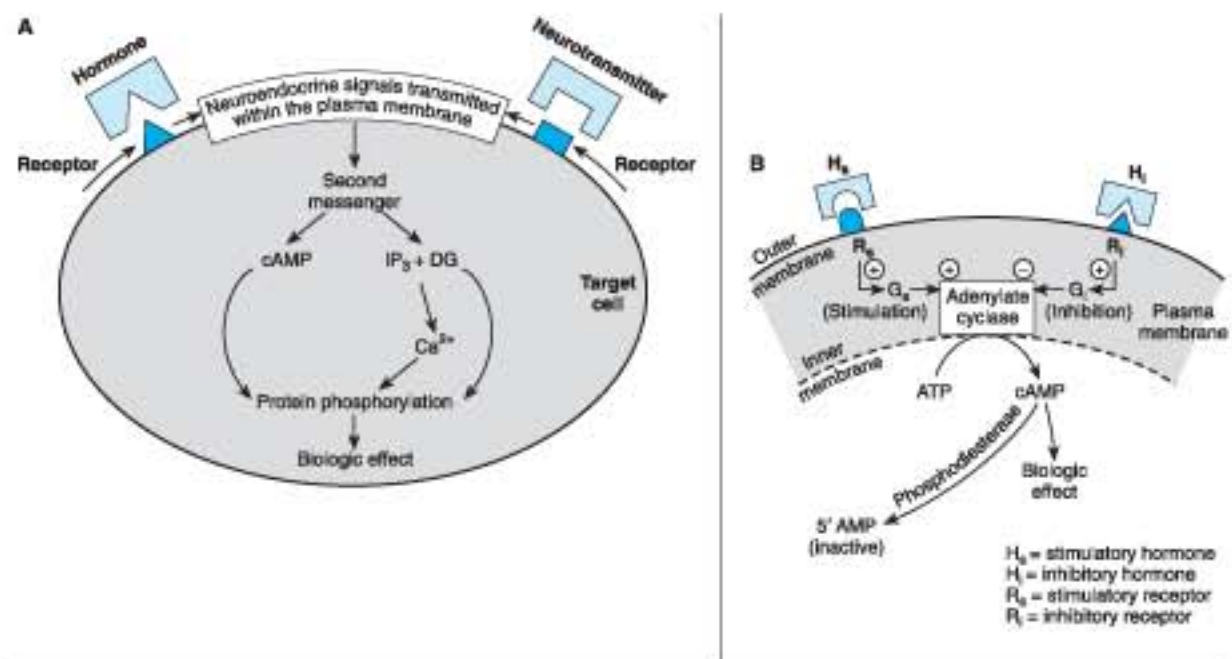


## Mechanisms of Catecholamine and Polypeptide Hormone Action: I (Receptors, Second Messengers, and Cyclic-AMP)



### C

#### Hormones Capable of Stimulating Adenylyl Cyclase

Secretin  
Calcitonin (CT)  
β-Adrenergic catecholamines (NE and Epi equally capable)  
Glucagon  
Follicle-stimulating hormone (FSH)  
Chorionic gonadotropin (CG)  
Luteinizing hormone (LH)  
Melanocyte-stimulating hormone (MSH)  
Parathormone (PTH)  
Thyroid-stimulating hormone (TSH)  
TSH-releasing hormone (TRH)  
Antidiuretic hormone (ADH)  
Adrenocorticotropic hormone (ACTH)

#### Hormones Incapable of Stimulating Adenylyl Cyclase

Angiotensin II  
α-Adrenergic catecholamines (NE more capable than Epi)  
Placental lactogen (PL)  
Growth hormone (GH)  
Insulin  
Oxytocin  
Prolactin (PRL)  
Somatomedins (e.g., IGF-1)  
Somatostatin (SS, GHI)  
Gastrin  
Cholecystokinin (CCK)

### D Biologic Effects of cAMP

Process (and Hormones)	Target Cells
Membrane permeability, ions (PTH, CT)	Kidney tubules, intestine, bone
Membrane permeability, water (ADH)	Kidney (collecting ducts)
Steroid hormone synthesis (ACTH, LH, FSH)	Adrenal cortex, testes, ovaries
Secretory responses (Secretin, TRH, TSH)	Pancreas, pituitary, thyroid
Lipolysis (NE, Epi)	Adipocytes
Glycogenolysis (NE, Epi, Glucagon)	Muscle, liver
Gluconeogenesis (NE, Epi, Glucagon)	Liver, kidney
Vasodilation (Epi)	Arterioles (β-receptors)

### Overview

- Only cells with appropriate receptors can respond to the presence of a hormone.
- Receptors for catecholamine and polypeptide hormones are found on the target cell surface.
- The number of receptors on a target cell can range from about 2000 to 100,000, depending on the physiologic conditions.
- The affinity of a hormone for its receptor also changes.
- The cAMP second messenger system is linked to G proteins attached to the cell membrane.
- Phosphodiesterase inactivates cAMP.

Target cells have **hormone-specific receptors** capable of recognizing and binding hormones; therefore, only those cells respond to the presence of hormones. This binding, in turn, initiates intracellular events leading to the final physiologic effect. Generally, receptors are hormone specific, but to a limited extent other hormones or drugs with similar structure may bind to them.

### Receptors

**Hormone receptors** occur in different cell locations, depending on the class of hormone they bind. Receptors for catecholamine and polypeptide hormones are found on the surface of target cells, while those for steroid and thyroid hormones are found in the cytoplasm and/or nucleus. The number of receptors per target cell ranges from about 2000 to 100,000, varying under different physiologic conditions.

For a protein to be a receptor for a hormone, it must exhibit certain properties. Because of the small number of hormone molecules usually present, a receptor must have a **high affinity** for the hormone; that is, a strong tendency to bind with the hormone. Second, the receptor should have **high specificity** for the hormone, and little tendency to bind other molecules. A third feature of receptors is their **low capacity**. This means that all available receptor sites are occupied at relatively low hormone concentrations; that is, the receptor is said to be **saturated**. Finally, the **distribution** of a putative receptor should correspond to known target cells for the hormone, and should be correlated with a specific physiologic effect.

The affinity of a hormone for its receptor and the number of receptors are not static. Receptor concentration is affected by genetics, the stage of growth, the stage of the target cell's cycle, and the degree of its differentiation. Receptor concentration and affinity for its hormone are affected by ionic balance and temperature, by concentration of the homologous hormone and heterologous hormones, and by antibodies against the receptor.

The **number of functional receptors** is modulated up (**up regulation**) or down (**down regulation**), permitting the cell to respond optimally to small changes in hormone concentration. Prolonged hormone exposure usually results in reduced functional cell-surface receptor molecules, thus desensitizing the cell to high hormone levels. This reduction is known to occur in at least 4 ways. **Receptors can** (1) be destroyed after endocytosis, (2) be internalized by endocytosis and remain stored in intracellular vesicles, (3) remain on the cell surface but change so they cannot bind the hormone, or (4) bind the hormone but form a receptor-hormone complex that does not induce a normal response. Conversely, in developmental conditions, the first contact of a hormone with its target cell may result in receptor **up-regulation**, with accelerated binding and actions of the hormone on its target cell.

### Second Messengers

The **two primary intracellular second messenger systems** that respond to the presence of nervous stimulation or catecholamine/polypeptide hormone binding on the cell surface are

the **cyclic adenosine monophosphate (cAMP)** and **calcium/diacylglycerol messenger systems (Part A)**. These two systems are not totally unrelated.

### The cAMP Messenger System

Hormones or neurotransmitters that affect cell metabolism via **cAMP** are bound on the cell surface to receptors specific for those substances. This binding results in either activation or inhibition of the enzyme **adenylyl cyclase** (or adenylyl cyclase), which is responsible for the formation of **cAMP** from **adenosine triphosphate (ATP)** (**Part B**). Transfer of the signal from the occupied receptor on the membrane's outer face to adenylyl cyclase, located on the cytoplasmic side of the membrane, occurs via guanosine triphosphate-binding proteins [**G<sub>s</sub> (stimulatory)** or **G<sub>i</sub> (inhibitory) proteins**]. Some hormones that activate adenylyl cyclase (**Part C**) have a sequence of five amino acids in common, with which they bind to gangliosides on the plasma membrane. This same amino acid sequence is found on the structures of the plant toxins abrin and ricin, and on cholera and diphtheria toxins, all of which have gangliosides as their membrane receptors. Peptide hormones that do not activate **cAMP** may activate other enzymes, such as **guanylate cyclase**, or regulate the intracellular concentration of **Ca<sup>2+</sup>**.

**Cyclic AMP** is often referred to as the second messenger, with the hormone stimulating its production being the first. It stimulates activation of **cAMP-dependent protein kinase**, (i.e., **protein kinase A (PKA)**), which facilitates phosphorylation of some protein products of the target cell. **Phosphodiesterase**, which inactivates **cAMP** to **5' AMP**, can be stimulated by **insulin** (in adipocytes and liver cells). Examples of some biologic effects of **cAMP** are listed in **Part D**.

**Protein kinase A** is the enzyme activated intracellularly by **cAMP**. This enzyme, in turn, is capable of activating a number of other intracellular enzymes by phosphorylating their kinases (see **Part A**), thus leading to a biologic effect specific for the cell type involved. Alternatively, **cAMP**-stimulated phosphorylation can deactivate other enzymes. Thus, after a hormone binds to its receptor, (e.g., epinephrine binding to β-adrenergic receptors), the **cAMP** messenger system generates a cascade of effects that ultimately alters the flux of metabolites within the cell. Activation or inactivation of reciprocal pathways within a responsive cell can inhibit metabolite release on the one hand, while stimulating storage on the other.

**Cyclic-AMP** can also act as a hormone second messenger by altering gene expression. Target DNA molecules are known to possess a **cAMP regulatory element (CRE)** that binds a protein transcription factor known as **cAMP response element binding protein (CREB)**. Cyclic-AMP activates protein kinase A; the catalytic subunit of the enzyme is then free to be translocated into the nucleus where it phosphorylates CREB. Phosphorylated CREB now becomes capable of complexing with CRE and another transcription protein, such as activated transcription factor-1. The final result of this rather complex series of reactions is the stimulation or inhibition of RNA polymerase and **transcription** of the target gene, and hence stimulation or inhibition of synthesis of a specific protein.

The actions of **cAMP** are terminated when it is hydrolyzed by **phosphodiesterase**, as discussed above. Because the activity of phosphodiesterase is also modulated by hormones via a G protein, **cAMP** levels inside cells are under dual regulation. Two hormones can function antagonistically if one stimulates adenylyl cyclase and the other stimulates phosphodiesterase (e.g., glucagon and insulin, respectively).

### cAMP in Primitive Forms of Life

Some functions of **cAMP** in primitive forms of life have been studied intensively. For example, in the slime mold, which is an aggregation of cells that were once dispersed as individual amoebae, **cAMP** appears to be the primary aggregating stimulus, and is secreted into the medium when nutrients are in short supply. Similarly, in glucose-deprived *E. coli*, the same substance causes derepression of the lac operon, which enables the organism to metabolize galactose.