Elevated Plasma and Urinary Guanosine 3':5'-Monophosphate and Increased Production Rate in Patients with Neoplastic Diseases


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ABSTRACT

The plasma and 24-hr urinary levels of cyclic adenosine 3':5'-monophosphate and of cyclic guanosine 3':5'-monophosphate (cGMP) were determined for 19 healthy normal patients, 54 patients with six types of nonneoplastic diseases (cholelithiasis, peptic ulcer, coronary heart disease, hypertension, regional ileitis, and cirrhosis), and 54 patients with five types of neoplastic disease (cancers of the lung, colon, and breast, acute myelocytic leukemia, and Hodgkin's disease). The cyclic adenosine 3':5'-monophosphate levels of urine and plasma in normal subjects, in noncancer subjects, and in cancer subjects did not differ significantly. The cGMP levels in the noncancer group were similarly unchanged from those in the normal group. However, mean cGMP levels in the urine and plasma of patients with neoplastic diseases were, respectively, 2- and 3-fold greater than the normal values (p < 0.005 for urine and p < 0.05 for plasma). Pharmacokinetic studies with [3H]cGMP in nine healthy controls and 15 patients with neoplasia showed that the mean production rate of this nucleotide in patients with metastatic cancer was elevated when compared to normal patients, but many values fell within the normal range. In acute leukemia, the production rate was seven times normal, with four of five patients having values clearly outside the normal range. The plasma clearance rate in patients with neoplasia was not decreased when compared to that in normal patients. It is proposed that an increased production rate, rather than any change in plasma clearance, accounts for the increased levels of cGMP in the plasma and urine of some patients with neoplastic disease.

INTRODUCTION

Observations in bacteria, mammalian cell cultures, and mammalian tumors have shown that the cyclic nucleotides cAMP and cGMP influence cell division and differentiation (1, 19). In Escherichia coli, intracellular cGMP was maximal and cAMP was minimal during logarithmic growth. This pattern was reversed in the stationary phase (1). When lymphocytes, splenic cells, or fibroblasts were stimulated to proliferate by phytohemagglutinin, periodate, or serum, intracellular cGMP increased markedly before mitosis took place (22, 23). Moreover, exogenous cGMP stimulated mouse fibroblasts to synthesize DNA and divide. Conversely, as fibroblasts cultured in serum passed from a dividing to a quiescent state with increasing cell density, intracellular cGMP declined and cAMP rose. In virally transformed fibroblasts unresponsive to contact inhibition, cAMP failed to rise and mitosis failed to stop as cell density increased (33).

Many studies have shown abnormalities in cAMP and cGMP in association with cancer. Although most initial cell culture work and some in vivo studies showed decreased levels of cAMP in transformed cells (14, 24-26, 35, 41), other in vivo cancers studied have had increased intracellular levels of cAMP (6, 8, 30, 35, 42). A wide range of values in the same tumor type has been noted (14, 18, 40).

Recently, there has been increased interest in the role of cGMP in cancer. In vivo studies have shown elevated intracellular cGMP levels in many lines of Morris hepatoma (24, 42), in ethionine-induced hepatomas (16), and in 1,2-dimethylhydrazine-induced rat colon carcinoma (41). Levels of cGMP were higher in human colon cancer tissue than in surrounding mucosa when expressed as pmol/g of wet weight; however, there was no significant difference between levels in cancerous and noncancerous tissue when expressed relative to g of protein or mg of DNA (14). When rats were exposed to 2 different carcinogens, increased tissue levels of cGMP were noted to coincide temporally with the onset of identifiable malignant cells (3, 15).

Crisis and Murad (10) and Murad et al. (31) demonstrated increased urinary excretion of cGMP in animals bearing transplanted hepatic or renal tumors of rapid or intermediate growth but normal excretion in animals bearing other tumors of slow or intermediate growth rate. Three human patients with hepatoma had markedly elevated urinary levels of cGMP when compared to normal patients (32). In another human study, the mean ratio of cGMP to creatinine in the urine was elevated in 26 patients with a variety of cancers (20). Changes in cGMP and cAMP excretion during pregnancy have also been noted (29). Our own preliminary studies (7) showed significant elevations of mean plasma cGMP in patients with Hodgkin's disease, AML, and cancers of the lung, colon, and breast. Mean urinary cGMP was elevated in all tumor types when corrected for creatinine excretion; uncorrected excretion of cGMP was increased only in Hodgkin's disease and AML. In contrast, mean cGMP plasma levels and urinary excretion did not differ significantly from normal in 33 patients with nonneoplastic diseases.

Because of these indications of the importance of abnormalities in cGMP metabolism in cancer, we have used pharmacokinetic techniques (5) to evaluate the extracellular metabolism of cGMP in patients with cancers. We specifically wanted to know whether the increased plasma and urinary levels were...
due solely to accelerated production of the nucleotide, as one might expect, or whether any abnormalities in clearance contributed to this picture. We also report the plasma and urinary values of cGMP in a larger group of patients than in our previous study.

MATERIALS AND METHODS

Materials

Kits for measurement of cAMP (by RIA) were purchased from New England Nuclear, Boston, Mass. Kits for cGMP were from Schwarz/Mann Laboratories, Orangeburg, N. Y. All ion-exchange resins and nucleotides (cGMP, ATP, ADP, AMP, adenosine and guanosine 2':3'-monophosphate, GMP, GDP, and GTP) were from Sigma Chemical Co., St. Louis, Mo. [3H]cGMP was from New England Nuclear, Boston, Mass.

Subjects

Normal. This group consisted of 19 healthy volunteers (10 men and 9 women), 24 to 61 years of age.

Nonneoplastic Diseases. This group consisted of 54 hospital patients (32 men and 22 women), 29 to 64 years of age, with 6 types of nonneoplastic cardiovascular or gastrointestinal diseases as shown in Table 1.

Neoplastic Diseases. This group consisted of 54 hospital patients (34 men and 20 women), 26 to 60 years of age, with 5 types of disseminated neoplastic disease as shown in Table 1.

Patients with urinary tract infection or elevated serum creatinine or blood urea nitrogen were excluded from the study. Medications had not been taken during the 4 days before the cyclic nucleotide analyses. Anticancer chemotherapy had not been given during the preceding month.

Experiments

In the first phase of the study, fasting plasma cAMP and cGMP and 24-hr urinary excretion of the 2 nucleotides were measured by RIA (39) in all 127 subjects. The validity and specificity of the cGMP and cAMP assays were determined as described by Broadus et al. (5).

Preparation of [3H]cGMP. Tritium-labeled cGMP (2.2 μCi/nmol) at a concentration of 500 μCi/ml was diluted to a concentration of 50 μCi/ml using sterile 0.85% NaCl solution. The final solution was sterilized by passage through a Millipore filter into a sterile vial and then stored at −20° until use.

Specimen Collection and Processing. Subjects took nothing other than water p.o. for at least 7 hr before study. A spot urine sample and a blood sample were then collected for determination of cAMP, cGMP, and creatinine. A vial of [3H]cGMP was thawed, and a 0.5-ml aliquot was taken for counting. A dose of approximately 10 to 15 μCi/sq m body surface area was rapidly injected into an antecubital vein. The actual dose administered was calculated by determining the volume of solution injected (weight of the syringe before the injection minus the weight of the syringe after the injection) and multiplying by the actual counts/ml as determined from the aliquot drawn for this purpose. Seven-ml blood samples were drawn at 2-min intervals for the first 20 min, at 5-min intervals for the next 20 min, then at 10-min intervals for 20 min, and finally at 20-min intervals for 1 hr. These samples were placed in chilled tubes and centrifuged for 10 min with 10 min of the time of collection. The plasma was immediately separated and frozen at −80° until analyzed. Urine was collected in refrigerated containers for 24 hr following tracer injection. Samples were then stored at −80° until analyzed.

Analysis of Plasma and Urine cGMP. Specimens were thawed and placed in an ice bath. One ml of plasma was then added to 1 ml of 10% trichloroacetic acid solution for deproteinization. This was centrifuged for 10 min, and the supernatant was applied to Dowex 50X-H column (0.5 x 5 cm) and eluted with 5 ml of water. The eluate was collected in a scintillation vial and evaporated to dryness. It was redissolved in 1 ml of water, and scintillation fluid was added. Samples were then counted for 10 min.

A background was obtained by counting 0.5 ml of base-line plasma and urine plus scintillation fluid directly. The urine and plasma levels of cAMP and cGMP were measured by the method of Broadus et al. (5) in 9 normal and 15 cancer patients. Details of the pharmacokinetic study are given below. Tracer studies were performed essentially as described by Broadus et al. (5).

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Table 1

Average urine and plasma levels of 19 normal subjects, 54 subjects with nonneoplastic diseases, and 54 subjects with metastatic cancers

<table>
<thead>
<tr>
<th>Group</th>
<th>cAMP</th>
<th>cGMP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Urine (nmol/24 hr)</td>
<td>Plasma (pmol/ml)</td>
</tr>
<tr>
<td>Normal subjects (19*</td>
<td>6422 ± 1744</td>
<td>15.0 ± 2.7</td>
</tr>
<tr>
<td>Cholelithiasis (5)</td>
<td>6262 ± 1293</td>
<td>16.0 ± 2.9</td>
</tr>
<tr>
<td>Peptic ulcer (9)</td>
<td>6000 ± 1945</td>
<td>13.6 ± 3.9</td>
</tr>
<tr>
<td>Coronary heart disease (10)</td>
<td>5569 ± 1238</td>
<td>13.5 ± 3.6</td>
</tr>
<tr>
<td>Hypertension (9)</td>
<td>6363 ± 1389</td>
<td>13.6 ± 3.3</td>
</tr>
<tr>
<td>Regional ileitis (7)</td>
<td>5243 ± 2582</td>
<td>14.1 ± 5.1</td>
</tr>
<tr>
<td>Cirrhosis (12)</td>
<td>7637 ± 2200</td>
<td>18.2 ± 4.0</td>
</tr>
<tr>
<td>Carcinoma of lung (9)</td>
<td>6994 ± 2689</td>
<td>16.2 ± 5.8</td>
</tr>
<tr>
<td>Carcinoma of colon (10)</td>
<td>5430 ± 2506</td>
<td>14.1 ± 4.3</td>
</tr>
<tr>
<td>AML (14)</td>
<td>6471 ± 2478</td>
<td>16.5 ± 4.2</td>
</tr>
<tr>
<td>Carcinoma of breast (11)</td>
<td>6590 ± 2175</td>
<td>15.8 ± 4.0</td>
</tr>
<tr>
<td>Hodgkin’s disease (10)</td>
<td>6475 ± 1855</td>
<td>16.5 ± 4.2</td>
</tr>
</tbody>
</table>

* Numbers in parentheses, number of subjects.
| Mean ± S.D. |
| p vs. normal, p < 0.005. |
| p vs. normal, p < 0.05. |

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plasma standards were prepared by adding [3H]cGMP to baseline plasma and urine submitting this sample with known counts to the above procedures. Recovery was 50 to 60%.

Endogenous cGMP and cAMP were measured by RIA as mentioned above.

Calculations. Calculations were performed essentially as described by Broadus et al. (5). The "2-compartment open model" adequately described the fate of bolus injections of [3H]cGMP. Plasma is the source of virtually all of the cGMP excreted (4, 5).

Plasma concentrations of [3H]cGMP were plotted on a logarithmic scale against time. Two distinct exponential components were resolvable from the curve; these were fitted graphically by the method of least squares using a computer. The plasma concentration of [3H]cGMP as a function of time could then be expressed as the sum of 2 exponentials:

\[ C_p = A e^{-\alpha t} + B e^{-\beta t} \]

where \( C_p \) is the concentration of [3H]cGMP at any point in time, \( A \) and \( B \) are the intercepts on the ordinate of the "fast" and "slow" components, \( \alpha \) and \( \beta \) are the slopes of the 2 exponential components, and \( t \) is time.

From this curve, the metabolic clearance rate, or PCR (ml/min), can be derived. This is defined as the volume of plasma completely and irreversibly cleared of cGMP per unit of time and is calculated from the formula:

\[ \text{PCR} = \frac{\text{Dose} [3H]cGMP \text{injected}}{\int C_p [3H]cGMP dt} \]

The PCR can be divided into the RCR and the ECR. The RCR is defined as the volume of plasma completely and irreversibly cleared of cGMP by urinary excretion per unit of time and may be calculated from the formula:

\[ \text{RCR} = \text{PCR} \times \frac{\text{total urinary [3H]cGMP}}{\text{total injected [3H]cGMP}} \]

The ECR is defined as the volume of plasma completely and irreversibly cleared of cGMP by nonrenal mechanisms and may be calculated from the formula:

\[ \text{ECR} = \text{PCR} - \text{RCR} \]

The other parameter which can be determined is the PR, which is the rate of entry of cGMP into the plasma. If the concentration of cGMP in plasma remains constant, the amount entering the plasma must equal that removed through clearance. Thus,

\[ \text{PR} = \text{PCR} \times [3H]cGMP \text{plasma} \]

The constancy of the plasma concentration of cGMP was demonstrated by serial determinations at 0, 15, 30, and 60 min.

RESULTS

Mean (±2 S.D.) levels of cAMP and cGMP in nontumor subjects were as follows: plasma cAMP, 15.0 ± 5.4 pmol/ml; plasma cGMP, 5.5 ± 2.4 pmol/ml; urine cAMP, 6,422 ± 3,488 nmol/24 hr; urine cGMP, 730 ± 304 nmol/24 hr (also see Table 1). There was no significant difference (p > 0.05) in the values due to age or sex of the subjects. Cyclic nucleotide contents of samples drawn at 8:00 a.m. or 4:00 p.m. did not differ significantly. In none of the 6 types of nonneoplastic diseases did plasma or urine levels of cAMP or cGMP differ significantly from normal (p > 0.05). These values were also within the range reported in the literature (5, 20). In cancer patients, plasma and urine cAMP did not differ from that in normal patients. In contrast, mean values of cGMP in plasma (p < 0.05) and in 24-hr urine collections (p < 0.005) were elevated in all 5 groups of cancer subjects. The extent of this increase was most marked in the AML patients and least in cancer of the colon.

Table 2 gives the results of pharmacokinetic experiments involving 9 controls and 15 patients with neoplastic diseases. The patients are arranged in order of increasing PR. The mean PCR, ECR, and RCR of cGMP were not significantly elevated as compared to controls. RCR averaged 9% of PCR in cancer patients as compared to 12% in our controls and 13.3% in the series of Broadus et al. (5).

PR ranged from 2.79 to 8.29 nmol/min, with a mean of 5.13, in our controls and from 6.6 to 12.7 nmol/min, with an average of 8.5, in the series of Broadus et al. (5). The PR in patients with solid tumors ranged from 4.61 to 13.6 nmol/min, with a mean of 8.03. In contrast, the PR in leukemic patients and lymphoma patients ranged from 8.32 to 70.34 nmol/min, with a mean of 38.02, and all of these patients except one had a PR of greater than 20 nmol/min. There was no correlation between numbers of circulating blasts and PR of cGMP. For example, Patient R. W. had a WBC of 38,500, 40% of which were blasts, and a PR of 8.32 nmol/min; Patient C. T. had a WBC of 4,100 with 1% blasts, a normocellular marrow with 28.3% blasts, and a PR of 70.34 nmol/min; and Patient L. J. had 184,000 circulating WBC, all of which were lymphoma cells, and a PR of 23.27 nmol/min.

The plasma level of cGMP was strongly correlated with its PR as shown in Chart 1. This could be expressed as:

\[ \text{Plasma cGMP (pmol/ml)} = 0.938 \times (\text{PR}) + 0.716 \]

The correlation coefficient was 0.88.

DISCUSSION

The elevated plasma and urine levels of cGMP in cancer patients as compared to normal controls and patients with various nonmalignant diseases provide further evidence that abnormal metabolism of this nucleotide is an important feature of human cancers. The pharmacokinetic studies indicate that this abnormality is intracellular; i.e., the extracellular metabolism of cGMP is normal.

The increased "PR" described here of course refers to an increased rate of entry of cGMP into plasma. This may be due to increased production of cGMP secondary to increased activity of guanylate cyclase, the enzyme primarily responsible for synthesis of this nucleotide, to decreased hydrolysis secondary to abnormalities in cGMP PDE or to increased cellular extrusion of the nucleotide.

Carcinogens may either stimulate or depress guanylate cyclase activity (9, 43); therefore, it is not surprising that total guanylate cyclase activity in the studies cited below has been found to be normal, reduced, or increased. In addition to abnormalities in total activity, variations in subcellular distribution have been described. In hepatic cancer, both transplanted...
Table 2

Urine and plasma levels of cGMP and its PCR, ECR, RCR, and PR. Subjects are ranked in order of increasing PR.

<table>
<thead>
<tr>
<th>Subject Diagnosis</th>
<th>Plasma cGMP (pmol/ml)</th>
<th>Urine cGMP (n mole/24 hr)</th>
<th>PCR (ml/min)</th>
<th>ECR (ml/min)</th>
<th>RCR (ml/min)</th>
<th>PR (nmol/min)</th>
</tr>
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<tbody>
<tr>
<td>Normal patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>3.8</td>
<td>820</td>
<td>798</td>
<td>2.79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4.0</td>
<td>610</td>
<td>968</td>
<td>3.34</td>
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<tr>
<td>3</td>
<td>9.4</td>
<td>900</td>
<td>444</td>
<td>3.35</td>
<td></td>
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</tr>
<tr>
<td>4</td>
<td>7.8</td>
<td>590</td>
<td>589</td>
<td>4.27</td>
<td></td>
<td></td>
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<tr>
<td>5</td>
<td>5.4</td>
<td>870</td>
<td>903</td>
<td>5.10</td>
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</tr>
<tr>
<td>6</td>
<td>4.3</td>
<td>770</td>
<td>1,280</td>
<td>5.76</td>
<td></td>
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<tr>
<td>7</td>
<td>7.3</td>
<td>910</td>
<td>914</td>
<td>6.54</td>
<td></td>
<td></td>
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<tr>
<td>8</td>
<td>7.1</td>
<td>770</td>
<td>952</td>
<td>6.76</td>
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<tr>
<td>9</td>
<td>8.0</td>
<td>910</td>
<td>1,090</td>
<td>8.29</td>
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<tr>
<td>Mean ± S.D.</td>
<td>6.3 ± 0.64</td>
<td>794 ± 39</td>
<td>882 ± 79</td>
<td>770 ± 109</td>
<td>100 ± 11</td>
<td>5.13 ± 0.58</td>
</tr>
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</table>

Cancer Patients

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Plasma cGMP (pmol/ml)</th>
<th>Urine cGMP (n mole/24 hr)</th>
<th>PCR (ml/min)</th>
<th>ECR (ml/min)</th>
<th>RCR (ml/min)</th>
<th>PR (nmol/min)</th>
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<tbody>
<tr>
<td>Adenocarcinoma colon</td>
<td>4.4</td>
<td>930</td>
<td>1,059</td>
<td>4.61</td>
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<tr>
<td>Adenocarcinoma colon</td>
<td>6.6</td>
<td>1,050</td>
<td>700</td>
<td>4.82</td>
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<td>Adult Wilms’ tumor</td>
<td>4.1</td>
<td>550</td>
<td>1,139</td>
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<td>Adenocarcinoma colon</td>
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<td>890</td>
<td>913</td>
<td>5.69</td>
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<td>Adenocarcinoma colon</td>
<td>6.5</td>
<td>485</td>
<td>864</td>
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<td>Breast cancer</td>
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<td>1,680</td>
<td>984</td>
<td>8.22</td>
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<tr>
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<td>4,650</td>
<td>750</td>
<td>8.32</td>
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<td>Adenocarcinoma colon</td>
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<td>780</td>
<td>1,545</td>
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<td>Carcinoma thyroid</td>
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<td>Adenocarcinoma colon</td>
<td>9.4</td>
<td>1,150</td>
<td>1,010</td>
<td>11.56</td>
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<td>Oat cell carcinoma lung</td>
<td>13.4</td>
<td>2,460</td>
<td>982</td>
<td>13.5</td>
<td></td>
<td></td>
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<tr>
<td>Lymphosarcoma cell leukemia</td>
<td>18.3</td>
<td>1,740</td>
<td>1,271</td>
<td>23.27</td>
<td></td>
<td></td>
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<tr>
<td>Immuneblastic lymphadenopathy</td>
<td>33.0</td>
<td>6,800</td>
<td>825</td>
<td>27.23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blast crisis of chronic myelocytic leukemia</td>
<td>60.3</td>
<td>12,400</td>
<td>1,038</td>
<td>65.42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± S.D.</td>
<td>17.9 ± 4.9</td>
<td>3,233 ± 904</td>
<td>1,001 ± 52</td>
<td>888 ± 59</td>
<td>84.8 ± 7.3</td>
<td>18.3 ± 5.3</td>
</tr>
</tbody>
</table>

*p vs. normal <0.05 <0.005 >0.05 >0.05 <0.05 <0.01

hr after unilateral nephrectomy (36). Other abnormalities in tumor guanylate cyclase have been observed, including inability to use magnesium as a cofactor (12) and failure to be activated by sodium azide (Na3N) (11, 12). Thus, abnormalities in guanylate cyclase in some cancers may lead to increased intracellular levels and ultimately to increased entry of cGMP into the plasma.

Abnormalities of the enzyme responsible for catabolism of cGMP (cGMP PDE) have also been reported and are also highly variable (34, 37). The increases in cGMP associated with compensatory renal hypertrophy after unilateral nephrectomy are caused by increased guanylate cyclase activity without a compensatory increase in cGMP PDE activity (36). Fetal guinea pig tissues show increased cGMP PDE activity (13). A longitudinal study of the effects of the carcinogen 3'-methyl-4-dimethyl-aminozobenzene on rat liver revealed early increases in both guanylate cyclase and cGMP PDE activity, with a decrease in cGMP levels. As recognizable malignant cells appeared, there was a further rise in guanylate cyclase activity without a further rise in cGMP PDE activity. Thus, the tumor was characterized by increased activity of both guanylate cyclase and cGMP PDE (3). Established ethionine-induced hepatomas also had elevated cGMP PDE activity, but this appeared to be an unsuccessful attempt to compensate for increased guanylate cyclase activity (16). Studies in yet another liver tumor (variants of Morris hepatoma) have shown decreased levels of cGMP PDE (24). In contrast, in human and murine lymphatic leukemic tissues, cGMP PDE activity was markedly elevated (17), and an increase in low-Km PDE’s of cAMP and cGMP was found in human breast cancer tissue (38). Hence, low PDE activity, either absolute or relative to guanylate cyclase activity, may also contribute to increased entry of cGMP into plasma in some tumor systems.

hepatomas (12, 25, 28) and ethionine-induced tumors (16) have an increased particulate fraction of guanylate cyclase relative to the soluble fraction. Similar changes are found in regenerating liver after hepatectomy and, interestingly, in non-involved host liver (28). This increase in the particulate fraction is not due to a translocation of enzyme from the soluble fraction (16): new protein synthesis is required (28). These changes were also observed in 2 transplanted renal tumors (11), but the opposite pattern was observed in human renal adenocarcinoma (27) and in the contralateral hypertrophying kidney 1
A third mechanism by which malignant cells might contribute to increased entry of cGMP into plasma is abnormal extrusion of the nucleotide. The extent to which this mechanism is used as a method of control of intracellular levels of cGMP is not known, although it is clear that such extrusion does occur (4, 21), especially during mitosis (44).

Solid tumors may hydrolyze large quantities of extracellular cGMP within the confines of the tumor before the nucleotide gains access to the plasma. Thus, the increased rate of entry of cGMP in patients with leukemia and lymphoma relative to other cancers may merely reflect the proximity of these cells to the plasma. However, it is also possible that abnormalities in cGMP metabolism are more marked in these cells than in other tumor cells. Studies of the intracellular metabolism of cGMP in leukemia are needed to resolve this issue.

Once cGMP is in the circulation of the cancer patient, its fate apparently resembles its fate in normal people. Renal excretion accounts for approximately 10% of the total metabolic clearance; the organs responsible for the remaining 90% are not known. In the dog, there is evidence for both hepatic and renal metabolism of cyclic nucleotides (2); presumably, this also occurs in humans. Shifts in the relative proportion of cGMP metabolized by various organs would not be detected by this method.

Although the probable source of this increased cGMP is the malignant tissue, increased production by organs not directly involved by the tumor must also be considered. Some of the increased circulating cGMP may represent the body’s reaction to increased entry of cGMP into plasma is abnormal extrusion of the nucleotide. The organs responsible for the remaining 90% are not known. In the dog, there is evidence for both hepatic and renal metabolism of cyclic nucleotides (2); presumably, this also occurs in humans. Shifts in the relative proportion of cGMP metabolized by various organs would not be detected by this method.

In conclusion, the increased plasma and urinary levels of cGMP in a variety of human cancers reflect an increased rate of entry of the nucleotide into the plasma; the extracellular metabolism of this compound apparently remains normal. Studies to define more clearly the nature of the intracellular abnormalities responsible for this increased rate of entry are clearly needed.

REFERENCES
Elevated Plasma and Urinary Guanosine 3′:5′-Monophosphate and Increased Production Rate in Patients with Neoplastic Diseases


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