Localization of Particulate Guanylate Cyclase in Plasma Membranes and Microsomes of Rat Liver*

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SUMMARY

The subcellular localization of guanylate cyclase was examined in rat liver. About 80% of the enzyme activity of homogenates was found in the soluble fraction. Particulate guanylate cyclase was localized in plasma membranes and microsomes. Crude nuclear and microsomal fractions were applied to discontinuous sucrose gradients, and the resulting fractions were examined for guanylate cyclase, various enzyme markers of cell components, and electron microscopy. Purified plasma membrane fractions obtained from either preparation had the highest specific activity of guanylate cyclase, 30 to 80 pmol/min/mg of protein, and the recovery and relative specific activity of guanylate cyclase paralleled that of 5'-nucleotidase and adenylyl cyclase in these fractions. Significant amounts of guanylate cyclase, adenylyl cyclase, 5'-nucleotidase, and glucose-6-phosphatase were recovered in purified preparation of microsomes. We cannot exclude the presence of guanylate cyclase in other cell components such as Golgi. The electron microscopic studies of fractions supported the biochemical studies with enzyme markers.

Soluble guanylate cyclase had typical Michaelis-Menten kinetics with respect to GTP and had an apparent Kₘ for GTP of 35 μM. Ca²⁺ stimulated the soluble activity in the presence of low concentrations of Mn²⁺. The properties of guanylate cyclase in plasma membranes and microsomes were similar except that Ca²⁺ inhibited the activity associated with plasma membranes and had no effect on that of microsomes. Both particulate enzymes were allosteric in nature; double reciprocal plots of velocity versus GTP were not linear, and Hill coefficients for preparations of plasma membranes and microsomes were calculated to be 1.60 and 1.58, respectively. The soluble and particulate enzymes were inhibited by ATP, and inhibition of the soluble enzyme was slightly greater. While Mg²⁺ was less effective than Mn²⁺ as a sole cation, all enzyme fractions were markedly stimulated with Mg²⁺ in the presence of a low concentration of Mn²⁺. Triton X-100 increased the activity of particulate fractions about 3- to 10-fold and increased the soluble activity 50 to 100%.

Recently our laboratory (1-3) and Chrisman et al. (4) reported that rat tissues have two forms of guanylate cyclase (EC 4.6.1.2) that catalyze the formation of guanosine 3',5'-monophosphate from GTP. The soluble and particulate enzymes from various rat tissues have different kinetic properties and molecular sizes. In some tissues such as lung and liver most of the enzymatic activity is found in soluble fractions of homogenates (1-11), and most of the early studies have been confined to soluble guanylate cyclase. However, in all tissues examined to date significant quantities of the enzyme have been found in particulate fractions (1). In tissues such as heart, intestinal mucosa, cerebral cortex, cerebellum, and others, the majority of the activity is particulate (1-3, 6, 11). The precise subcellular localization of the particulate activity has not been determined. In order to obtain a better understanding of the metabolism of cyclic GMP in tissues and its possible regulation, we determined the cellular localization of guanylate cyclase in rat liver. Although rat liver has only 15 to 30% of the guanylate cyclase activity in particulate fractions of homogenates, we chose this tissue for these studies because of the previous work by a number of laboratories in developing techniques to separate liver cellular components (12-14). We found the particulate enzyme located in both plasma membranes and microsomes that were characterized with various marker enzymes and electron microscopy. Some of the properties of the particulate enzymes are also described and compared to those of the soluble fraction. Some of these observations have been reported previously in abstract form (15).

MATERIALS AND METHODS

Male Sprague-Dawley rats weighing 150 g to 200 g maintained with Purina laboratory chow and tap water ad libitum were used after fasting overnight. Rats were decapitated and livers were quickly removed and placed into cold 0.25 M sucrose. The livers were blotted, weighed, minced with scissors, and homogenized with 3 volumes of 0.25 M sucrose in a Potter-Elvehjem glass homogenizer (A. H. Thomas Co.) by five strokes of a Teflon pestle at 4°C. Homogenates filtered through four layers of gauze were used...
directly or after subcellular fractionation. All subsequent procedures for preparation of enzymes were carried out at 4°C, and all sucrose solutions used contained 5 mM Tris-HCl buffer, pH 8.0. Concentrations of sucrose solutions were determined with an osmometer (Advanced Instruments, Inc.). Subcellular fractions of liver homogenates were prepared with a modification of the method of Schneider and Hogeboom (12) and deDuve et al. (13). Plasma membranes were prepared from both crude nuclear and microsomal fractions with a slight modification of that of Touster et al. (14). Crude nuclear fractions were obtained by centrifugation of filtered homogenates at 750 × g for 10 min. The precipitates were washed four times with one-half the original homogenate volume of fresh solution. The final centrifugation was carried out at 30,000 × g for 20 min. The resulting pellets were suspended in 57% sucrose to a volume equal to that of the original homogenate and used for the subsequent preparation of plasma membranes. All supernatant fractions from each centrifugation were combined and centrifuged at 11,700 × g for 20 min. The pellets were washed twice and suspended in 0.25 M sucrose. All of the resulting supernatant fractions were diluted and centrifuged at 78,000 × g for 90 min. The crude microsomal fractions were suspended in 57% sucrose to a volume equal to that of the original homogenate. Ten milliliters each of the suspended crude nuclear and microsomal fractions were placed in centrifuge tubes for the Beckman SW27 rotor. Twenty-three milliliters of 37.2% sucrose were layered above the nuclear sample followed by 5 ml of 0.25 M sucrose. On the microsomal fraction were layered 12 ml of 40% sucrose. Samples were centrifuged at 105,000 × g for 60 min. The precipitates were fixed in 3% glutaraldehyde containing 0.1 M phosphate buffer, pH 7.6, 10 mM theophylline, 15 mM creatine phosphate, 20 mM glucose 6-phosphate (22) in a final volume of 0.2 ml. Both materials were obtained or prepared as described previously (1, 17, 19). The methods for preparation of enzymes were carried out at 4°, and all materials were diluted with water and centrifuged at 105,000 × g for 60 min. The precipitates were washed twice and suspended in 0.25 M sucrose. All of the materials were obtained or prepared as described previously (1, 17, 19).

RESULTS

When homogenates of livers were fractionated with differential centrifugation, 79% of the guanylate cyclase activity of homogenates was found in soluble fractions (Table I). In contrast to

### Table I

**Distribution of guanylate cyclase and several enzymes in fractions from rat liver homogenates**

| Fraction          | Guanylate Cyclase (4) | 5'-Nucleotidase (4) | Adenylate Cyclase (4) | Glucose-6-phosphatase (4) | Succinic Dehydrogenase (1) | Protein (4) |
|-------------------|-----------------------|---------------------|-----------------------|--------------------------|---------------------------|-------------|
|                   | pmol/min/g liver      | % Distribution     | pmol/min/g protein    | % Distribution          | % Distribution           | % Distribution |
| Homogenate        | 3.43 ± 0.43           | 100                 | 19.53 ± 2.75          | 100                      | 100                       | 100         |
| "Nuclear fraction" | 0.27 ± 0.06           | 7.1 ± 2.6           | 5.99 ± 0.66           | 46.4 ± 3.0               | 26.9 ± 4.3                | 19.4        |
| "Mitochondrial fraction" | 0.05 ± 0.01       | 1.5 ± 0.6           | 1.29 ± 0.13           | 8.7 ± 1.1                | 2.4 ± 0.4                 | 6.0 ± 1.1 |
| "Microsomal fraction" | 0.37 ± 0.03         | 11.1 ± 1.6          | 12.9 ± 1.41           | 54.4 ± 8.0               | 54.4 ± 6.3                | 67.6 ± 5.1 |
| "Soluble fraction" | 2.70 ± 0.37           | 79.2 ± 4.7          | 38.55 ± 3.70          | 8.3 ± 0.7                | 0                         | 1.6 ± 0.8 |
| Recovery          | 98.9 ± 6.3            | 117.8 ± 10.6        | 83.7 ± 2.0            | 86.1 ± 1.5               | 67.1                      | 88.4 ± 3.4 |

GTP, creatine phosphate, creatine phosphokinase, 5'-AMP, and glucose 6-phosphate were purchased from Sigma Chemical Co. 2-(p-Iodophenyl)-3-(p-nitrophenyl)-5-phenyltetrazolium chloride was obtained from Eastman Kodak Co. All other materials were obtained or prepared as described previously (1, 17, 19).**
Fig. 1. Fractionation with a discontinuous sucrose gradient of a crude nuclear fraction from a rat liver homogenate. Fractions were obtained after discontinuous sucrose gradient centrifugation of a crude nuclear fraction of a rat liver homogenate as described under "Materials and Methods." Activities of guanylate cyclase, 5'-nucleotidase, succinic dehydrogenase, and protein are shown. The three major peaks of activity (A, B, C) were pooled as designated for further analyses.

Guanylate cyclase, 5'-nucleotidase, and adenylate cyclase in Fraction A were also similar. 5'-Nucleotidase in Fraction A was purified 32-fold from the homogenate with a recovery of 15%. The activity of 5'-nucleotidase in Fraction A was also similar to the report of Touster et al. (14). The purification of adenylate cyclase from homogenates of 11.7-fold with 5.4% recovery in Fraction A was comparable to that of Pohl et al. (29). These investigators obtained a 13-fold purification with 8% recovery with the use of a different technique for preparing liver plasma membranes. We cannot compare the degree of purification of guanylate cyclase from the homogenate to that of 5'-nucleotidase or adenylate cyclase since most of guanylate cyclase in liver is soluble. These studies indicated that Fraction A was primarily plasma membranes. Glucose-6-phosphatase and succinic dehydrogenase were found primarily in Fractions B and C; each fraction contained 2 to 6% of the homogenate activity. When the nuclei were prepared from the 750 x g pellet by the method of Maggio et al. (30), less than 10% of the guanylate cyclase activity with less specific activity was recovered in the sedimentable fraction. From these results we concluded that particulate guanylate cyclase in the crude nuclear fraction of liver homogenates is predominantly in plasma membranes. The activity in other fractions could represent activity in other structures or their contamination with plasma membranes.

Three peaks each of guanylate cyclase, 5'-nucleotidase, and protein were obtained (Fractions A, B, and C) when crude microsomal fractions were examined with discontinuous sucrose gradients (Fig. 2). Two peaks of glucose-6-phosphatase activity (Fractions B and C) were obtained. The activities recovered and the degree of purification for guanylate cyclase, adenylate cyclase, and 5'-nucleotidase were very similar to one another in Fractions A and B (Table II). However, more adenylate cyclase activity was recovered in Fractions B and C than would be predicted from previous reports (28, 29). From the original homogenate 5'-nucleotidase and adenylate cyclase were purified 28- and 11.2-fold, respectively, in Fraction A (not shown) which is comparable to previous reports (14, 29). Fraction C contained 58.4% of the guanylate cyclase, 69.2% of the glucose-6-phosphatase, and 17.2% of the 5'-nucleotidase from the crude microsomal fraction.
TABLE II
Distribution of guanylate cyclase and marker enzymes in fractions obtained from discontinuous sucrose gradient centrifugation of crude nuclear and microsomal fractions from rat liver homogenate

Enzyme activities were assayed as described under "Materials and Methods." Preparations of crude nuclear and microsomal fractions and fractions obtained from discontinuous sucrose gradient centrifugation are those obtained in the experiments of Figs. 1 and 2. Some values are reported as relative activities compared to the crude nuclear or microsomal fraction.

| Fraction | Guanylate Cyclase | 5'-Nucleotidase | Adenylyl Cyclase | Glucose-6-phosphatase | Succinic Dehydrogenase |
|----------|------------------|----------------|-----------------|-----------------------|-----------------------|
|          | pmol/min/mg protein | Relative Activity | pmol/min/mg protein | Relative Activity | pmol/min/mg protein | Relative Activity | pmol/min/mg protein | Relative Activity | pmol/min/mg protein | Relative Activity |
| Nuclear Fraction | 5.0 | 1 | 100 | 0.20 | 1 | 100 | 38.9 | 1 | 100 | 8.05 | 1 | 100 |
| Fraction A | 27.1 | 7.6 | 23.7 | 1.83 | 9.2 | 29.3 | 380.9 | 9.3 | 29.7 | 68.4 | 1 | 100 |
| Fraction B | 1.6 | 0.5 | 35.9 | 0.03 | 0.2 | 11.6 | 20.8 | 0.5 | 34.7 | 0.03 | 0.6 | 33.3 |
| Fraction C | 6.1 | 9.8 | 28.2 | 0.30 | 0.5 | 18.7 | 54.6 | 1.1 | 37.6 | 0.07 | 1.4 | 44.9 |
| Microsomal Fraction | 30.8 | 7.4 | 23.7 | 1.83 | 9.2 | 29.3 | 380.9 | 9.3 | 29.7 | 68.4 | 1 | 100 |
| Fraction A | 31.1 | 7.4 | 28.4 | 1.60 | 5.6 | 29.8 | 365.8 | 5.4 | 20.0 | 0.21 | 0.2 | 1.4 |
| Fraction B | 15.4 | 1.8 | 31.3 | 0.61 | 1.9 | 41.7 | 289.5 | 1.7 | 57.4 | 0.31 | 0.6 | 12.9 |
| Fraction C | 7.0 | 0.7 | 38.4 | 0.66 | 0.2 | 17.2 | 42.2 | 0.3 | 33.0 | 0.66 | 0.8 | 69.2 |

Fig. 2. Fractionation with a discontinuous sucrose gradient of a crude microsomal fraction from a rat liver homogenate. Fractions were obtained after discontinuous sucrose gradient centrifugation of a crude microsomal fraction of a rat liver homogenate and no purification was achieved. The high recoveries of guanylate cyclase and glucose-6-phosphatase compared to that of 5'-nucleotidase indicated that guanylate cyclase was also present in microsomes (see below). Small amounts of succinic dehydrogenase activity were present in Fractions B and C, and only one-third of the activity in the crude microsomal fraction was recovered. From these results it was evident that particulate guanylate cyclase of rat liver was localized in both plasma membranes and microsomes.

The conclusions on the basis of biochemical studies are supported by the electron microscopic examination of fractions obtained after discontinuous sucrose gradient centrifugation. Nuclear Fraction A contained essentially homogeneous vesicular plasma membrane elements with little other cell components (Fig. 3A). Fraction B contained mainly mitochondria with some plasma membranes and microsomes, while the sedimented Fraction C contained various cell components including nuclei (electron micrographs are not shown). Fraction A from the microsomal fraction (Fig. 3B) contained predominantly plasma membranes and Golgi with some unidentified structures. Fraction B (Fig. 3C) contained primarily small vesicles with some plasma membranes, microsomes, and unidentified structures. Fraction C (Fig. 3D) was predominantly smooth and rough endoplasmic reticulum. Thus, the findings with electron microscopy are consistent with the profile of enzyme markers and indicate that particulate guanylate cyclase of rat liver is about equally distributed between plasma membranes and microsomes. Further fractionation and characterization of the microsomal Fractions A and B are currently in progress to determine whether guanylate cyclase is located in the components other than plasma membranes and microsomes such as Golgi.

Soluble and particulate guanylate cyclase separated with centrifugation at 105,000 × g from homogenates of heart (1) and lung (4) have been shown to have different properties. We,
FIG. 3. Electron micrographs of fractions isolated after discontinuous sucrose gradient centrifugation. Panel A is obtained from Fraction A of the crude nuclear experiment in Fig. 1 and Panels B, C, and D from Fractions A, B, and C, respectively, of the crude microsomal experiment in Fig. 2. Magnification is $\times 93,000$. 
Liver preparations were prepared with discontinuous sucrose gradients as described. Tubes containing the greatest activities in nuclear Fraction A and microsomal Fractions B and C were used in this experiment. All particulate activities were determined after pretreatment with 1% Triton X-100 and with 1 mM GTP as described under "Materials and Methods." Other conditions are as indicated. The soluble fraction was obtained from a supernatant fraction of a rat liver homogenate after centrifugation at 78,000 × g for 90 min. The free Mn²⁺ concentration of 3 mM represents the cation concentration in excess of that of GTP and ATP. The high specific activity of particulate fractions is due to the activation and solubilization of the enzyme by Triton X-100 (1).

**Effects of various cations and ATP on guanylate cyclase activities from liver subcellular fractions**

| Cyclic GMP formed (pmoles/min/mg protein) | Nuclear Fraction A | Microsomal Fraction B | Microsomal Fraction C | Soluble Fraction |
|------------------------------------------|--------------------|-----------------------|-----------------------|------------------|
| Mn²⁺, 3 mM                               | 647 100            | 287 100               | 377 100               | 44 100           |
| Ca²⁺, 3 mM                               | 24 3.7             | 9 3.1                 | 1 2.7                 | 2 4.5            |
| Mg²⁺, 3 mM                               | 48 7.4             | 19 6.6                | 2 5.4                 | 4 9.1            |
| Mn²⁺, 0.5 mM                             | 158 100            | 56 100                | 5 100                 | 2 100            |
| Mn²⁺, 0.5 mM + Ca²⁺, 3 mM                | 104 65.8           | 50 89.2               | 6 120.0               | 20 1000.0        |
| Mn²⁺, 0.5 mM + Mg²⁺, 3 mM                | 673 299.3          | 187 335.0             | 16 100 n              | 13 650.0         |
| free Mn²⁺, 3 mM                          | 567 100            | 250 100               | 41 100                | 47 100           |
| free Mn²⁺, 3 mM + ATP, 0.1 mM            | 547 96.4           | 260 92.7              | 33 80.5               | 38 80.9          |
| free Mn²⁺, 3 mM + ATP, 1.0 mM            | 243 43.2           | 103 39.8              | 14 34.1               | 12 27.7          |
| free Mn²⁺, 3 mM + ATP, 2.0 mM            | 164 28.9           | 63 24.3               | 8 19.5                | 7 16.9           |

**Discussion**

The present study demonstrates that 80% of the guanylate cyclase activity in rat liver homogenates is associated with the soluble fraction. This value is similar to previous reports (1-3, 5, 7) and the particulate guanylate cyclase activity is located in both purified plasma membranes and microsomes that were prepared by the method of Touster et al. (14). The enrichment of guanylate cyclase in plasma membranes paralleled that of 5'-nucleotidase and adenylyl cyclase, i.e. the recoveries and relative specific activities of the two enzymes were similar in Fraction A derived from the crude nuclear fraction (Table II). With electron microscopy this fraction appeared to be a homogeneous preparation of plasma membranes (Fig. 3A). On the other hand, the recovery of guanylate cyclase from crude microsomal fractions was similar to that of glucose-6-phosphatase in Fraction C, and it did not parallel that of 5'-nucleotidase and adenylyl cyclase (Table II). Electron microscopy of this fraction demon-
FIG. 4. Effects of Ca\textsuperscript{2+} on guanylate cyclase activities from subcellular fractions from rat liver. Activities of guanylate cyclase were determined as described under "Materials and Methods" except 1 mM GTP, 0.5 mM MnCl\textsubscript{2}, and various concentrations of CaCl\textsubscript{2} were used. Activities of nuclear A, microsomal A, B, and C fractions from discontinuous sucrose gradients were determined after treatment with 0.5% Triton X-100. Protein used was 1.02, 4.6, 10.7, and 30.0 \(\mu\)g for nuclear A, microsomal A, B, and C fractions, respectively. Protein (128 \(\mu\)g) was used for the soluble fraction. Activities are expressed as percentages of basal activities which were determined without CaCl\textsubscript{2}. The inset is an enlargement of the same data.

The recoveries and relative specific activities of guanylate cyclase, 5'-nucleotidase, and adenylate cyclase were similar in Fraction A from the crude microsomal pellet (Table II). From homogenates 5'-nucleotidase and adenylate cyclase were purified 28- and 11-fold, respectively, in this fraction. These values are comparable to previous reports (14, 29). Touster et al. (14) characterized this fraction as an enriched preparation of plasma membranes with the use of other criteria. Thus, we can conclude that guanylate cyclase in crude microsomal fractions is present in both plasma membranes and microsomes. However, the electron micrographs of Fraction A from the crude microsomal fraction (Fig. 3B); significant quantities of Golgi were present as characterized by cisternae and vesicles containing dense particles that are presumably very low density lipoproteins. Since the specific activities of guanylate cyclase, adenylate cyclase, and 5'-nucleotidase were similar in Fraction A from either crude nuclei or crude microsomal fractions (Table II), we can conclude that these three enzymes are located in other cell components such as Golgi.

Fig. 5. Hill plots for guanylate cyclase from liver subcellular fractions versus GTP concentration. Activities were determined with 1 mM MnCl\textsubscript{2} and various concentrations of GTP. Activities of the nuclear A (2.3 \(\mu\)g of protein/tube) and microsomal C (47 \(\mu\)g of protein/tube) fractions from discontinuous sucrose gradients were determined after treatment with 0.5% Triton X-100. The soluble fraction (8 \(\mu\)g of protein/tube) was purified with Bio-Gel P-300 column chromatography as described previously (1). Maximum velocities were obtained from extrapolation of double reciprocal plots of velocity versus GTP concentration. Slopes (n) were calculated by the least squares method.

Ehrenreich et al. (31) and Bergeron et al. (32) have reported 5'-nucleotidase activity in preparations of Golgi. Also the method used by Ehrenreich et al. (31) and Bergeron et al. (32) to prepare Golgi is quite similar to that of Touster et al. (14) which we used for preparing plasma membranes.

Fraction B from the crude microsomal fraction contains large amounts of guanylate cyclase, 5'-nucleotidase, and adenylate cyclase. Since little of the glucose-6-phosphatase activity was obtained in this fraction, it seems unlikely that this can be attributed to microsomes in the preparation. The electron micrographs demonstrated primarily small vesicles with some plasma membranes and microsomes. Additional studies to further characterize this fraction are in progress in this laboratory.

It has been postulated that the endoplasmic reticulum provides precursors for Golgi that in turn provide precursors or determinants of the cell membrane and lysosomes (33). If indeed this is true, nucleomicrosomal enzymes such as particulate guanylate cyclase, adenylate cyclase (28), 5'-nucleotidase (26), sialidase (34), and others might be expected to be found in all of these structures. Some reports have described 5'-nucleotidase in microsomes (21, 27) and Golgi (32). Entman et al. (35) and Katz et al. (36) reported some adenylate cyclase activity in sarcolemmal reticulum of heart. Adenylate cyclase has also been re-
ported in Golgi and plasma membranes from porcine pituitary (37). White (38) recently reported guanylate cyclase activity in rat heart sarcoplasmic reticulum. Some enzymes such as galactosyltransferase, glycolipid glucosyltransferase, and sulfotransferase are reported in Golgi and microsomes but not plasma membranes (39-41).

The properties of soluble and particulate guanylate cyclase from rat liver were similar to preparations from several other tissues (1, 4-11). As with other tissues the properties of the soluble and particulate enzyme were different. Calcium ion stimulated the soluble activity, inhibited the activity in plasma membranes, and had no effect on the activity in microsomes (Table III, Fig. 4). The effect of Ca²⁺ has been the only difference that we have observed to date in the plasma membranec and microsomal enzyme. Mn²⁺ was much more active than Mg²⁺ or Ca²⁺ as the sole cation. However, in contrast to reports from other laboratories working with other tissues (8, 9, 11), Mg²⁺ effectively stimulates all guanylate cyclase activities from rat liver preparations when low concentrations of Mn²⁺ were present (Table III). With the low concentrations of Mn²⁺ normally present in tissues (42), the stimulatory effect of Mg²⁺ may be important in regulating cyclic GMP synthesis and accumulation. Therefore, while most of the guanylate cyclase in liver is soluble, significant quantities are associated with plasma membranes and microsomes. The three or perhaps more subcellular locations of the enzyme raise a number of questions about their physiological significance and role in cyclic GMP synthesis. In other experiments we have found increased particulate guanylate cyclase activity and decreased soluble enzyme activity in regenerating rat liver, fetal rat liver, and hepatomas (43). These observations suggest that increased particulate enzyme is associated with liver growth and are of interest in view of the recent reports describing stimulatory effects of cyclic GMP on cell culture proliferation (44-46).

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