The structure, catalytic mechanism and regulation of adenylyl cyclase
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The recent structure determinations of the mammalian effector enzyme adenylyl cyclase reveal the structure of its catalytic core, provide new insights into its catalytic mechanism and suggest how diverse signaling molecules regulate its activity.

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Abbreviations
2'd3'AMP 2'-deoxy-3'-AMP
IIIC2 AC2 C2a domain
AC adenylyl cyclase
C cytoplasmic domain
CaM calmodulin
Gβi G protein βi subunits
Gαs inhibitory G protein α subunit
Gαs+ stimulatory G protein α subunit
M membrane-spanning domain
myr myristoylated
N N-terminal domain
PK protein kinase
PPi pyrophosphate
VC1 AC5 C1a domain

Introduction
The actions of multiple signal transduction pathways are often coordinated, with an appropriate cellular response relying on the simultaneous activation or repression of several pathways. The effector enzyme adenylyl cyclase coordinates many pathways by virtue of the fact that its activity is regulated by molecules from different signaling cascades. In response to a particular set of signals, the enzyme produces an appropriate amount of a single second messenger, cyclic AMP (cAMP), which, in turn, regulates processes as diverse as glycogen metabolism, cardiac output and long-term potentiation.

In mammals, there are at least nine isoforms of adenylyl cyclase (AC1–AC9), each with distinct regulatory properties [1–4]. All characterized isoforms have a low basal activity that is markedly enhanced upon binding the stimulatory G protein α subunit (Gαs). Other regulators act specifically on only a few isoforms of adenylyl cyclase and can have dramatically different effects from one isoform to the next. The activity of adenylyl cyclase is also potently affected by various small molecules. Forskolin is a hypotensive agent that activates all isoforms except AC9 [5,6]. ‘P-site’ inhibitors [7–9] are typically 3’-adenosine nucleotide analogs that bind to the activated pyrophosphate (PPi) complex of adenylyl cyclase [10,11]. It is not known whether adenylyl cyclase is regulated in vivo by analogs of either forskolin or P-site inhibitors.

The primary structure of adenylyl cyclase is indicative of its regulatory complexity [1]. The approximately 120 kDa glycoprotein consists of a small, cytoplasmic N-terminal domain (N), followed by two repeats of a unit comprising a membrane-spanning domain (M) and two cytoplasmic domains (C) (NM1C1aC1bM2C2aC2b) (Figure 1). Although C1a, C1b and C2a are known to bind regulatory molecules, each of the domains of adenylyl cyclase could play a role in modulating enzymatic activity. Domains M1 and M2 could serve as a membrane voltage sensor that conformationally regulates adenylyl cyclase [12]. Alternatively, these domains may only target adenylyl cyclase to the membrane and provide a scaffold around which other signaling proteins can assemble. C1a and C2a are homologous to each other and to the catalytic domains of the guanylyl cyclases. Together they constitute the catalytic moiety of adenylyl cyclase [13–15]. C1a is the primary binding site for the inhibitory G protein α subunit (Gαi) [16*], whereas C2a is the primary binding site for Gαs [17,18**,19] and, potentially, the G protein βγ subunits (Gβγ) [20,21]. C2a also

Figure 1

Schematic of a typical mammalian adenylyl cyclase. The M1 and M2 domains are each predicted to contain six transmembrane helices. C1a and C2a form a pseudosymmetric heterodimer that represents the catalytic core of the enzyme. The active site is formed within their domain interface. The domains with which regulators are known to primarily interact are indicated. The N, C1a and C2a domains are variable among adenylyl cyclases and their structure and location with respect to the membrane and catalytic core are unknown.
contains phosphorylation sites for protein kinase (PK) C and calmodulin (CaM) kinase II [22,23]. Clb is a regulatory locus for Ca\textsuperscript{2+}\textcdot CaM, Ca\textsuperscript{2+}, PKA and CaM kinase IV [24–26]. The functional roles of N and C\textsubscript{2b} are unknown.

Understanding the molecular basis behind the complex regulation of adenylyl cyclase is thus a fascinating but challenging biophysical problem. In the past year, much has been learned about this system, thanks in part to high resolution crystal structures of the AC\textsubscript{2} C\textsubscript{2a} domain (IIIC\textsubscript{2}) homodimer [27*], the ternary complex of G\textsubscript{ac} with the C\textsubscript{1a} domain from AC5 (VC\textsubscript{1}) and IIIC\textsubscript{2} (G\textsubscript{ac}\textdash VC\textsubscript{1}\textdash IIIC\textsubscript{2}), and the complex of G\textsubscript{ac}\textdash VC\textsubscript{1}\textdash IIIC\textsubscript{2} with the P-site inhibitor 2′-deoxy-3′-AMP and PP\textsubscript{i} (2′d3′AMP\textcdot PP\textsubscript{i}) [18**]. This review will focus primarily on what has recently been learned about the catalytic mechanism of adenylyl cyclase and how adenylyl cyclase might be regulated by molecules that directly interact with the catalytic core, such as G\textsubscript{ac}, forskolin, G\textsubscript{\alpha}\textcdot PKC, CaM kinase II and G\textsubscript{\beta\gamma}.

The C\textsubscript{1a}\textcdot C\textsubscript{2a} catalytic core

C\textsubscript{1a} and C\textsubscript{2a} can be expressed independently in Escherichia coli as inactive fragments [6,14,15,16*,28] that can be mixed to reconstitute adenylyl cyclase activity, as
Adenylyl cyclase structure and homology to DNA and RNA polymerases. (a) The C1α•C2α heterodimer as defined by the structure of Gsα•VC1•IC2 [18°]. The view is towards the putative cytoplasmic or ‘ventral’ face of the molecule, along the pseudosymmetric twofold axis. Helices are represented by cylinders and β strands by arrows. For clarity, the α helices are labeled in (a) and the β strands in (b). The switch II helix of Gsα is drawn as a red cylinder to indicate the Gsα-binding site on C1α•C2α. ATP and forskolin (FSK) are drawn as stick models in the ventral cleft. Only metal A, drawn as a silver sphere, is visible in this view. C1α and C2α are drawn in tan and mauve, respectively. The primary differences between the homologous C1α and C2α domains are located in their α1-α2 and β7-β8 loops. The α1-α2 structure of C1α is responsible for forming the P loop of the active site and part of the binding site for Gsα where in C2α it forms parts of both the Gsα and forskolin-binding sites. In C1α, the β7-β8 loop is an omega loop consisting of helices α6 and α7, while in C2α it is a β ribbon that contributes to the active site. The orange letters S and T mark the location of a serine and threonine residue that are putative phosphorylation sites for CaM kinase II in AC3 and PKC in AC2, respectively. (b) The C1α domain of AC5. The view is 45° around a vertical axis from the C1α domain in (a). Elements of the structure drawn in light gray are those that can be superimposed on analogous structures from Pol I family nucleotide polymerases. The ‘arm’ and C-terminal subdomains, as defined in the text, are drawn in red and blue, respectively. Pol I family polymerases contain a ‘fingers’ domain, inserted after the first β strand of its palm domain. The analogous ‘fingers’ domain of C1α is the α1 helix (green), which is functionally analogous to the first helix of the fingers domain of polymerases. In both proteins, the N terminus of this helix forms a P loop responsible for binding the β and γ phosphates of the nucleotide substrate (c). The two invariant aspartic acids that are hallmarks of the adenylyl cyclase and Pol I polymerase active sites are drawn as stick residues. Metals A and B are drawn as magenta spheres. (c) The active sites of adenylyl cyclase and T7 polymerase [37°]. The view of the adenylyl cyclase active site is rotated roughly 180° in the plane of the page with respect to the image in (b). The active site of adenylyl cyclase corresponds to the structure of Gsα•VC1•IC2 complexed with 2'd3'AMP•PPi [18°]. ATP was modeled in the site by superimposing its purine on that of 2'd3'AMP and its β and γ phosphates on PPi. The ribose pucker is 3'-endo, allowing the 3'-hydroxy to closely approach metal A and attack the α phosphate between its pro-R and pro-S unesterified oxygens. The T7 polymerase active site was aligned with that of adenylyl cyclase by superimposing the four strands and segments from each of the three associated helices of their core palm domains (root mean square deviation of 1.1 Å for 51 Ca atoms). The substrates of T7 polymerase are represented by the 5'-nucleotide of the replicating DNA strand and 2',3'-dideoxy-GTP. The 3'-hydroxy of the 5'-nucleotide was modeled because the original structure had a 2',3'-dideoxy nucleotide at this position. Metal A and metal B are drawn as silver spheres. Carbon atoms are colored gray, nitrogen is blue, oxygen is red and phosphorous is green. Structural elements that are not part of the core palm domain of each enzyme are colored mauve. In adenylyl cyclase, the mauve elements are donated by the C2α domain (residue numbers for C1α correspond to AC5 and numbers for C2α correspond to AC2). In T7 polymerase, they are donated by the ‘fingers’ domain. The similarity between the structures of their core ‘palm’ domains, their active sites and the chemical transformations they perform all suggest that nucleotide cyclases and Pol I family polymerases have a common ancestor. Panels (a–c) were drawn with the program BOBSCRIPT [45] and rendered using POVRAY [46].

The active site and two metal ion catalysis

In 1981, Eckstein et al. [33] demonstrated that mammalian adenylyl cyclase converted ATP to 3',5'-cAMP with inversion of stereochemistry at the α phosphate. The finding was most easily explained by a direct in-line displacement of PPi, by the 3'-hydroxyl of ribose. Therefore, it appears that adenylyl cyclase must perform two feats. First, the enzyme must provide an active site that is complementary to an energetically unfavorable conformation of ATP. Second, because the 3'-hydroxyl is a poor nucleophile, the enzyme must activate this group for catalysis.

Crystal structures demonstrate that the catalytic core of adenylyl cyclase can adopt at least two conformations—open and closed. ATP cannot be modeled into the native (open) structure of Gsα•VC1•IC2 so that both its adenine ring and β and γ phosphates occupy their respective binding sites simultaneously [34]. When 2'd3'AMP•PPi binds to Gsα•VC1•IC2, however, the β2-β3, α1-α2 and α3-β4 loops of VC1, and the β7-β8 loop of IC2 collapse around the inhibitor [18°]. In this ‘closed’ conformation of adenylyl cyclase, ATP can be convincingly modeled into the active site (Figure 2c). The purine ring of ATP binds between the C1α and C2α domains, within a hydrophobic pocket containing groups in IC2 that dictate nucleotide specificity (Lys938, Asp1018 and the carbonyl oxygen of residue 1019). By mutating Lys938 and Asp1018 to their counterparts in soluble guanylyl cyclase, glutamate and cysteine, respectively, adenylyl cyclase was converted into a nonspecific nucleotide cyclase [35°]. The reverse exchange in guanylyl cyclase resulted in complete reversal of nucleotide specificity from GTP to ATP [35°,36°].

The ribose and polyphosphate tail of ATP are bound by two Mg2+ ions (A and B) and three basic residues (Arg484...
from VC1, and Arg1029 and Lys1065 from IIC2. Metals A and B are in turn chelated by two invariant aspartic acids and the carbonyl oxygen of Ile397. A nearly identical configuration is found in the active site of T7 polymerase [37**] (Figure 2c). Although metal A was not modeled in the original crystal structure of adenylyl cyclase with Zn2+ or Mn2+, clearly reveal the presence of two distinct metal sites within the active site. Zn2+, a likely inhibitor of adenylyl cyclase, preferentially binds in the metal A site. Mg2+, a much more potent cofactor than the physiological metal, preferentially binds in the metal B site (JTG Tesmer, unpublished data). These binding preferences are the same as those for Zn2+ and Mn2+ in the active site of the T7 polymerase [37**]. Two metal-binding sites are also implicated in studies of mutants that are defective in binding metal ions, but not ATP [39].

Based on the presence of the two metals and its structural and mechanistic similarities to Pol I DNA polymerases, adenylyl cyclase is now expected to employ two metal ion catalysis [40] (Figures 2 and 3). Metal A binds the 3'-hydroxyl of ATP and lowers its pKα to the extent that its proton is presumably donated to the solvent. Metal B binds the β and γ phosphates. Both metals may also stabilize the transition state by binding the pro-R oxygen of the expected pentavalent α phosphate intermediate. The superposition of the active sites of T7 polymerase and adenylyl cyclase reveals additional features that are important for catalysis (Figure 2c). Both enzymes provide a hydroxyl group that interacts with the β phosphate (Thr401 in VC1 and Tyr526 in T7) and three basic residues that interact with the triphosphate tail of the nucleotide substrate (Arg1029 in IIC2 and Lys522 in T7, Lys1065 in IIC2 and His506 in T7, Arg484 in VC1 and Arg518 in T7). Although the functional groups of these residues fall in similar positions, they are donated by unrelated structures in each enzyme. Thus, the nonhomologous regions of adenylyl cyclase and T7 polymerase have convergently evolved to provide four sidechains that help bind the nucleotide substrate, stabilize the pentavalent transition state and neutralize the negative charge on the PPi leaving group.

Activation by interfacial hinging: Gsα and forskolin

The association of C1α and C2α is clearly required for activity and activators of adenylyl cyclase, such as Gsα and forskolin, dramatically increase the affinity of C1α for C2α in the soluble system [14,15]. This does not mean, however, that activators only serve as 'molecular glue' holding the domains together or that the domains are necessarily dissociated in the basal or inhibited state of the full-length enzyme. Gsα and forskolin increase the maximum basal rate of catalysis by C1α•C2α without greatly affecting the Km for ATP or the Ki for ATP analogs, implying an allosteric mechanism of activation [14]. Because the active site is located within the C1α•C2α interface, a regulator can profoundly influence catalysis by slightly reorienting C1α and C2α with respect to each other. This conformational change is facilitated by the arm subdomains from each domain (Figure 2b), which form a flexible double hinge across the C1α•C2α interface [18**]. Both Gsα and forskolin appear to exploit this feature in order to regulate adenylyl cyclase.

The primary binding site for Gsα is a cleft between the α1–α2 and α3–β4 loops of C2α (Figure 2a). Gsα also binds a few hydrophobic residues at the N terminus of C1α [17,18**], an interaction that is not required to form the C1α•C2α•Gsα complex, but it is necessary for the stimulation of adenylyl cyclase by Gsα [28]. Gsα may also interact with structural elements of adenylyl cyclase that are not present in C1α or C2α [26,28]. Using the IIC2 homodimer [27*] as a crude model for the C1α•C2α catalytic core in the absence of Gsα, an allosteric mechanism can be proposed. Upon binding, Gsα expands the cleft between the α1–α2 and α3–β4 loops of C2α. The α1–α2 loop in turn exerts pressure on the C1α domain. Tethered to Gsα at its N terminus (part of the flexible arm subdomain), the C1α domain then rotates 10° with respect to the C2α core,
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Figure 4

Model of the regulation of adenylyl cyclase. C1a and C2a are drawn as oblong blocks. The arm subdomains are drawn as hinges linking the two blocks. The basal states of adenylyl cyclase have very low catalytic activity. After Gsa (or forskolin, etc.) binds, C1a and C2a rotate by 100° with respect to each other, priming the active site for catalysis and stimulating activity (top versus bottom complexes). ATP binds concomitantly with the collapse of several active site loops, which is represented by an inward shift at the end of each block (right versus left complexes). Stimulatory and inhibitory regulators are enclosed in circles and rectangles, respectively, and are grouped with respect to the step during which they are believed to exert their effects. In this simplified model, regulators that dramatically activate adenylyl cyclase (Gsw forskolin and, perhaps, Ca2+-CaM) facilitate the transition from the basal to the activated complexes. Regulators with more subtle effects or those that are conditional on the presence of other regulators (Gip, Gi2, PKC and CaM kinase II) facilitate or hinder the collapse of active site loops and sidechains around ATP during the transition from the ground state to the activated enzyme-substrate (E-S) and transition-state (E-S*) complexes. PKA, CaM kinase IV and Ca2+ interact with or modify the Clb domain rather than the catalytic core, and PKA and CaM kinase IV may directly interfere with the binding of both Gsa to AC6 [26] and Ca2+-CaM to AC1 [25]. Therefore, these regulators are shown inhibiting the transition from the bottom to top complexes. It should be emphasized that good models do not exist for the two bottom complexes.

Around an axis inclined roughly 45° with respect to the ventral cleft of the C1a•C2a heterodimer (Figure 4). The resulting shift in the domain interface presumably reorients the catalytic residues and primes the active site for converting ATP to cAMP [18**].

Since forskolin binds within the C1a•C2a interface, adjacent to the Gsa-binding site (Figure 2a), the drug is clearly in an optimal position to manipulate the relative orientation of the C1a and C2a domains in an manner analogous to Gsa. In isoforms in which activation by forskolin is synergistic with Gsa, the molecule must induce its own unique twist on the domain interface to augment catalysis.

Regulating collapse: Gia, PKC, CaM kinase II and Gβγ

Gia is closely related to Gsa, but it is a noncompetitive inhibitor of Gsa-stimulated AC5 or AC6 [41]. The homology between C1a and C1b suggests that Gia could bind pseudosymmetrically to Gsa within the cleft between the α1–α2 and α3–β4 loops of VC1. Importantly, these are two of the loops that collapse upon the active site when ATP binds. Gia may therefore function by preventing the productive collapse of catalytic residues around ATP. Recently, Dessauer et al. [16*] showed that mutations in the α1–α2 and α3–β4 loops of VC1 can either greatly increase or decrease the IC50 for inhibition by myristoylated Gia (myr-Gia). In addition, a 1:1 complex between VC1 and myr-Gia has been observed by gel filtration and sedimentation equilibrium. It is not yet clear whether myr-Gia interacts with any portion of the C2a domain. It is also not clear why myr-Gia is specific for only a few isoforms, because the mutations that had the most dramatic effects were of residues that are conserved across all isoforms of adenylyl cyclase. The C1b domain may contribute some specificity since a soluble construct of VC1 that includes the Clb domain is inhibited by myr-Gia to a much greater extent than the C1a domain alone [16*].

Phorbol esters stimulate the production of cAMP presumably via the activation of PKC and the subsequent phosphorylation of PKC-sensitive adenylyl cyclases [1]. The putative phorbol ester-sensitive phosphorylation site of AC2 was recently shown to be Thr1057 in the β7 strand of the C-terminal subdomain of C2a [23], although a chimera AC2 lacking a serine or threonine at this position
had previously been shown to retain sensitivity to phorbol esters [42]. Although located nowhere near the C11a•C2a interface, phosphorylation of Thr1057 could influence the position of the β7-β8 ribbon of C2a, which bears a catalytically important lysine residue (Lys1065 in AC2) [29]. This ribbon is another structural element that collapses on the active site upon the binding of 2'd3'AMP•PP (and presumably ATP) to Gαα-VC1-IC2. Therefore, phosphorylation of AC2 by PKC may help stabilize the β7-β8 ribbon in its active conformation.

In contrast, the phosphorylation of AC3 by CaM kinase II is inhibitory [22]. The proposed phosphorylation site is a solvent-exposed serine located at the C terminus of helix α4 (Figure 2a). Phosphorylation of this residue would probably perturb the conformation of an adjacent arginine residue that is believed to make an important contribution to the transition-state complex (Arg1029 in Figure 3) [18°7, 43]. It is not yet clear, however, whether this residue is phosphorylated in vivo, nor why such an event would be specific for AC3 given that this region is highly conserved among all isoforms of adenylyl cyclase.

The βγ subunits of the heterotrimeric G protein inhibit AC1, co-activate AC2 and AC4 with Gαs, but have no effect on other characterized isoforms of adenylyl cyclase. A peptide derived from the α3 helix and its preceding loop in the C2a domain of AC2 has been shown to block the stimulation of AC2 and other effectors by sequestering Gβγ [21]. It has not, however, been rigorously tested whether the α3 region of intact AC2 truly represents the Gβγ-binding site. As the α3 region is distant from the Gαρ-cyclase interface, the C11a•C2a interface and the active site, the dependence of Gβγ on the presence of Gαs is not easily explained. Superstimulation of Gαρ-activated AC2 by Gβγ is blocked by PKC [44]. Therefore, it seems likely that at least part of the Gγ-binding site encompasses the region around Thr1057. If true, then Gβγ may also activate AC2 via manipulation of the β7-β8 ribbon of C2a.

Conclusions

Two plausible mechanisms for the regulation of adenylyl cyclase are evident from recent work (Figure 4). The first is to manipulate the C11a•C2a interface that houses the active site. This would produce the most profound changes in activity and is probably the mechanism used by activators, such as Gαs and forskolin. Ca2+•CaM, a potent activator of AC1 and AC8, could indirectly use this mechanism if its target, the C1b domain, interacts with the arm subdomains of the catalytic core. The second mechanism is to manipulate the loops and sidechains that presumably collapse on the active site upon binding ATP. This could be the method used by Gαi, Gβγ (for AC2), PKC and other regulatory molecules. Regulation by the second mechanism is less robust and its effects are often only apparent after the activation of adenylyl cyclase via the first mechanism. The structural correlate is that the active site must be primed for catalysis before the manipulation of active-site loops and residues will have a significant effect.

A better understanding of Gαs-mediated regulation of adenylyl cyclase requires knowledge of a structure of C11a•C2a that mimics the basal state of the enzyme. Only then can the conformational changes imposed by Gαs be properly assessed. Solving the structure of the complex between Gαs and one or more domains of adenylyl cyclase is now within grasp and, with the structure of the basal enzyme, would complete a chapter on the bidirectional regulation of an important physiological enzyme.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest
• of outstanding interest


The authors used mutagenesis to map the Gβγ binding site on adenylyl cyclase to the cleft on Gβγ that is pseudosymmetrically related to the Gs~γ cleft on Gβγ. They also used various biophysical methods to demonstrate that the Gβγ binding cleft on Gβγ is similar to the cleft on Gi6γ.


The structure determination reveals details of the interaction between Gαα and the catalytic core of adenylyl cyclase. By soaking 2'-deoxy-3'-AMP·PPi into the crystal, the authors were able to define the active site of adenylyl cyclase and the potential roles of catalytic residues. According to comparisons with the structure of the PII homodimer, an allosteric model for the activation of adenylyl cyclase by Gαα was proposed.


The structure of the IIC1 homodimer-forskolin complex is a complex of the PII homodimer. Two molecules of forskolin bind within a cleft between the two subunits, suggesting that forskolin activates adenylyl cyclase by stabilizing the Gαα-GTP complex within the PII homodimer. The structure determination also greatly facilitated the structure determination of the Gαα-GTP·S complex.


Artyukh and co-authors point out that the polymerase I palm is similar to the adenylyl cyclase structure. Current crystal structures show that the two enzyme families have an ancestral relationship.


This paper confirms the validity of the proposed adenyline-binding site within the structure of Gαα-GTP·S. The nucleotide specificities of adenylyl cyclase and the closely related, soluble guanylyl cyclase were altered simply by swapping a few residues in their purine-binding pockets. Adenylyl cyclase became a nonselective purine cyclase, whereas guanylyl cyclase became specific for ATP. The altered adenylyl and guanylyl cyclases were still responsive to their respective stimulators. This paper provides the ultimate proof that P-site inhibitors act at the active site of adenylyl cyclase, not at a separate regulatory site.


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An important paper, not only for the general nucleotide polymerase field, but also for illuminating the catalytic mechanism of adenylyl cyclase. This elegant structure captures for the first time a polymerase active site complete with two metal, DNA template, replicating strand and nucleotide substrate. The structure effectively ends much of the debate on the polymerase catalytic mechanism. The striking similarity of its active site to that of adenylyl cyclase is confirmation of a common catalytic mechanism and, together with their structural similarity, a common ancestry.


46. Persistence of Vision Ray Trace v3.02 on World Wide Web URL: http://www.povray.org