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Full form of cAMP:

Cyclic Adenosine Monophosphate

cAMP (CYCLIC ADENOSINE MONOPHOSPHATE)

cAMP or 3',5'- cyclic adenosine monophosphate is a hydrophilic secondary messenger molecule that is synthesized from adenylyl cyclase. It transduces a wide variety of physiological signals in different cell types in multicellular organisms. The effect of cAMP is mediated through activation of Protein Kinase A (PKA), which is also called cAMP-dependent kinase.
cAMP phosphorylates multiple intracellular target proteins expressed in different cell types.

Location – cAMP is synthesized from ATP by adenylate cyclase located on the inner side of the plasma membrane.

Targets- cAMP generated by adenylyl cyclase has 3 major targets:

i. The cyclic AMP dependent protein kinase (PKA)
ii. cAMP regulated guanine nucleotide exchange factors termed EPACs (Exchange protein directly activated by cAMP)
iii. via PKA phosphorylation, a transcription factor named CREB (cAMP response element binding protein)

Mode of action:

a. cAMP is a second messenger, synthesized by ATP by enzyme adenylyl cyclase.
b. Adenylate cyclase is activated by stimulatory G (G_s) protein-coupled receptors.
c. Inhibited by adenylate cyclase inhibitory G (G_i) protein-coupled receptors.
d. Inactive PKA is a tetramer which consists of two regulatory (R) subunits and two catalytic (C) subunits.
e. Each R subunit contains a pseudosubstrate domain whose sequences resembles that of a peptide substrate and binds to the active site in the catalytic domain but is not phosphorylated.
f. Thus, this pseudosubstrate domain inhibits the activity of catalytic subunits
g. Inactive PKA is turned on by binding of cAMP
h. Each R subunit has two distinct cAMP-binding sites, called as CNB-A and CNB-B
i. Binding of cAMP to both sites cause a conformational change in the R subunit. including its pseudosubstrate domain so that it can no longer bind to and inhibit the catalytic domain.
j. Thus, the kinase activity is activated.
k. Binding of cAMP by an R sub-unit of PKA occurs in a cooperative fashion.
l. Binding of the first cAMP molecule to CNB-B lowers the K_d for binding of the second cAMP to CNB-A.
m. Thus, small changes in the level of cytosolic cAMP can cause proportionately large changes in the number of dissociated C subunits and hence in cellular kinase activity.

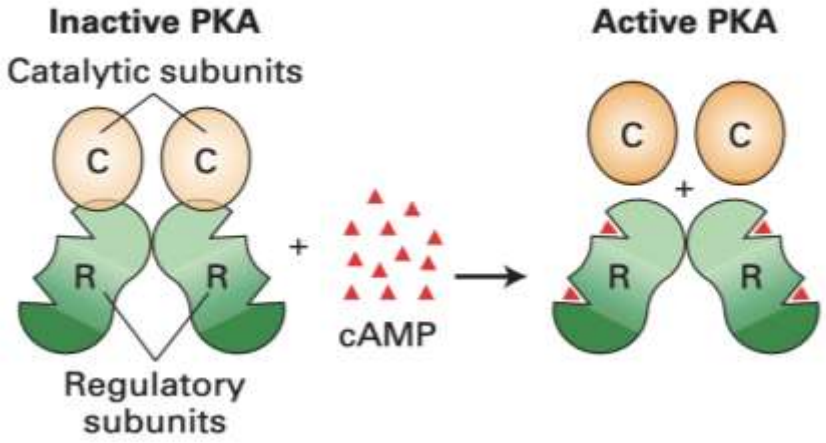


Fig: Structure of PKA and its activation by cAMP

I. Regulation of glycogen metabolism by cAMP and PKA:

i. Effect of increase in cAMP-

- Increase in cytosolic cAMP activates PKA
- PKA phosphorylates glycogen synthase
- This leads to inhibition of glycogen synthesis.
- Active PKA also promotes glycogen degradation via a protein kinase cascade.
- At high cAMP conc, PKA phosphorylates an inhibitor of phosphoprotein phosphatase (PP)
- Binding of the phosphorylated inhibitor to PP prevents this phosphatase from de-phosphorylating the activated enzymes in the kinase cascade or the inactive glycogen synthase.

ii. Effect of decrease in cAMP-

- Decrease in cAMP inactivates PKA
- This leads to the release of the active form of PP
- The activation of PP promotes glycogen synthesis and inhibits glycogen degradation
- PKA mediates a large array of hormone-induced cellular responses in multiple tissues.

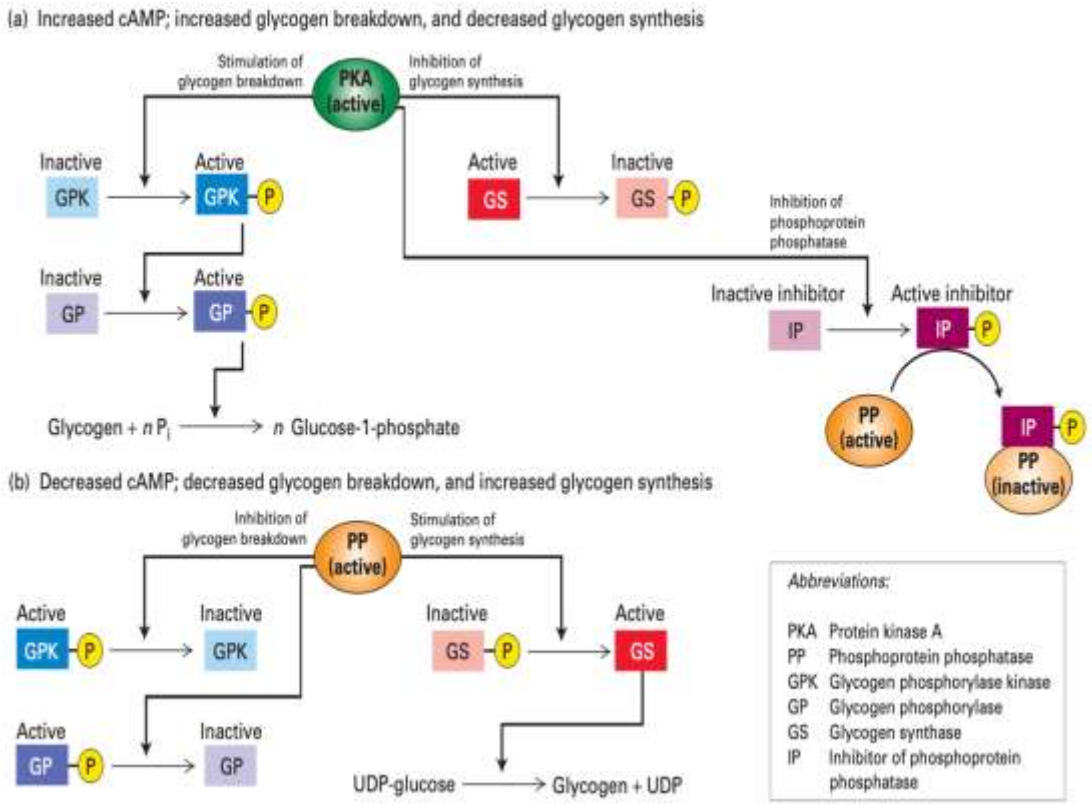


Fig: Regulation of glycogen metabolism by cAMP and PKA

II. Inhibition of cAMP:

i. cAMP decomposition into AMP is catalyzed by the enzyme phosphodiesterase
ii. They work by hydrolyzing the cyclic 3',5'-phosphodiester bond in cAMP and cGMP; thereby terminating the action.

III. Role of cAMP in lac operon:

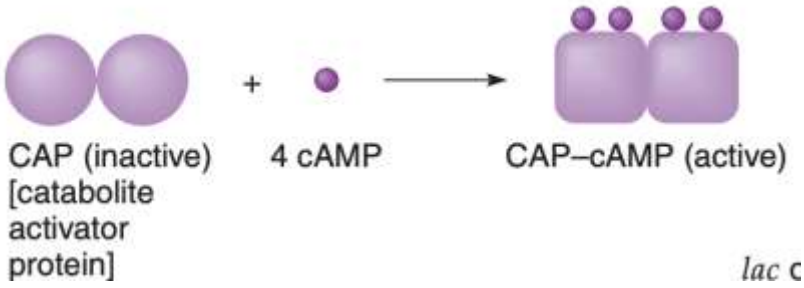
a. Positive regulation of lac operon-

i. When lactose is present, but glucose is absent.
ii. A protein called Catabolite Activator Protein (CAP) binds with cAMP to form a CAP-cAMP complex.
iii. The CAP protein is a dimer of two identical polypeptides
iv. Next, the CAP-cAMP complex binds to the CAP site which is upstream of the site where RNA Polymerase binds to the promoter.
v. CAP then recruits RNA polymerase to the promoter and then transcription is initiated.

b. Negative regulation of lac operon-

i. When glucose is present along with lactose, glucose is preferentially used because catabolite repression (also called as the glucose effect) occurs.

ii. In catabolite expression, lac operon is expressed only at very low levels of lactose present in the medium.
iii. This is because, glucose causes the amount of cAMP in the cell to be reduced greatly.
iv. Thus, insufficient CAP-cAMP complex is available to recruit RNA Polymerase to the lac promoter, and thus transcription of lac operon takes place at a very low level.
v. Thus, RNA Polymerase cannot bind to the promoter efficiently without the aid of CAP-cAMP complex.
vi. Thus, cAMP plays a crucial role in catabolite repression.



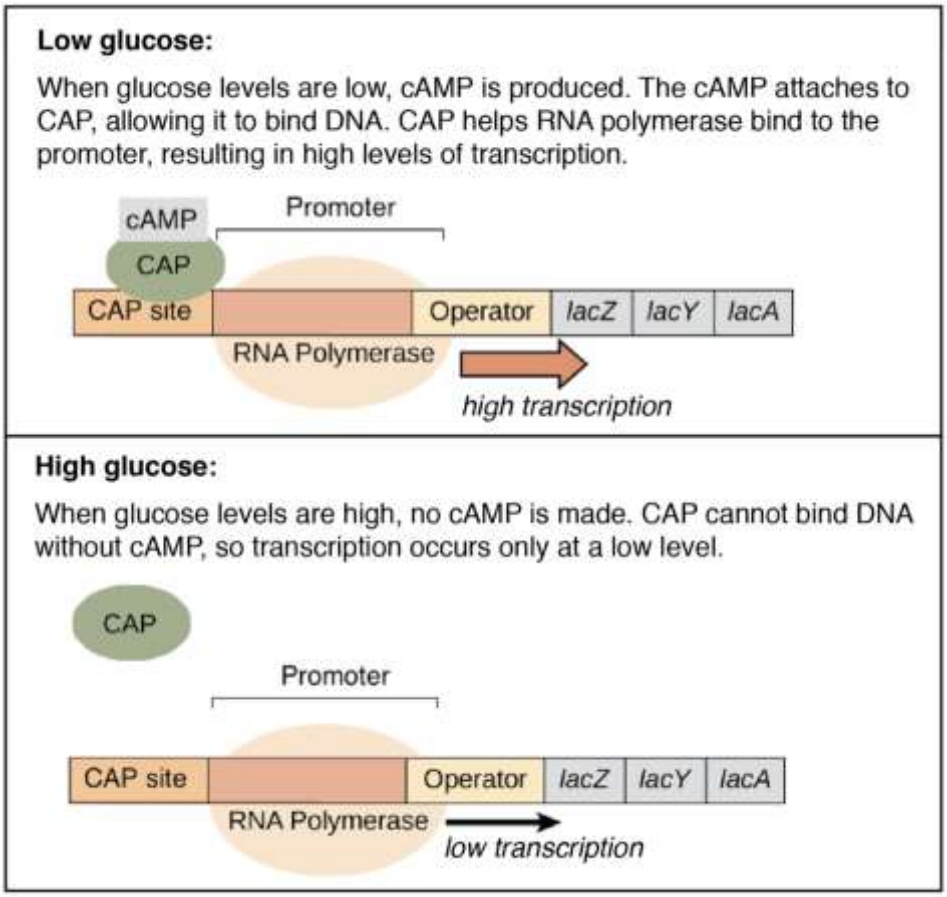


Fig: Positive and negative regulation of lac operon

Functions of cAMP in biological system:

Table : *Cellular Responses to hormone-induced Rise in cAMP in Various Tissues*

Tissue	**Hormone inducing Rise in cAMP**	**Cellular Response**
Adipose	Epinephrine; ACTH; glucagon	Increase in hydrolysis of triglyceride; decrease in amino acid uptake
Liver	Epinephrine; norepinephrine; glucagon	Increase in conversion of glycogen to glucose, inhibition of glycogen synthesis; increase in amino acid uptake; increase in gluconeogenesis (synthesis of glucose from amino acids)
Ovarian follicle	FSH; LHL	Increase in synthesis of estrogen, progesterone
Adrenal cortex	ACTH	Increase in synthesis of aldosterone, cortisol
Cardiac muscle	Epinephrine	Increase in contraction rate
Thyroid gland	TSH	Secretion of thyroxine
Bone	Parathyroid hormone	Increase in resorption of calcium from bone
Skeletal muscle	Epinephrine	Conversion of glycogen to glucose-1-phosphate
Intestine	Epinephrine	Fluid secretion
Kidney	Vasopressin	Resorption of water
Blood platelets	Prostaglandin I	Inhibition of aggregation and secretion

Source: Lodish Molecular Cell Biology (8th edition)

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