We have recently demonstrated that a 37-amino acid peptide corresponding to the cytoplasmic domain of the natriuretic peptide receptor C (NPR-C) inhibited adenylyl cyclase activity via pertussis toxin (PT)-sensitive Gi protein. In the present studies, we have used seven different peptide fragments of the cytoplasmic domain of the NPR-C receptor with complete, partial, or no Gi activator sequence to examine their effects on adenylyl cyclase activity. The peptides used were KKYRITIER-RNH (peptide 1), RRHQQESENSIGK (peptide 2), HREL-REDSIRSH (peptide 3), RRHQQESENSIGKRELP (peptide 4), QEEQSNIGK (peptide X), ITIERRNH (peptide Y), and ITITYKRRNHIRE (peptide Z). Peptides 1, 3, and 4 have complete Gi activator sequences, whereas peptides 2 and Y have partial Gi activator sequences with truncated carboxyl or amino terminus, respectively. Peptide X has no structural specificity, whereas peptide Z is the scrambled peptide control for peptide 1. Peptides 1, 3, and 4 inhibited adenylyl cyclase activity in a concentration-dependent manner with apparent K_i between 0.1 and 1 nM; however, peptide 2 inhibited adenylyl cyclase activity with a higher K_i of about 10 nM, and peptides X, Y, and Z were unable to inhibit adenylyl cyclase activity. The maximal inhibitions observed were between 30 and 40%. The inhibition of adenylyl cyclase activity by peptides 1–4 was absolutely dependent on the presence of guanine nucleotides and was completely attenuated by PT treatment. In addition, the stimulatory effects of iso-proterenol, glucagon, and forskolin on adenylyl cyclase activity were inhibited to different degrees by these peptides. These results suggest that the small peptide fragments of the cytoplasmic domain of the NPR-C receptor containing 12 or 17 amino acids were sufficient to inhibit adenylyl cyclase activity through a PT-sensitive Gi protein. The peptides having complete structural specificity of Gi activator sequences at both amino and carboxyl termini were more potent to inhibit adenylyl cyclase activity as compared with the peptides having a truncated carboxyl terminus, whereas the truncation of the amino-terminal motif completely attenuates adenylyl cyclase inhibition.

Atrial natriuretic peptide (ANP), a member of the family of natriuretic peptides (NP), discovered by de Bold et al. (1, 2), regulates a variety of physiological parameters including the blood pressure, progesterone secretion, renin release, and vasopressin release by interacting with different receptors on the plasma membrane (3–11). The other members of the natriuretic peptide family are brain natriuretic peptide (BNP) and C-type natriuretic peptide (CNP) (12–14). The role played by ANP and BNP as endocrine hormones is apparently to be antagonists to vasopressin, endothelins, and the renin-angiotensin-aldosterone system (12, 15). The role of CNP in vivo is less well defined. Although CNP might not be a significant modulator of diuresis and natriuresis (16, 17), it is a vasodilator expressed by endothelial cells (14, 18). Compared with ANP, BNP has an additional six-amino acid sequence at its amino-terminal end (5, 13, 19), whereas CNP lacks the carboxyl-terminal extension (14).

Molecular cloning techniques revealed three subtypes of natriuretic peptide receptors (NPR): NPR-A (20, 21), NPR-B (22, 23), and NPR-C (24, 25). NPR-A and NPR-B are membrane guanylyl cyclases, whereas NPR-C (clearance receptor) lacks guanylyl cyclase activity. NPR-A catalyzes the production of cGMP in response to ANP and BNP, whereas NPR-B is the target for CNP. NPR-C receptors on the other hand are coupled to adenylyl cyclase inhibition through inhibitory guanine nucleotide-regulatory protein (25, 26) or to activation of phospholipase C (27).

NPR-C receptors are disulfide-linked homodimers of 64–66 kDa, having a single transmembrane domain (24, 28, 29), an extracellular domain of ~440 amino acids, and a short 37-amino acid cytoplasmic domain or tail. We have recently demonstrated that the 37-amino acid peptide (R37A) corresponding to the cytoplasmic domain of the NPR-C receptor inhibited adenylyl cyclase activity in rat heart particulate fractions, which was completely blocked by the polyclonal rabbit antisera raised against R37A (30). The inhibition was dependent on the presence of GTP and was blocked by pertussis toxin (PT) treatment. Furthermore, inhibition of adenylyl cyclase by R37A was not due to the positive charges, because a scrambled peptide K37A with the same composition as that of R37A but a different sequence did not inhibit adenylyl cyclase activity (30). These data suggested that certain structural specificity present in the cytoplasmic domain of the NPR-C receptor may be responsible for exerting inhibitory effects on adenylyl cyclase. Okamoto et al. (31) have shown that a short intracellular region of 14 amino acids (Arg^{2410}-Lys^{2423}) of insulin-like growth factor II receptor having a specific Gi activator sequence was able to activate Gi protein directly in the same manner as that of conventional Gi-coupled receptors. This sequence (Gi activator) was characterized by the presence of two basic amino acids peptide; C-ANP-(4–23); [des-Gln^{28} Ser^{29}Gly^{30} Leu^{31}Gly^{32}]rat ANP-(4–23); NPR, natriuretic peptide receptor; PT, pertussis toxin; GTPγS, guanosine 5′-3′-O-(thio)triphosphate.
at the NH₂ terminus and BRXB or BBXXB at the COOH terminus, where B and X denote basic amino acid and nonbasic amino acid, respectively. The cytoplasmic domain of NPR-C receptor contains several of these Gᵢ activator sequences. In the present studies, we have used seven different synthetic peptide fragments of the cytoplasmic domain of NPR-C receptor with complete, partial, or no Gᵢ activator sequence in order to examine their effects on adenylyl cyclase activity. We have shown that small fragment peptides of the cytoplasmic domain of the NPR-C receptor with complete Gᵢ activator sequence were more

**FIG. 1.** Sequence of the entire cytoplasmic domain of NPR-C and the various synthetic peptides corresponding to different regions of the cytoplasmic domain. B, basic amino acid; X, nonbasic amino acid.

**FIG. 2.** Effect of different peptides on adenylyl cyclase activity in rat heart (A) and vascular smooth muscle cells (B). The effect of peptides on adenylyl cyclase activity was determined as described under "Experimental Procedures" in the presence of 10 μM GTPγS. The basal adenylyl cyclase activity was 225 ± 9 pmol of cAMP/mg of protein/10 min in heart and 180 ± 6 pmol of cAMP/mg of protein/10 min in vascular smooth muscle cells. Values are the means ± S.E. of three to four separate experiments.
Effect of different concentrations of peptides 1, 2, 3, 4, X, Y, and Z on adenylyl cyclase activity was determined as described under "Experimental Procedures" in the presence of 10 μM GTPγS. The basal adenylyl cyclase activity was 225 ± 9 pmol of cAMP/mg of protein/10 min. Values are the means ± S.E. of four separate experiments.

**EXPERIMENTAL PROCEDURES**

**Materials**—ATP, cAMP, and isoproterenol were purchased from Sigma. Creatine kinase (EC 2.7.4.3) and GTPγS were purchased from Roche Molecular Biochemicals. [α-32P]ATP was purchased from Amer sham Pharmacia Biotech. Pertussis toxin was from List Biochemicals (Campbell, CA). Rat ANP, a ring-deleted analog of ANP, c-ANP (4–23), and angiotensin II were from Peninsula Laboratories (Belmont, CA). Peptides R37A, 1, 2, 3, 4, X, Y, and Z were synthesized by standard solid phase techniques and highly purified (95–99%) by high performance liquid chromatography (Peninsula Laboratories and Chiron Technologies).

**Preparation of Heart Particulate Fractions**—Heart ventricles were dissected from Harlan Sprague-Dawley rats (200–300 g), quickly frozen in liquid nitrogen, and stored at −80 °C until used. Frozen hearts were pulverized to a fine powder with a mortar and pestle precooled in liquid nitrogen. The heart powder was homogenized using a Teflon-glass homogenizer (12 strokes) in a buffer containing 10 mM Tris-HCl and 1 mM EDTA, pH 7.5, and finally suspended in the same buffer and used for adenylyl cyclase assay. Preincubation of the membranes at 30 °C for 30 min in the absence or presence of PT resulted in a significant loss of enzyme activity (−40%), which was independent of the presence of PT in the incubation medium. However, the percentage inhibition of adenylyl cyclase activity by the different peptides used remained unchanged.

**Adenylyl Cyclase Activity Determination**—Adenylyl cyclase activity was determined by measuring [32P]cAMP formation from [α-32P]ATP as described previously (26, 33). The typical assay medium contained 50 mM glycollglycine, pH 7.5, 0.5 mM MgATP, [α-32P]ATP (1–1.5 × 10⁶ cpm), 5 mM MgCl₂, 100 mM NaCl, 0.5 mM cAMP, 1 mM 3-isobutyl-1-methylykanthine, 0.1 μM EGTA, 10 μM GTPγS, and an ATP-regenerating system consisting of 2 mM creatine phosphate, 0.1 μg of myokinase per ml in a final volume of 200 μl. Incubations were initiated with the addition of reaction mixture to the membranes (30–70 μg), which had been preincubated at 37 °C for 10 min. The reactions conducted in triplicate at 37 °C for 10 min were terminated by the addition of 0.6 ml of 120 mM zinc acetate, and cAMP was purified by co-precipitation of other nucleotides with ZnCl₂ by the addition of 0.5 ml of 144 mM Na₂CO₃ and by subsequent chromatography using the double column system (35). Under these assay conditions, adenylyl cyclase activity was linear with respect to protein concentration and time of incubation.

**RESULTS**

**Effect of Different Fragments of the Cytoplasmic Domain of NPR-C Receptor on Adenylyl Cyclase Activity**—The 37-aa acid peptide (R37A) corresponding to the cytoplasmic domain of the NPR-C receptor has been shown to inhibit adenylyl cyclase activity by interacting directly with G proteins (30). In order to investigate if the small peptide fragments of the cytoplasmic domain that consist of partial or complete Gi activator sequences could also mimic the effect of R37A or ANP on NPR-C receptor-mediated inhibition of adenylyl cyclase, seven different synthetic peptides were used to examine their effects on adenylyl cyclase activity. The peptide fragments represent different parts of the cytoplasmic domain as shown in Fig. 1. These consist of 12 amino acids (peptides 1, 2, 3, and Z), 17 amino acids (peptide 4), or 8 amino acids (peptides X and Y). Peptides 1, 3, and 4 possess the required Gαi activator sequences: two basic amino acids at the NH2 terminus and BBXXS, and an ATP-regenerating system (35). Under these assay conditions, adenylyl cyclase activity was linear with respect to protein concentration and time of incubation.

![Fig. 3](https://via.placeholder.com/150)

**Fig. 3. Inhibition of rat heart adenylyl cyclase activity.** The effect of different concentrations of peptides 1, 2, 3, 4, X, Y, and Z on adenylyl cyclase activity was determined as described under "Experimental Procedures" in the presence of 10 μM GTPγS. The basal adenylyl cyclase activity was 225 ± 9 pmol of cAMP/mg of protein/10 min. Values are the means ± S.E. of four separate experiments.

**Cell Culture and Incubation**—The A10 cell line from embryonic thoracic aorta of rat was obtained from the American Type Culture Collection (Manassas, VA). The cells were plated in 7.5-cm² flasks and incubated at 37 °C in a 5% air and 5% CO₂ humidified atmosphere in Dulbecco’s modified Eagle’s medium (with glucose, t-glutamine, and sodium bicarbonate) containing antibiotics and 10% heat-activated calf serum. The cells were passaged upon reaching confluence with 0.5% trypsin containing 0.2% EDTA and utilized between passages 5 and 15. The cells were scraped into ice-cold homogenization buffer using a rubber policeman and collected by centrifugation at 4 °C for 10 min at 600 × g. The cells were then homogenized in a Dounce homogenizer (10 strokes), and the homogenate was used for an adenylyl cyclase assay.

**PT Treatment**—PT treatment was performed as described earlier (25, 33, 34). Briefly, heart particulate fractions were incubated in 25 mM glycollglycine buffer, pH 7.5, containing 1 mM NAD, 0.4 mM ATP, 0.4 mM GTP, 15 mM thiodiothreitol, and ovalbumin (0.1 mg/ml) with and without PT (5 μg/ml) for 30 min at 30 °C. The particulate fraction was washed two to three times with 10 mM Tris, 1 mM EDTA buffer, pH 7.5, and finally suspended in the same buffer and used for adenylyl cyclase activity determination. Preincubation of the membranes at 30 °C for 30 min in the absence or presence of PT resulted in a significant loss of enzyme activity (−40%), which was independent of the presence of PT in the incubation medium. However, the percentage inhibition of adenylyl cyclase activity by the different peptides used remained unchanged.

**Fig. 2A** shows that peptides 1, 2, 3, and 4 of the cytoplasmic domain of the NPR-C receptor at 10⁻⁷ M inhibited adenylyl cyclase activity by 40, 30, 35, and 36%, respectively, in rat heart particulate fractions. In addition, ANP (99–126), C-ANP (4–23), R37A, and angiotensin II, as reported earlier (3, 26, 30, 36), also inhibited the enzyme activity by about 20–25%. However, peptides X, Y, and Z did not inhibit adenylyl cyclase activity. Similar results were also observed in A-10 vascular smooth muscle cells (Fig. 2D); however, the inhibitions were greater (55%) in these cells. These results suggest that small peptides of the cytoplasmic domain of the NPR-C receptor with 12 amino acids or more with specific Gi activator sequence could inhibit adenylyl cyclase activity.
tions of adenylyl cyclase activity by peptides 1, 2, 3, and 4 were about 40, 30, 35, and 36% respectively. The inhibitory effect of these peptides was not due to the positive charges per se, because the scrambled peptide (peptide Z) of peptide 1 that has the same amino acid composition was unable to exert any inhibitory effect on adenylyl cyclase. In addition, peptides X and Y also did not inhibit adenylyl cyclase activity. These data suggest that the peptides possessing the required Gi activator sequence at the carboxyl terminus as well as at the amino terminus are more potent inhibitors of adenylyl cyclase activity than the peptides having partial or no structural specificity.

Dependence of Peptide 1-, 2-, 3-, and 4-mediated Inhibition of Adenylyl Cyclase on Guanine Nucleotides—The inhibitory effect of the R37A peptide corresponding to the cytoplasmic domain of the NPR-C receptor on adenylyl cyclase activity has been reported to be dependent on the presence of guanine nucleotides (30). In order to investigate if the inhibition of adenylyl cyclase by all four peptides of the cytoplasmic domain of NPR-C is also dependent on the presence of guanine nucleotides.

Effect of PT on Peptide 1-, 2-, 3-, and 4-mediated Inhibition of Adenylyl Cyclase—The coupling of NPR-C receptors to adenylylate cyclase through Gi has been demonstrated (25, 30). Furthermore, we have shown that R37A inhibited adenylyl cyclase through a PT-sensitive Gi protein. To examine if the inhibition of adenylyl cyclase by these four peptides is mediated through Gi, the effect of PT treatment on the inhibitory effects of the four peptides on adenylyl cyclase activity was examined. Fig. 5 shows that all four peptides inhibited the enzyme activity in a concentration-dependent manner in control heart particulate
fractions, which was attenuated by PT treatment. These results indicate that, like R37A, the small peptides of the cytoplasmic domain of NPR-C receptor also inhibit adenylyl cyclase through a PT-sensitive Gi protein.

Inhibition of Agonist-stimulated Adenylyl Cyclase Activity by Small Peptide Fragments of Cytoplasmic Domain—Since ANP-(99–126) and C-ANP-(4–23) as well as R37A peptide have been shown to inhibit the stimulatory effects of various agonists on adenylyl cyclase activity (25, 26, 30), it was of interest to examine if small peptides of the cytoplasmic domain of the NPR-C receptor are also capable of inhibiting the stimulated adenylyl cyclase activity in heart particulate fractions. As shown in Fig. 6, glucagon, isoproterenol, and forskolin stimulated adenylyl cyclase activity by about 160, 190, and 1000%, respectively, which was inhibited by all four peptides (0.1 μM) to various degrees. Glucagon-mediated stimulation was inhibited by about 30%, whereas isoproterenol-stimulated enzyme activity was inhibited by about 20–25%, and forskolin-stimulated enzyme activity was inhibited by about 15–35%.

**DISCUSSION**

We have previously shown that 37-amino acid synthetic peptide (R37A) corresponding to the cytoplasmic domain of NPR-C receptor inhibited adenylyl cyclase activity via PT-sensitive Gi protein (30). In the present studies, we demonstrate for the first time that the cytoplasmic domain peptide of NPR-C receptor has several Gi activator sequences that inhibit adenylyl cyclase activity in a GTP-dependent manner via PT-sensitive Gi proteins. The small peptide fragments of the cytoplasmic domain of the NPR-C receptor containing 17 amino acids (Arg^{10–Arg^{26}}, peptide 4) with a consensus sequence of BB at the NH_{2} terminus and BBXXB at the COOH terminus also inhibited adenylyl cyclase activity in these tissues/cells. Both of these peptide fragments (peptides 1 and 4) inhibited the enzyme activity in a concentration-dependent manner with an apparent \( K_{i} \) between 0.1 and 1 nM, and the maximal inhibition observed was about 30–35%. The potency of these peptide fragments to inhibit adenylyl cyclase activity was in the same range as that of the entire cytoplasmic domain peptide R37A as reported earlier (30). The inhibitory effect of these peptides on adenylyl cyclase was not due to the net positive charge present (i.e. amino acid composition), since the scrambled peptide Z with the same composition as peptide 1 but lacking the Gi activator sequence at the NH_{2} and COOH terminus did not inhibit adenylyl cyclase activity. On the other hand, the presence of partial COOH-terminal motif (BXXB) but intact N-terminal motif (BB) in the peptide did not change the potency of the peptide to inhibit adenylyl cyclase activity, suggesting that a partial COOH-terminal motif in the peptide may be sufficient to exert inhibitory effect on adenylyl cyclase activity. However, the truncation of COOH-terminal motif (BXXB) from peptide 2 (Arg^{10–Lys^{21}}) inhibited adenylyl cyclase activity with lower potency (\( K_{i} \) ~10 nM), suggesting that the COOH-terminal motif may be important to increase the potency of the peptides to elicit adenylyl cyclase inhibition. These results are in agreement with the recent studies of Kanwal et al. (37), who have shown that the 15-amino acid peptide fragment of NPR-C receptor (Arg^{1–Gln^{15}}) that lacks the COOH-terminal motif attenuated dopamine efflux in pheochromocytoma cells (PC12). Similarly, R37A peptide corresponding to the cytoplasmic domain of the NPR-C receptor that lacks the COOH-terminal motif BXXB has also been reported to inhibit adenylyl cyclase activity (30) as well as neurotransmission (37). However, our results are in contrast with studies of Murthy and Makhloof (38), who have shown that the cytoplasmic domain peptide...
fragment of the human NPR-C receptor that lacks the COOH terminus was inactive in stimulating phospholipase Cβ activity in gastric and tenia coli smooth muscle. The truncation of the NH2-terminal motif of peptide 2 results in inactivation of the peptide to inhibit adenylyl cyclase activity, suggesting that NH2-terminal consensus sequence is important to interact with G proteins to exert inhibition of adenylyl cyclase. This is further substantiated by our results showing that peptide Y that has the consensus sequence at the COOH terminus but lacks the NH2-terminal sequence was unable to inhibit adenylyl cyclase activity. However, Murthy and Makhlouf (38) have shown that peptide containing the consensus sequence at the NH2 terminus was unable to stimulate phospholipase Cβ in tenia coli smooth muscle cell membranes. This apparent discrepancy may be attributed to the difference in the cell/tissue system utilized in the two studies. Moreover, these investigators have shown that the 17-amino acid peptide of the human NPR-C receptor cytoplasmic domain stimulated phospholipase Cβ activity at higher concentrations with an EC50 value of 1.3 μM, whereas we have shown that the potency of the active peptides 1, 3, and 4 was at least 1000-fold higher in inhibiting adenylyl cyclase activity. In addition, peptide 2 that lacks the COOH-terminal motif sequence was less active than peptides 1, 3, and 4 but was still able to inhibit adenylyl cyclase activity, whereas Murthy and Makhlouf (38) did not observe any effect of the peptide lacking the COOH-terminal consensus sequence on phospholipase Cβ activity. The lack of effect of this peptide in their studies may be due to the possibility that this peptide also did not have the NH2-terminal consensus sequence and thus is similar to peptide X in our studies, which was also unable to inhibit adenylyl cyclase activity. Taken together, it can be suggested that the NH2-terminal motif of these peptides may be the important site for the interaction with G1 protein and thereby to activate the effector systems.

Our studies on the dependence on guanine nucleotides of active peptides-mediated inhibitory adenylyl cyclase inhibition and its attenuation by PT treatment are consistent with previous reports (25, 26, 30) and suggest that the small active peptide fragments of the cytoplasmic domain of NPR-C receptor, like the entire cytoplasmic domain peptide R37A, could also inhibit adenylyl cyclase via PT-sensitive G1 protein. In addition, the inhibition of glucagon-, isoproterenol-, and forskolin-mediated stimulation of adenylyl cyclase by small peptides is also consistent with our previous studies on ANP, C-ANP-(4–23), and R37A and adenylyl cyclase signaling (25, 26, 30).

In conclusion, we have provided the first evidence to demonstrate that the cytoplasmic domain peptides of the NPR-C receptor of 12 amino acids possessing complete G1 activator sequence at the COOH and NH2 termini are sufficient to inhibit adenylyl cyclase cycle activity through a PT-sensitive G1 protein with the same potency as that of the entire cytoplasmic domain peptide, whereas the peptides with a truncated COOH terminus inhibited the enzyme activity with low potency; however, the truncation of the NH2-terminal motif completely attenuates adenylyl cyclase inhibition.

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G\textsubscript{i} Activator Sequences of NPR-C Inhibit Adenylyl Cyclase

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Cytoplasmic Domain of Natriuretic Peptide Receptor C Constitutes $G_i$ Activator Sequences That Inhibit Adenylyl Cyclase Activity
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