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Clinical Research and Clinical Reports

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Review Article

Adenylyl Cyclase: Structure, Function, Role in Diseases and Therapeutic Strategies

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Received Date: July 01, 2025 **Accepted Date**: July 10, 2025 **Published Date**: August 01, 2025.

Citation: Houhong Wang, (2025), Adenylyl Cyclase: Structure, Function, Role in Diseases and Therapeutic Strategies, *Clinical Research and Clinical Reports,* 8(3); **DOI:**10.31579/2835-8325/162

Abstract

Adenylyl cyclase (AC) is a pivotal enzyme in cellular signal transduction, catalyzing the conversion of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP), a crucial second messenger. There are multiple isoforms of AC, each with distinct regulatory properties and tissue distributions. AC-mediated cAMP signaling pathways are involved in a wide range of physiological processes, including metabolism, neurotransmission, and cell growth. Dysregulation of AC activity has been associated with various diseases, such as cardiovascular disorders, neurological diseases, and cancers. This review comprehensively summarizes the structural characteristics, biological functions, roles in disease pathogenesis, and current therapeutic strategies related to adenylyl cyclase. In-depth understanding of AC provides a basis for the development of more effective and targeted therapeutic approaches.

Key words: adenylyl Cyclase; Camp; Signal Transduction; Cardiovascular Diseases; Neurological Diseases; Cancer; Therapeutic Strategies

1.Introduction:

Cellular signal transduction is essential for cells to respond to extracellular stimuli and maintain normal physiological functions. Adenylyl cyclase (AC) is a key enzyme in the generation of the second messenger cyclic adenosine monophosphate (cAMP), which plays a central role in numerous signaling pathways. By catalyzing the conversion of ATP to cAMP, AC initiates a cascade of events that modulate various cellular processes, including gene expression, ion channel activity, and protein phosphorylation. There are multiple isoforms of AC, which are differentially regulated by various factors such as G-protein coupled receptors (GPCRs), calcium ions, and protein kinases. Dysregulation of AC activity can disrupt normal cAMP signaling, contributing to the development of various diseases. This review aims to provide an overview of the structure, function, roles in diseases, and therapeutic implications of adenylyl cyclase.

2. Structure of Adenylyl Cyclase

2.1 Isoforms and general structure

In mammals, there are nine membrane-bound AC isoforms (AC1 - AC9) and one soluble AC (sAC). Membrane-bound ACs share a common structural pattern, consisting of two large hydrophobic domains, each containing six transmembrane segments, and two large cytosolic domains. The cytosolic domains contain the catalytic regions responsible for converting ATP to cAMP. These catalytic regions have a high degree of sequence similarity among different AC isoforms, but the regulatory regions vary, leading to different sensitivities to various regulatory factors [1].

The soluble AC (sAC) has a distinct structure compared to membrane-bound ACs. It contains two homologous catalytic domains in tandem, and its activity is regulated by bicarbonate ions and calcium ions, rather than by GPCR - mediated pathways like most membrane - bound ACs [2].

2.2 Structural insights from crystallography

X - ray crystallography studies have provided detailed structural information about the catalytic domains of AC. These structures have revealed the molecular mechanisms of ATP binding and cAMP formation. The binding of ATP to the catalytic site of AC induces conformational changes that facilitate the cyclization reaction to form cAMP. Structural studies have also helped in understanding how different regulatory factors interact with AC to modulate its activity. For example, the binding of G - protein subunits to specific regions of AC can induce conformational changes that either enhance or inhibit its catalytic activity [3].

3. Biological Functions of Adenylyl Cyclase

3.1 Regulation of cAMP signaling

The primary function of AC is to generate cAMP, which then activates protein kinase A (PKA). Activated PKA phosphorylates a wide range of target proteins, leading to diverse cellular responses. In the heart, AC - mediated cAMP signaling can increase the contractility of cardiac myocytes by phosphorylating L - type calcium channels, enhancing calcium influx. In adipose tissue, cAMP signaling stimulates lipolysis by activating hormone - sensitive lipase through PKA - mediated phosphorylation [4].

3.2 Integration of multiple signals

AC can integrate signals from different sources. Many membrane - bound AC isoforms are regulated by GPCRs. Different GPCRs can couple to either stimulatory G - proteins (Gs) or inhibitory G - proteins (Gi). Activation of Gs - coupled GPCRs leads to the activation of AC and an increase in cAMP levels, while activation of Gi - coupled GPCRs inhibits AC activity and reduces cAMP levels. Additionally, some AC isoforms are sensitive to calcium ions. Calcium can either activate or inhibit AC activity depending on the isoform, allowing cells to integrate calcium - mediated signals with GPCR - mediated signals [5].

3.3 Other functions

AC - mediated cAMP signaling is also involved in neurotransmission. In neurons, cAMP can regulate the release of neurotransmitters, the plasticity of synapses, and the expression of genes related to neuronal survival and differentiation. AC has also been implicated in the regulation of cell growth and proliferation. Dysregulation of cAMP signaling through AC can affect the balance between cell growth - promoting and growth - inhibitory signals, influencing processes such as angiogenesis and tumorigenesis [6].

4. Adenylyl Cyclase in Diseases

4.1 cardiovascular diseases

In cardiovascular diseases, dysregulation of AC activity has been observed. In heart failure, the function of AC may be impaired, leading to reduced cAMP production and decreased contractility of cardiac myocytes. Abnormal regulation of AC - mediated cAMP signaling can also contribute to arrhythmias. For example, altered sensitivity of AC to G - protein - coupled receptor signals can disrupt the normal electrical activity of the heart [7].

4.2 Neurological diseases

In neurological diseases such as Alzheimer's disease and Parkinson's disease, dysregulation of AC - cAMP signaling has been implicated. In Alzheimer's disease, reduced cAMP levels and abnormal PKA activity have been associated with impaired synaptic plasticity and cognitive decline. In Parkinson's disease, dysregulation of AC in dopaminergic neurons can affect the survival and function of these neurons, contributing to the motor symptoms of the disease [8].

4.3 Cancers

In cancer, AC - mediated cAMP signaling can have both pro - tumorigenic and anti - tumorigenic effects, depending on the context. In some cancers, overactivation of AC and increased cAMP levels can promote cell proliferation and survival by activating signaling pathways that enhance angiogenesis and inhibit apoptosis. In other cases, however, cAMP signaling can act as a tumor suppressor, inhibiting cell migration and invasion [9].

5. Therapeutic Strategies Targeting Adenylyl Cyclase

5.1 Small molecule modulators

Small molecule drugs that can modulate AC activity are being developed. For example, forskolin is a natural compound that directly activates AC, increasing cAMP levels. It has been used in research and has shown potential in the treatment of certain diseases, such as glaucoma, by increasing the outflow of aqueous humor. On the other hand, inhibitors of AC are also being investigated. These inhibitors may be useful in diseases where overactive AC - mediated signaling is involved, such as some types of cancers [10].

5.2 Gene - based therapies

Gene - based therapies targeting AC are emerging. For example, gene delivery techniques can be used to introduce functional AC genes into cells with impaired AC activity, such as in some genetic disorders affecting AC. RNA interference (RNAi) - based approaches can also be used to knockdown the expression of specific AC isoforms in diseases where their overexpression is pathogenic [11].

5.3 Combination therapies

Combination therapies that target AC - mediated cAMP signaling along with other relevant pathways are being explored. In cancer treatment, combining AC modulators with chemotherapy or targeted therapies may enhance the efficacy of treatment. In neurological diseases, combination therapies that address multiple pathological processes, including dysregulation of AC - cAMP signaling, may offer more comprehensive treatment options [12].

6. Challenges and Future Directions

Despite the progress in understanding adenylyl cyclase and developing related therapeutic strategies, several challenges remain. One major challenge is the complexity of AC isoforms and their diverse regulatory mechanisms. The different sensitivities of various AC isoforms to regulatory factors make it difficult to develop drugs with specific and predictable effects. Another challenge is the potential off - target effects of AC modulators, as cAMP signaling is involved in many physiological processes. Future research should focus on further elucidating the molecular mechanisms of AC regulation, developing more selective and effective modulators, and exploring novel combination therapies. The application of advanced technologies, such as single - cell sequencing and artificial intelligence in drug design, may help to overcome these challenges and accelerate the development of effective treatments.

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