Functional Analysis of the Interface Regions Involved in Interactions between the Central Cytoplasmic Loop and the C-terminal Tail of Adenylyl Cyclase*

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The mammalian adenylyl cyclase is a membrane-bound enzyme that is predicted to have 12 trans-membrane spans. Between membrane spans 6 and 7 there is a large cytoplasmic loop, which, along with the C-terminal tail, makes up the catalytic site of the enzyme. Crystal structures of these soluble cytoplasmic domains have identified the regions that are involved in interactions with each other. The functional consequences of these interactions in the full-length membrane-embedded enzyme have not been established. In this study, we analyzed the role of various interaction regions within the central cytoplasmic loop (C1) and the C-terminal tail (C2) on basal, Gs-, forskolin-, and Mn2+-stimulated activities of adenylyl cyclases 2 and 6 (AC2 and AC6). We tested synthetic peptides encoding the different interface surfaces of both the C1 and C2 domain on different activities of membrane-bound AC2 and AC6 expressed in insect cells. We found the C1-a2/b2-b3 and C2-b2′-b3′ regions to be involved in stimulation by Gs and forskolin but not in the basal or Mn2+-stimulated activities. Both the C1-b4/b5-a4 region and the C2-a3′-b4′ region play a role in the Gs- and forskolin-stimulated activities as well as basal activity, because the peptides encoding these regions inhibit basal activity by 30%. In contrast, the C2-a2′ region peptide inhibits both basal and Mn2+-stimulated activity by >50%. These results suggest that the different stimulated activities may involve distinct interface interactions in the intact enzyme and, consequently, the distinct mechanisms by which Mn2+ activates the enzyme as compared with Gs and forskolin, leading to the possibility that the full-length adenylyl cyclase may have multiple catalytically competent configurations.

Mammalian adenylyl cyclases are prototypic, membrane-bound, G protein effectors that produce cAMP in response to Gs stimulation (1, 2). They remain very interesting enzymes in terms of structure-function relationships. The crystal structure of the catalytic domains of mammalian adenylyl cyclases with Gs-GTP·S and forskolin (3) has provided an initial insight into the mechanisms by which Gs binds to and activates adenylyl cyclase. However, our understanding of the functional implications of the interactions identified in the crystal structure within the native enzyme is largely incomplete.

The crystal structure of the truncated central cytoplasmic loop of AC5 (VC1) and the C-terminal tail of AC2 (IIC2) has identified the interface regions. Using the criterion that interatomic distances within 4 Å indicate interacting residues, there are 28 residues in VC1 and 33 residues in IIC2 that are involved in interactions between the two domains (3). Because soluble VC1 has both N-terminal and C-terminal truncations, full-length adenylyl cyclase may have a greater number of residues involved in C1-C2 interactions. The interfaces are widely distributed on the C1 and C2 domains. They are primarily located in the β1 to a2, b2, and b4 to b5 regions of the C1 domain and the corresponding regions β′1 to a′2, b′2, and b′4 to b′5 of the C2 domain. In the crystal structure, the total area of interface is ~3300 Å2. The interacting residues on the C1-C2 interface are largely conserved, and they share high similarities between all known membrane-bound adenylyl cyclases except AC9. Tang et al. (4), using mutagenesis analysis, identified regions that affect adenylyl cyclase activity. Yan et al. (5) also identified some residues on the interface regions of C2 while searching for the Gs binding site by using a site-directed mutagenesis approach. Hatley et al. (6) found that there are several residues on the C2 interface (I1010M, K1014N, and P1015Q) that, when mutated, result in constitutive activation of adenylyl cyclase and also increase affinity between the two domains. These data indicate the importance of the interactions between the C1-C2 interface in regulating adenylyl cyclase activity. We have been interested in understanding the role that specific interface regions may play in both basal activity and the activity stimulated by Gs and forskolin as well as Mn2+. To address this question, we designed peptides encoding the various interface regions and tested the effects of these peptides on full-length AC2 and AC6 expressed in Hi5 cells. These studies reveal a potentially unique role for the 899–926 region in the C2 domain in basal and Mn2+-stimulated activities.

EXPERIMENTAL PROCEDURES

Materials—Amino acids and reagents for peptides were from Novabiochem and Peptides International. [α-32P]ATP was from PerkinElmer Life Sciences. Tissue culture reagents and fetal calf serum were from Invitrogen. Protease inhibitors were from Sigma. All other reagents were of the highest analytical grade that was commercially available.

Peptide Synthesis—Peptides were synthesized on a Symphony (Protein Technologies) peptide synthesizer and purified by high pressure liquid chromatography on 1–75% acetonitrile gradients. Purified peptides were lyophilized and stored at −20 °C, and each peptide container was filled with nitrogen for long term storage. Peptides containing Cys

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or Trp were stored under nitrogen at −80 °C, when required peptides were dissolved in water to a final concentration of 1–3 mM. For each assay, peptide stock solutions were freshly prepared. Identity and purity of the peptides were verified by mass spectrometry.

**Expression of G Protein Subunits and Adenylyl Cyclases**—Hexahistidine Q213L-Gα9 (kind gift of Dr. T. Patel, Loyola University School of Medicine, Chicago, IL) was expressed in JM109 (DE3) cells. The protein in cell lysates was purified on nickel-nitrilotriacetic acid columns according to a protocol kindly provided by the Patel laboratory. This protocol is essentially similar to the method described by Graziano et al. (7). AC2 and AC6 were expressed in Hi5 cells by infection with recombinant baculovirus. Membranes were prepared from infected cells and used for the assays (8).

**Adenylyl Cyclase Assays**—Enzymatic activity was measured by conversion of [α-32P]ATP to [32P]cAMP. AC2 and AC6 assays have been described (9, 10). When required, the peptides were mixed with adenylyl cyclase-containing membranes and held on ice for 10 min prior to assays. Approximately 1–2 μg of AC2 Hi5 cell membranes and 3–5 μg of AC6 membrane per assay tube were used. The concentration of activated Gαs was 2 μM, and that of forskolin was 30 μM. All assays contained a mixture of proteinase inhibitors. Final concentration of proteinase inhibitors was 3.2 μg/ml leupeptin, 2 μg/ml aprotinin, 1 mM phenanthroline, and 1 mM phenylmethylsulfonyl fluoride. The proteinase inhibitor mixture was always freshly prepared.

All experiments were repeated three or more times with qualitatively similar results. Typical experiments are shown. Values are means of triplicate determinations. Co-efficient of variance was always <7%.

**RESULTS**

The interface surfaces used for the design of the peptides are shown in Fig. 1, A and B. In Fig. 1A the regions used for the peptides are shown in color in a ribbon diagram format from the crystal structure solved by Sprang and co-workers (3). The interface regions can be thought to form two symmetrical lock and key interactions, which are shown in a schematic diagram in Fig. 1B. The details of the peptides used in these experiments are summarized in the table within Fig. 1. For each of the peptides used, a control peptide was synthesized by replacing some of the contact residues with other amino acids. These control peptides are labeled with the suffix “m” to indicate their mutated status. The sequences of the peptides used and their corresponding residues in AC2, AC5, and AC6 are given in Fig. 1A.

The first peptide we tested was from the C1a region of the central cytoplasmic loop. The peptide encoding the 899–926 region of the C2 domain inhibited basal activity substantially (Fig. 2). The inhibition was 55% for both AC2 and AC6, but the inhibition was lost in the substituted peptide, indicating the specificity of the contacts required for the effect. Two other peptides, C1-β4-β5-α4 and C2-α3'-β4', inhibited basal activity by ~30%. The substituted peptides showed no significant inhibition (Fig. 2). The peptides were then tested for...
**Fig. 2.** Effect of varying concentrations of the five interface peptides on basal (10 mM Mg$^{2+}$) adenyl cyclase activity of AC2 (left panel) and AC6 (right panel). Open symbols represent peptides with native sequences. Solid symbols represent control peptides in which selected contact residues were substituted. Peptides are labeled as C1-1, C1-2, C2-1, C2-2, and C2-3. Substituted peptides have the letter m at the end of the label. Substitutions are detailed in the second column from the left in Table I. Values are means of triplicate determinations. A typical experiment of 10 panels is shown.
effects on the Mn\(^{2+}\)-stimulated activities of AC2 and AC6. Here also, the AC2 899–926 peptide encoding \(\alpha2\) region substantially inhibited Mn\(^{2+}\)-stimulated activity of AC2 and AC6. Both the extent of the inhibition of the Mn\(^{2+}\)-stimulated activity as well as the observed potency of the peptide were similar to that seen with basal activity. The other peptides did not affect Mn\(^{2+}\) activity significantly (Fig. 3). These results were somewhat surprising, because it was anticipated that many if not all of the interface peptides would inhibit all adenylyl cyclase activities, since the interface interactions are thought to be required for the formation of the catalytic site. One explanation for the observed effects is that most of the interfaces are precluded and that the addition of the exogenous peptides is insufficient to disrupt these interactions. If this is the case, then only the \(\alpha2\) peptide should inhibit forskolin- and Gas-stimulated activities as well. This was tested in Fig. 4 for Gas and Fig. 5 for forskolin. Here we found all of the peptides inhibited both Gas- and forskolin-stimulated activities. In all cases, substitution of key interaction residues led to loss of inhibition. The extent of the inhibition of Gas stimulation was quite substantial. It ranged from 69% for the C1 domain peptides to 89% for the C2-\(\alpha3\)-\(\beta4\) peptide, which is close to the Gas binding sites. The IC\(_{50}\) values and the percentages of inhibition for the various peptides for the different activities of AC2 and AC6 are summarized in Table I.

**DISCUSSION**

The ability to express portions of the central cytoplasmic loop and C-terminus of adenylyl cyclases (11) provided both conceptual and experimental breakthroughs in understanding the catalytic activity of adenylyl cyclase (12) as well as its regulation by Gas and forskolin (5, 13). The crystal structure of the soluble fragments of adenylyl cyclase with Gas has provided structural insight into the catalytic mechanisms (14, 15) as well as the mechanisms by which Gas and forskolin stimulate adenylyl cyclase (15, 16). The structure of the basic catalytic core postulated from the crystal structure is both simple and attractive. It is a primitive version of the “palm” domain of DNA polymerase I. The actions of both Gas and Goi have been explained on the basis of the catalytic core formed from the fragments of the C1 and C2 domains by the collapse of the palm domain around the substrate. These models, although plausible and quite attractive in their simplicity, have never been experimentally tested in detail in the intact full-length enzymes. In particular, the nature of the interface interactions involved in the expression of the various activities had not been determined. We decide to use a peptide-based approach to test the predicted functions of the various interfaces, because this approach allows for the testing of contiguous regions within the enzymes. Additionally, the issue of changes in conformations of local domains, which often affects the interpretation of mutational data, does not generally affect data obtained with peptide probes.

We tested all of the interface peptides on the various adenylyl cyclase activities of full-length AC2 and AC6. We had typically expected to see a profile where each peptide would either inhibit all of the activities or none and that this might occur to different extents at varying peptide potencies for the different adenylyl cyclases, depending on how tightly the interfaces are coupled for a given adenylyl cyclase. Much to our surprise, we found that most of the interface peptides did not affect Mn\(^{2+}\)-stimulated activities. Additionally, although the \(\alpha2\) peptide from the C2 region inhibited Mn\(^{2+}\)-stimulated activity, its C1 domain binding partner in the crystal structure encoding the \(\beta4\)-\(\beta5\)-\(\alpha4\) region of C1 did not inhibit Mn\(^{2+}\)-stimulated activity. These observations indicate that there may be other sites of interaction for the \(\alpha2\) region of the C2 domain. Also noteworthy is the divergence of the extent of the inhibition of basal activity in the presence of Mg\(^{2+}\) as compared with that of Gas-stimulated activity. In all cases except that of the \(\alpha2\) region peptide (C2-1) of AC2, inhibition of the basal activity was about a half or a third of that observed with Gas-stimulated activity. This effect is different from that observed with other inhibitors of adenylyl cyclase such as Goi or P-site inhibitors and may be indicative of the differential capabilities and configurations of adenylyl cyclases for the expression of different activities; hence, we consider the implications of our observations for basal and Gas-stimulated activities separately.

**Basal Activity**—Although the different full-length adenylyl cyclases have substantial basal activities (8), the soluble cytoplasmic fragments have very little measurable activity. This observation, combined with the observations in this study that show that whereas the \(\alpha2\) region peptide of the C2 domain inhibits basal and Mn\(^{2+}\)-stimulated activities by 50–60%, its binding partner region in the soluble complex, the \(\beta4\)-\(\beta5\)-\(\alpha4\) region of the C1 domain, is only half as effective in inhibiting Mg\(^{2+}\)-dependent basal activity and quite ineffective in inhibiting Mn\(^{2+}\)-stimulated activities. A reasonable interpretation of this result might be that, in the full-length adenylyl cyclase, the \(\alpha2\) region of the C2 domain, in addition to interacting with the \(\beta4\)-\(\beta5\)-\(\alpha4\) region of the C1a region, might interact with other regions of the full-length adenylyl cyclase. Where might these regions be? One possibility is the C1b region, which is not part of the soluble adenylyl cyclase fragments used in determining the crystal structure. The structure for the C1b domain has not been solved. Yeast two-hybrid studies had suggested that the C1b domain might interact with the C2 domain of adenylyl cyclase (17). In the *Dictyostelium* adenylyl cyclase, a point mutation in the region linking the end of the sixth transmembrane domain with the central cytoplasmic loop constitutively activates the enzyme (18). How the C2 domain may interact with this region to yield high basal activity is not yet understood. It is possible that such interactions are also necessary for the Mn\(^{2+}\) activity. The functions of these different sites that may be involved in basal and Mn\(^{2+}\)-stimulated activities and the nature of the interactions will have to be determined in future studies.

The difference in the effects of the interface peptides on the Mn\(^{2+}\)-stimulated versus the Gas- and forskolin-stimulated activities is noteworthy. In the case of the latter two activities, all of the interface peptides inhibited both activities. This is the predicted result from the crystal structure. In addition, the inhibitory effect of these peptides was lost upon the substitution of key interacting residues as seen by the mutant control peptides, indicating that the interfaces align and interact within the full-length enzyme to produce Gas- and forskolin-stimulated activities in a manner similar to that observed in the crystal structure. Thus, it is likely that the catalytic site for the Gas-stimulated activity in the intact full-length enzyme is likely to be very similar to that observed in the crystal structure of Gas and forskolin in complex with the C1 and C2 fragments. If this were the case, how then can the interface peptides’ effects on the basal and Mn\(^{2+}\) effects on AC2 and AC6 be explained? One intriguing possibility is that there may be additional configurations of the full-length protein that can produce competent catalytic sites. Recently, it has been shown that Goi cannot inhibit the Mn\(^{2+}\)-stimulated activity of full-length AC5, although it inhibits the activity of the soluble enzyme (19). It had been shown previously that the full-length Mn\(^{2+}\)-stimulated enzyme cannot be inhibited by Goi (20). These observations are consistent with the hypothesis that a different catalytic configuration may be used for the Mn\(^{2+}\)-
Fig. 3. Effect of varying concentrations of the five interface peptides on 10 mM Mn$^{2+}$-stimulated adenylyl cyclase activity of AC2 (left panel) and AC6 (right panel). Open symbols represent peptides with native sequences. Solid symbols represent control peptides in which selected contact residues were substituted. Peptides are labeled as C1-1, C1-2, C2-1, C2-2, and C2-3. Substituted peptides have the letter m at the end of the label. Substitutions are detailed in the second column from the left in Table I. Values are means of triplicate determinations. A typical experiment of 10 panels is shown.
Interactions within the Cytoplasmic Regions of Adenylyl Cyclase

**Fig. 4.** Effect of varying concentrations of the five interface peptides on 2 μM Q213L-Gαs-stimulated and 100 μM GTP-stimulated adenylyl cyclase activity of AC2 (left panel) and AC6 (right panel). Open symbols represent peptides with native sequences. Solid symbols represent control peptides in which selected contact residues were substituted. Peptides are labeled as C1-1, C1-2, C2-1, C2-2, and C2-3. Substituted peptides have a letter m at the end of the label. Substitutions are detailed in the second column from the left in Table I. Values are means of triplicate determinations. A typical experiment of 10 panels is shown.
FIG. 5. Effect of varying concentrations of the five interface peptides on 30 μM forskolin-stimulated adenylyl cyclase activity of AC2 (left panel) and AC6 (right panel). Open symbols represent peptides with native sequences. Solid symbols represent control peptides in which selected contact residues were substituted. Peptides are labeled as C1-1, C1-2, C2-1, C2-2, and C2-3. Substituted peptides have a letter m at the end of the label. Substitutions are detailed in the second column from the left in Table I. Values are means of triplicate determinations. A typical experiment of 10 panels is shown.
Interactions within the Cytoplasmic Regions of Adenylyl Cyclase

Table I

| Peptide | Region of adenylyl cyclase/control peptides* | AC2 | AC6 |
|---------|---------------------------------------------|-----|-----|
|         | IC50 (μM) | Basal | FSK | Gas | Mn2+ | IC50 (μM) | Basal | FSK | Gas | Mn2+ |
| C1-1    | C5C1 (427–444) | 1.7 30.4 28.4 | 7.53 | 58.88 | 68.93 | −0.13 | 148.5 46.1 32.0 | 8.13 | 54.38 | 69.72 | −2.99 |
| C1-1m   | R434D, K436D, I437P | 5.75 | 0.22 | 3.10 | 0.05 | 0.93 | 2.47 |
| C1-2    | C5C1 (487–511) | 26.5 22.0 19.3 | 30.18 | 51.46 | 68.72 | −2.45 | 34.0 16.5 29.6 | 28.96 | 62.71 | 84.64 | 9.12 |
| C1-2m   | G498P, K501E, Q503R | 3.48 | 10.69 | 6.38 | 1.65 | 1.14 | 0.50 |
| C2-1    | AC2C2 (899–926) | 22.2 64.7 14.7 | 11.7 | 58.96 | 54.71 | 80.03 | 53.44 | 37.9 19.2 23.4 | 27.7 | 52.13 | 63.26 | 71.32 | 56.56 |
| C2-1m   | E910K, R913P, N916A, E917K, I926S | 5.21 | 10.72 | 7.57 | 10.54 | 7.86 | 4.68 |
| C2-2    | AC2C2 (927–948) | 43.3 19.3 17.1 | 19.97 | 64.05 | 73.23 | 2.86 | 130.1 61.8 | 13.4 | 10.99 | 59.29 | 70.51 | 1.63 |
| C2-2m   | K936D, I937F, K938D, K940F | 0.37 | 0.63 | 3.73 | 0.05 | 4.03 | 2.59 |
| C2-3    | AC2C2 (984–1015) | 14.7 51.7 23.3 | 29.52 | 64.92 | 88.75 | 14.91 | 53.9 46.6 | 25.8 | 28.32 | 64.80 | 83.92 | 14.37 |
| C2-3m   | H989D, F991K, N992K, K995G, I1012Q, Q1013K | 6.92 | 3.59 | 8.42 | 12.59 | 6.96 | 20.77 |

* Adenylyl cyclase regions are given for the non-mutated peptides, and substitutions are given for the mutated (control) peptides. Control peptides (Cx-Yx) were designed by substituting contact residues between C1 and C2 as determined in the crystal structure.

† Percentage of inhibition data were determined at saturating concentrations of peptide (300 μM).

**stimulated activity.** Does this mean that the catalytic site uses different contact residues to interact with the metal-ATP complex to achieve catalysis, or does it mean that different sets of interactions between the central cytoplasmic loop and the C-terminal tail can yield the same catalytic site, with the crystal structure providing us with a picture of one such set of interactions? The latter option is conceptually simpler and would be thermodynamically more feasible. It is instructive in this line of reasoning to take note of the methodology by which the crystalline configuration of the soluble domains of adenylyl cyclase complexed with the P-site inhibitors or with ATP analogs and Mn2+ were obtained. In all cases, the preformed Gas-C1-C2 crystals were soaked with the nucleotide-divalent cation mixtures. Although this procedure has been quite valuable in elucidating the catalytic site in the presence of Gas, by its very design this procedure precludes the possibility of observing alternative configurations that may be catalytically competent. The necessary starting point to resolve these issues will have to be a crystal structure of the membrane-bound, full-length enzyme.

Gas-stimulated Activity—Based on the crystal structure, Tesmer and Sprang (15) had proposed that the Gas binding to the C2-C1 complex might “prime” the active site for catalysis, suggestive of a relatively stable interaction between the interfaces of the C2 and C1 domains of adenylyl cyclase in the presence of Gas. Such a model might result in partial inhibition of the Gas-stimulated activity, depending on the relative affinity of each interface surface for its binding partner as part of the intact protein versus the free peptide. However, in all cases, given the low IC50 values of the peptides it would appear unlikely that the extent of inhibition would be as substantial as is observed. A more dynamic model where the C1 and C2 interfaces are being constantly formed and separated might better explain the data in this study using the full-length enzymes. Here, the frequency of the opening of the interface regions in the presence of Gas might provide the low affinity peptides with the opportunity to interact with the interface regions and thus inhibit the formation of the catalytically competent C1-C2 complex. In this regard, inhibition of Gas-stimulated activity by the interface region peptides may differ from the Gai inhibition. In the latter case, the formation of the Gai-C1 complex precludes the formation of the Gas C1-C2 complex and, hence, the inhibition. In the case of the interface peptides, it appears that the ability to block the formation of the C1-C2 complex would occur irrespective of whether or not Gas binds the C2 domain, and the dynamics of the C1-C2 interactions would account for the observed extent of inhibition. Dynamic structures are needed to assess the validity of such models.

In summary, this functional analysis of the predicted catalytically competent configuration from the crystal structure, while providing significant support for the validity of the use of the soluble fragments to understand the functions of adenylyl cyclases, suggests the possibility of the existence of dynamic structures. Future studies identifying and characterizing such structures should provide new insight into how adenylyl cyclase functions under various types of regulation.

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