

Second messengers and neuronal functions

Second messengers and signaling molecules

Second messengers

cyclic nucleotides (cAMP, cGMP)
diacylglycerol
IP3 (inositol 1,4,5 triphosphate)
Ca²⁺ and calmodulin
nitric oxide (NO)
arachidonic acid and eicosanoids

Protein kinases and phosphatases

Kinase: catalyze phosphorylation

Phosphatase: catalyze dephosphorylation

cAMP dependent-protein kinase (PKA)
cGMP dependent protein kinase (PKG)
Ca²⁺-calmodulin dependent-protein kinase II (CaMK II)
Protein kinase C (PKC)
Tyrosine kinases and phosphatases

cAMP and cGMP

* cAMP-more general action * cGMP- action restricted
phototransduction in vertebrate retina
smooth muscle tension (through NO)

* Metabolism: ATP $\xrightarrow{1}$ cAMP $\xrightarrow{2}$ 5' AMP
adenylate cyclase phosphodiesterase
(GTP \rightarrow cGMP \rightarrow 5' GMP)

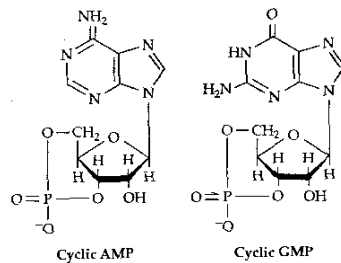


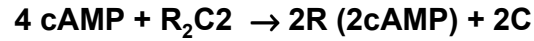
Fig. 2, Chap. 7
page 209

FIGURE 2. Structures of the second messengers cAMP and cGMP.

Two major roles for cAMP

1. Activation of PKA (common in most cell types)

PKA: 2 regulatory (R) subunits and 2 catalytic (C) subunits



Target protein phosphorylation

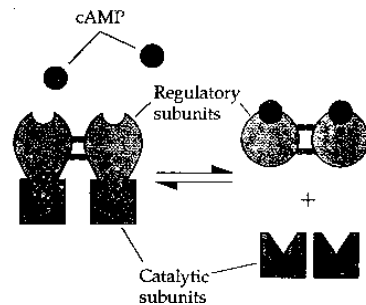
Hall pp. 210

2. Regulation of target protein by direct binding ex. cAMP-gated ion channel

Two major roles for cAMP

1. Activation of PKA (common)

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Hall pp. 210

2. Regulation by direct binding ex. cAMP-gated ion channel

Short and Long-lasting effect by PKA

Target protein phosphorylation in the cytosol
example: ion channel phosphorylation

Effect lasting seconds to minutes

Phosphorylation of transcription factors in the nucleus
nuclear translocation of catalytic subunit
protein synthesis

Effect lasting days or weeks

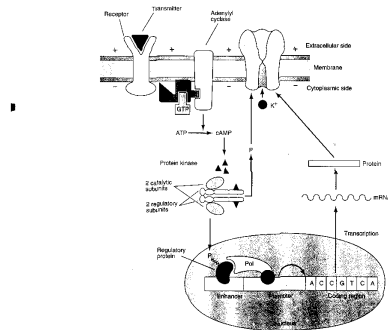


FIGURE 12-15
 A single chemical transmitter can produce synaptic actions with different time courses. In this example a single exposure to the transmitter activates the cAMP second messenger system, which in turn activates the cAMP-dependent protein kinase that phosphorylates a K⁺ channel to produce a synaptic potential that modulates neuronal excitability for minutes. With repeated activation, the transmitter, acting through the cAMP-dependent protein kinase, also phosphorylates one or more transcriptional activator proteins that regulate gene expression. This produces a protein that modifies the channel and results in more enduring closure of the channel and changes in neuronal excitability lasting days or weeks.

Regulation of Protein Kinases (PK)

in the absence of second messenger: inactive
second messenger binding to PK:

A common mechanism used for inactive state

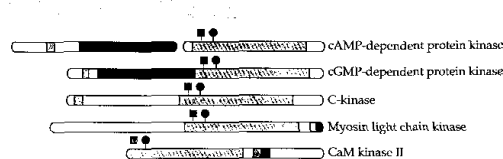
Autoinhibitory domain

Amino acid sequence of the domain:

very similar to the their phosphorylation sequence

but critical A.A. (Ser or Thr) are substituted with another A.A.

Pseudosubstrate domain= Autoinhibitory domain



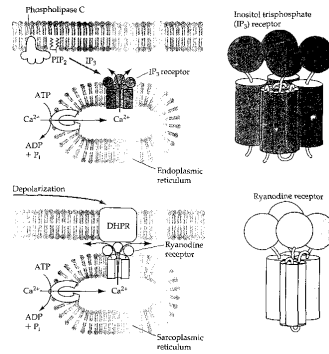
- Catalytic domain
- Pseudosubstrate or autophosphorylation domain
- Regulatory-binding domain
- Gly-X-X-Gly-X-X-Gly nucleotide-binding motif
- ATP-binding lysine residue

FIGURE 11-11 Pseudosubstrate domains and internal autophosphorylation sites within protein kinases. In the absence of activating second-messenger messengers that bind to the regulatory domains, these domains interact with the active site to inhibit kinase activity. (After G. Hardie, 1988, *Nature* 335: 592-597.)

IP3 receptor in ER and Ryanodine receptor in SR

Signal dependent intracellular Ca²⁺ release

Fig 11, p.226



Ca²⁺ signal and homeostatis Fig. 10, p.224

