GUANOSINE 3', 5'-CYCLIC MONOPHOSPHATE LEVEL IN PLASMA OF PATIENTS WITH CANCER AND VARIOUS DISEASES

BY

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ABSTRACT

Guanosine 3' 5'-cyclic monophosphate (cGMP) in the plasma of normal persons and patients with lung or breast cancer and other kinds of neoplasma or other diseases was determined using radioimmunoassay. In comparison with normal persons, significant elevation occurred in the cGMP in the plasma of patients with various kinds of cancer or renal insufficiency.

The average cGMP values in the plasma of eight normal persons, 16 patients with lung cancer, 16 patients with breast cancer, five patients with oesophagus cancer, three patients with liver cancer, three patients with stomach cancer, ten patients with renal insufficiency and two patients with myocardial infarction, were respectively 3.46, 9.05, 5.33, 5.42, 7.33, 1.66, 19.55, and 8.0 pmol per ml of plasma. There was no elevation in the cGMP in the plasma of the patients with other diseases studied.

INTRODUCTION

Cyclic nucleotides (cAMP, cGMP) have been demonstrated to mediate the hormonal response by acting as "second messengers" in a variety of living cells (Robison et al.10). There have been many studies on the role of cAMP in cultured cells and various mammalian tissues. However, there is relatively little information about the possible role of cGMP, although cGMP has been postulated to be a positive intracellular mediator triggering cell growth (Hadden et al.4).

We are interested in whether the level of cGMP in the serum would be useful as a clinical test in evaluating several kinds of cancers or other metabolic disorders. So we tried to measure the cGMP in the plasma of the patients with cancer or other diseases, using radioimmunoassay to observe the function of the cGMP in the human body.

MATERIALS AND METHODS

All the patients, except those with renal insufficiency, had a normal renal function (endogeneous creatinine clearance greater than 90 ml/min).

The diagnosis of cancer was proven by biopsy or by autopsy.

Venous blood, drawn either from volunteer laboratory workers or patients, was mixed with Versene (final concentration 5 mM) and centrifuged at 750×g for 15 minutes at 4°C. The plasma was removed with a capillary pipette and stored at −20°C for cGMP determination.

An 100 µl-aliquot of plasma was then analyzed for cGMP by using the Yamasa cGMP assay kit which contains a succinylation reagent, 125I-labelled succinylated cGMP tyrosine methyl ester and anti-cGMP rabbit serum, according to the method of

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Table 1. Average Values of cGMP in Plasma and Their Standard Deviations Calculated From Fig. 1

<table>
<thead>
<tr>
<th>Donor</th>
<th>No of patients</th>
<th>Average values of cGMP in plasma pmol/ml</th>
<th>Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>8</td>
<td>3.46</td>
<td>0.52</td>
</tr>
<tr>
<td>Miscellaneous cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>16</td>
<td>9.05</td>
<td>4.85</td>
</tr>
<tr>
<td>Breast</td>
<td>16</td>
<td>5.39</td>
<td>1.79</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>5</td>
<td>5.42</td>
<td>1.15</td>
</tr>
<tr>
<td>Liver</td>
<td>3</td>
<td>7.33</td>
<td>3.90</td>
</tr>
<tr>
<td>Stomach</td>
<td>3</td>
<td>11.66</td>
<td>6.02</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>10</td>
<td>19.55</td>
<td>9.19</td>
</tr>
<tr>
<td>Aplastic anemia</td>
<td>8</td>
<td>4.05</td>
<td>2.48</td>
</tr>
<tr>
<td>Acute myelogenous leukemia</td>
<td>4</td>
<td>2.42</td>
<td>1.36</td>
</tr>
<tr>
<td>Acute lymphoblastic leukemia</td>
<td>4</td>
<td>2.93</td>
<td>1.13</td>
</tr>
<tr>
<td>Arteriosclerosis</td>
<td>4</td>
<td>4.35</td>
<td>1.23</td>
</tr>
<tr>
<td>Gastritis</td>
<td>3</td>
<td>3.60</td>
<td>0.83</td>
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<tr>
<td>Hepatitis</td>
<td>4</td>
<td>4.50</td>
<td>1.50</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>2</td>
<td>8.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Fig. 1. Levels of cGMP in Plasma of Normal Persons and Patients With Various Kinds of Cancer and Other Diseases

Honma et al.  

RESULTS

The normal level of plasma cGMP was 3.46±0.52 pmol/ml of plasma. Fig. 1 and Table 1 show the level of cGMP in the plasma of patients with cancers or other diseases. Of the 16 patients with lung cancer, three had values of 3.5 pmol of cGMP per ml of plasma and the others had values ranging from 5.6 to 18 pmol per ml of plasma. Of the 16 patients with breast cancer, an average value of 5.39 pmol per ml of plasma was observed. The average value of cGMP in the plasma of five patients with oesophagus cancer shows almost the same level as in the case of breast cancer. Of the six patients with liver or stomach cancer, three had values of 15.0, 20.0 and 9.0 pmol of cGMP per ml of plasma. Not shown in Fig. 1 are the results obtained that the cases of pancreatic cancer and colon cancer had values of 17.0 and 5.4 pmol cGMP per ml of plasma, respectively.

A significant increase in the plasma cGMP level in the patients who did not have cancer was not observed, except in the patients with renal insufficiency and two cases of myocardial infarction studied. Patients with acute myelogenous and lymphoblastic leukemia show rather less cGMP in the plasma. The plasma cGMP level of ten pa-
tients with renal insufficiency ranged from 7.0 to 30.5 pmol per ml of plasma.

**Discussion**

The presence of cGMP has been demonstrated in all mammalian tissues (Ishikawa et al., Goldberg et al.). Because of the analytical difficulties of cGMP associated with its quantitative detection in biological materials, the average values obtained by different investigators for the plasma range from 5.0 to 9.5 nmol per liter (Brodus et al., Pattern et al., Rosman et al., Rudman et al.) and are usually about one-third to one-half of the cAMP level. Due to the paucity of data and the multiple techniques used, it is quite difficult to say which values are the most plausible.

Many hormones and drugs mediate their effects by altering the intracellular levels of cAMP and/or cGMP (Goldberg et al., Schultz et al., Murad et al., Kimura et al.). In Morris hepatoma explants, the cAMP and cGMP levels became elevated in the tumor tissue, although no apparent correlation was observed between the rate of tumor growth and cyclic nucleotide levels (Thomas et al.). The increased amounts of plasma cGMP in the patients with certain kinds of cancers or myocardial infarction may have originated from the organ tissues, although the mechanism involved in the increase of plasma cGMP from these tissues is not elucidated. Although the specificity of altered cGMP in the plasma deserves attention, basal cGMP in the plasma is useful diagnostically in evaluating the cell function.

**Acknowledgement**

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**References**


