA. These findings are in accord with the postulate that the carboxaldehyde groups of HMPA are the major part of the molecule responsible for the observed cytotoxicity and antineoplastic activity. The hydroxyl groups, ortho to each aldehyde, decreased the potency of HMPA relative to OPA (which lacks the hydroxyl groups) in vitro as well as in vivo (13). However, there did not appear to be any discernible qualitative difference in the effects of HMPA and OPA, and HMPA because of its better capacity for formulation would appear to be the superior candidate for ultimate clinical trial.

$[^3H]$Thymidine and $[^3H]$uridine require activation to their respective triphosphates before they can be incorporated into DNA and RNA by polymerase enzymes. The acid-soluble fraction was examined to determine if the effect of HMPA occurred

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**Table 7**

**Effects of HMPA on adenine nucleotide pool sizes of Sarcoma 180 cells in vitro**

Packed Sarcoma 180 cells collected from the ascitic fluid of tumor-bearing mice were diluted 100-fold with PBS and incubated in the absence and presence of the indicated concentrations of HMPA for 45 min. The control samples contained 1.3 mmol AMP per 10⁶ cells, 2.0 mmol ADP per 10⁶ cells, and 3.5 mmol ATP per 10⁶ cells.

<table>
<thead>
<tr>
<th>Concentration (μM)</th>
<th>AMP</th>
<th>ADP</th>
<th>ATP</th>
<th>AMP + ADP + ATP</th>
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<tr>
<td>25</td>
<td>114</td>
<td>109</td>
<td>90</td>
<td>82</td>
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<td>115</td>
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<tr>
<td>100</td>
<td>36</td>
<td>15</td>
<td>5</td>
<td>18</td>
</tr>
</tbody>
</table>

\[
\text{% of control} = \frac{\text{Sample} - \text{Control}}{\text{Control}} \times 100
\]

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*Actions of Phthalaldehydes*

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at an enzymatic step that preceded polymerization into the nucleic acids. The total amount of radioactive material in the acid-soluble fraction of cells was reduced greatly by treatment with HMPA, suggesting that the transport and/or phosphorylation of both nucleosides (i.e., \(^{3}H\)thymidine and \(^{3}H\)uridine) was inhibited. The accumulation of \(^{3}H\)thymidine and \(^{3}H\)uridine in the nucleotide fraction and particularly in the ribonucleoside triphosphate portion of the acid-soluble material was decreased by HMPA in a concentration-dependent manner; however, the decreases did not entirely account for the depression in the amount of radioactivity incorporated into the acid-insoluble fraction.

The ratio of ATP to ADP in the acid-soluble fraction of Sarcoma 180 cells incubated with HMPA in vitro was reduced in a concentration-dependent manner. Since ATP pool sizes were determined under conditions different from those described for measurement of nucleic acid and protein synthesis, quantitative comparisons between this and other effects of HMPA cannot be made. However, ATP is important in nucleoside phosphorylation and macromolecular synthesis; thus, the decrease in ATP produced by HMPA may contribute to the inhibition of these other processes. The findings are also consistent with the original premise of possible differences in the mechanism of action of the aromatic aldehydes and the periodate oxidation products of nucleosides, inasmuch as Kinahan et al. (11) have reported that the antineoplastic agent cytidine was inhibited. The accumulation of \[^{3}H\]thymidine and \[^{3}H\]uridine in the nucleotide fraction and particularly in the ribonucleoside triphosphate portion of the acid-soluble material was decreased by HMPA in a concentration-dependent manner; however, the decreases did not entirely account for the depression in the amount of radioactivity incorporated into the acid-insoluble fraction.

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