

- cyclic adenosine monophosphate (cAMP)
- diacylglycerol (DAG)
- inositol triphosphate (IP₃)
- eicosanoids

Cyclic adenosine monophosphate (cAMP) is formed when an activated G-protein activates the membrane-bound enzyme *adenylyl cyclase*, which converts ATP to cAMP (Fig. 3.9). cAMP is released to the cytosol and usually functions by:

- activating a cAMP-dependent protein kinase, protein kinase A
- activating the protein Epac («exchange protein directly activated by cAMP»), which, in turn, activates other signal molecules in the cell
- binding to ion channels and altering their activity

The activity of adenylyl cyclase can be affected by numerous membrane receptors coupled to either stimulatory or inhibitory G-proteins (Fig. 3.10). A hormonally regulated intracellular enzyme, a specific *phosphodiesterase*, converts cAMP to inactive AMP.

Protein kinase A consists of two regulatory and two catalytic subunits. cAMP is bound to the regulatory subunits (Fig. 3.9). The binding leads to release of the catalytic subunits, which then catalyze phosphorylation of different key proteins in the target cell. Phosphorylation alters the function of these cellular proteins and is responsible for the biological response of the target cell.

cAMP can also alter the expression of certain genes (Fig. 3.11). The target genes have a *cAMP-response element* (CRE), which can bind a transcription factor called *CRE-binding protein*

(CREB). The free catalytic subunit of protein kinase A may enter the nucleus through pores in the nuclear envelope and phosphorylate CREB. Together with other transcription factors, phosphorylated CREB binds to CRE and stimulates or inhibits RNA polymerase and transcription of the target gene. Thus, cAMP also participates in regulation of the synthesis of cellular proteins.

Epac, which is activated by cAMP, in turn activates a particular type of monomeric G-protein. There are many different monomeric signaling proteins in the cells that can bind GTP or GDP. The functions of these monomeric G-proteins differ from the functions of the heterotrimeric G-proteins. In their inactive form, the monomeric G-proteins have bound GDP, and are activated when GDP is replaced by GTP. The monomeric G-proteins that are activated by Epac are related to the Ras-proteins, which are described on p. 95. The activated monomeric G-proteins affect various cellular processes. The same processes are often affected by both protein kinase A and Epac, and their effects may be either opposing or synergistic.

Diacylglycerol (DAG) is formed when the enzyme *phospholipase C* in the cell membrane cleaves a phospholipid called phosphatidylinositol-bisphosphate (PIP₂). Phospholipase C is

Synthesis of cAMP is catalyzed by adenylyl cyclase

Phosphodiesterase converts cAMP to inactive AMP

cAMP activates protein kinase A

cAMP can affect gene transcription

cAMP activates Epac

Phospholipase C catalyzes the cleavage of PIP₂ to DAG and IP₃

Figure 3.9 Formation of cyclic adenosine monophosphate (cAMP) and activation of protein kinase A. The binding of certain signal molecules to their receptors activates the enzyme adenylyl cyclase (1). This stimulates formation of the second messenger cAMP (2), which activates the enzyme protein kinase A (3). This enzyme is composed of regulatory and catalytic subunits. When protein kinase A is activated, the catalytic subunits dissociate from the regulatory subunits (4) and catalyze the transfer of phosphate groups from ATP to proteins in the cell (5). The protein phosphorylation evokes a biological response in the cell (6).

