Chapter 5
Control of Cells by Chemical Messengers
= How hormones and other signals work

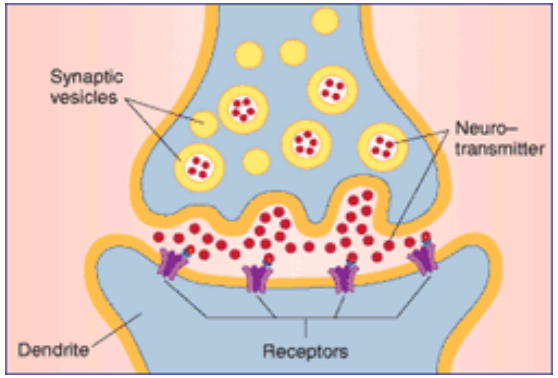
Intercellular Communication

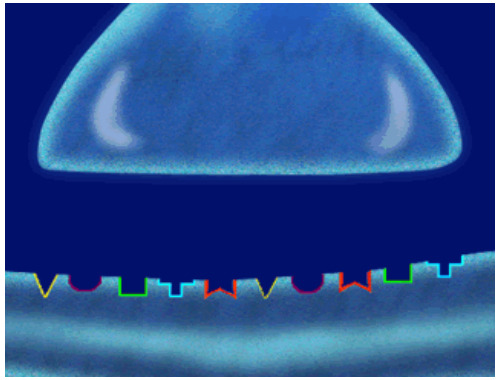
= Intercellular Signal Transmission

- Chemical communication
- Electrical communication

Intercellular signal transmission

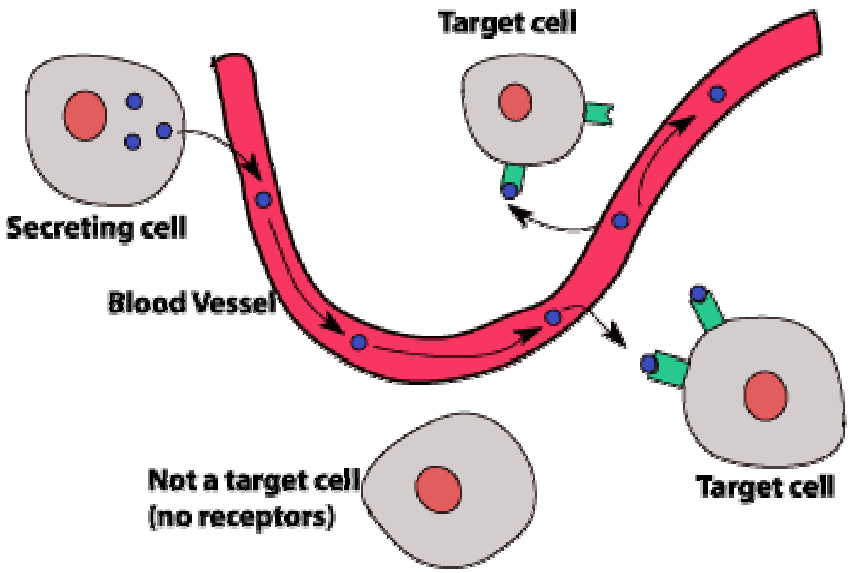
- Chemical transmission
  - Chemical signals
    - Neurotransmitters:





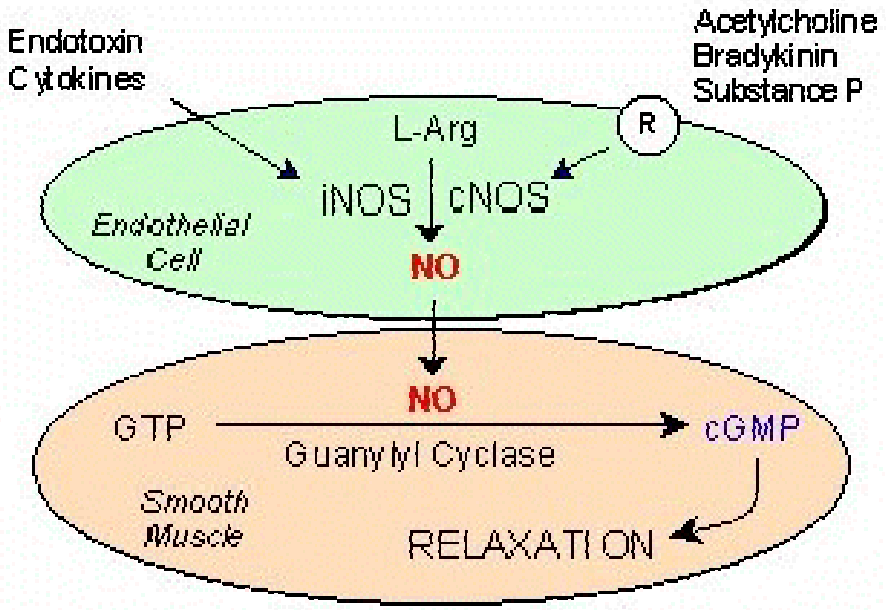
Intercellular signal transmission

- Chemical transmission
  - Chemical signals
    - Neurotransmitters:
    - Humoral factors:
      - Hormones
      - Cytokines
      - Bioactivators



Intercellular signal transmission

- Chemical transmission
  - Chemical signals
    - Neurotransmitters:
    - Humoral factors:
    - Gas: NO, CO, et



Communication requires:

signals (ligands) and receptors (binding proteins).

The chemical properties of a ligand predict its binding site:

- **Hydrophobic/lipid-soluble: cytosolic or nuclear receptors**

  examples: steroid hormones, thyroid hormones…

- **Hydrophilic/lipid-insoluble: membrane-spanning receptors**

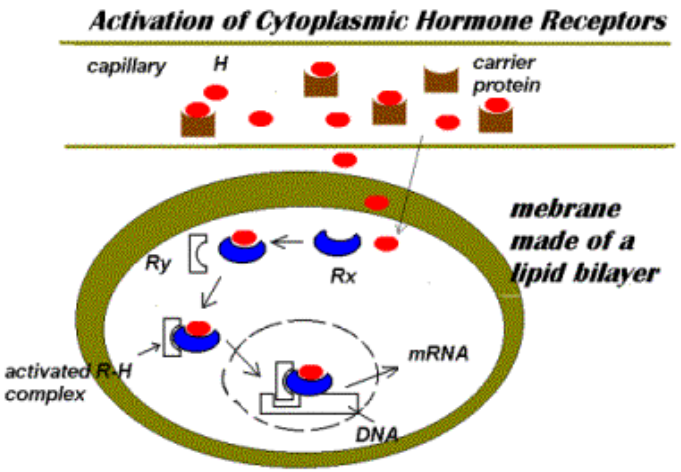
  examples: epinephrine, insulin…

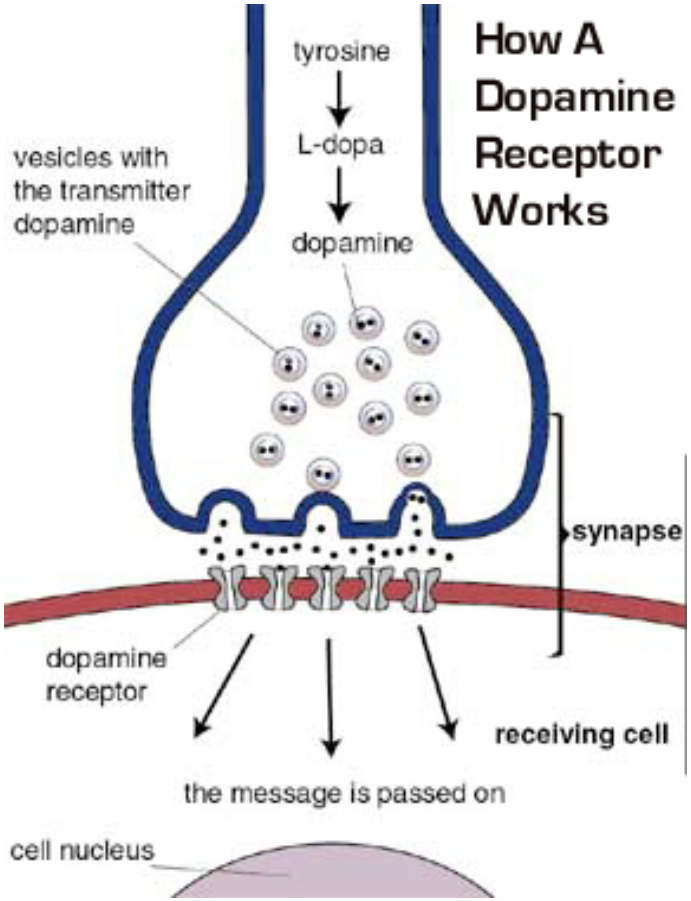
Receptors are proteins that can bind only specific ligands and they are linked to response systems.

- **Hydrophobic signals typically change gene expression, leading to slow but sustained responses.**
- **Hydrophilic signals typically activate rapid, short-lived responses that can be of drastic impact.**

Intercellular signal transmission

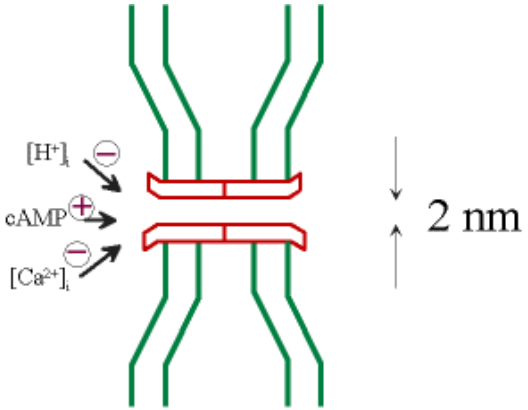
- Chemical transmission
  - Chemical signals
  - Receptors
    - Membrane receptors
    - Intracellular receptors





Intercellular signal transmission

- Electrical transmission
  Gap junction



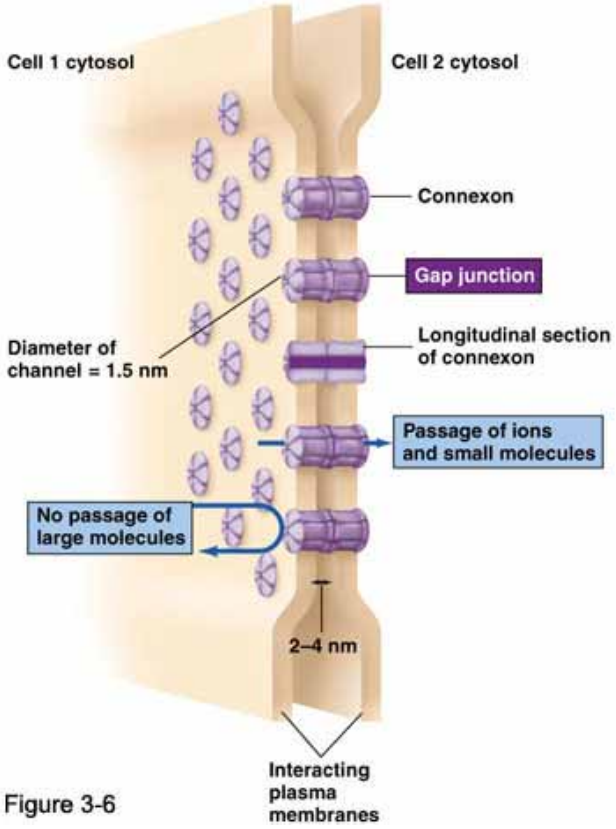
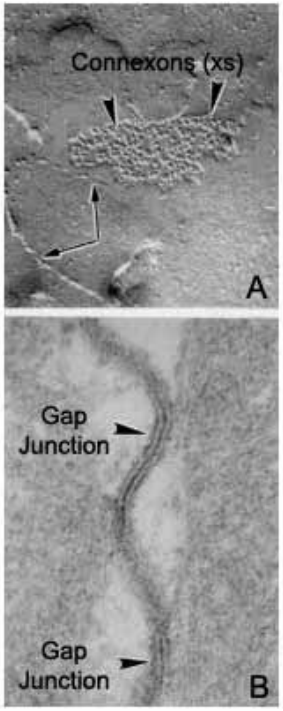
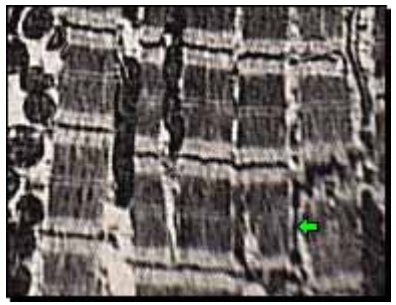


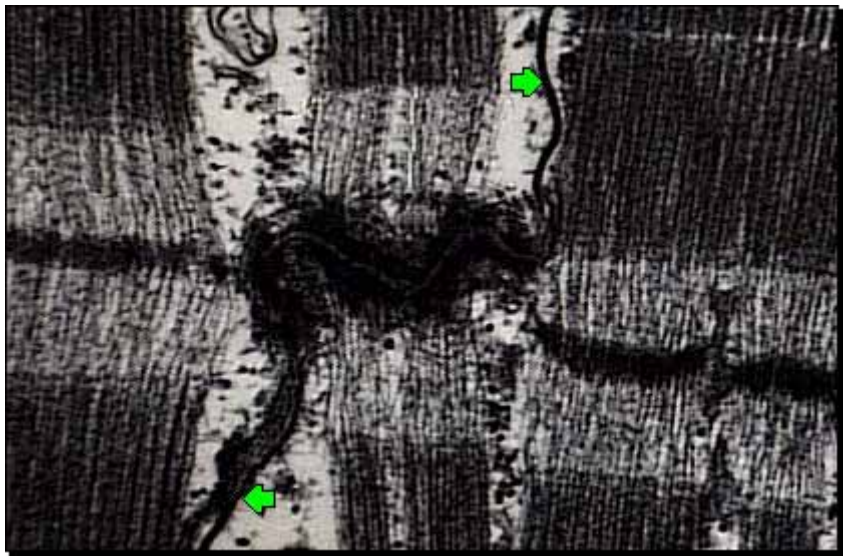
Figure 3-6



Cardiac Muscle



Low Magnification View



The intercalated disk is made of several types of intercellular junctions. The gap junction provides a low resistance pathway for the action potential to spread from cell to cell.

Receptors on the surface of a cell are typically proteins that span the membrane.

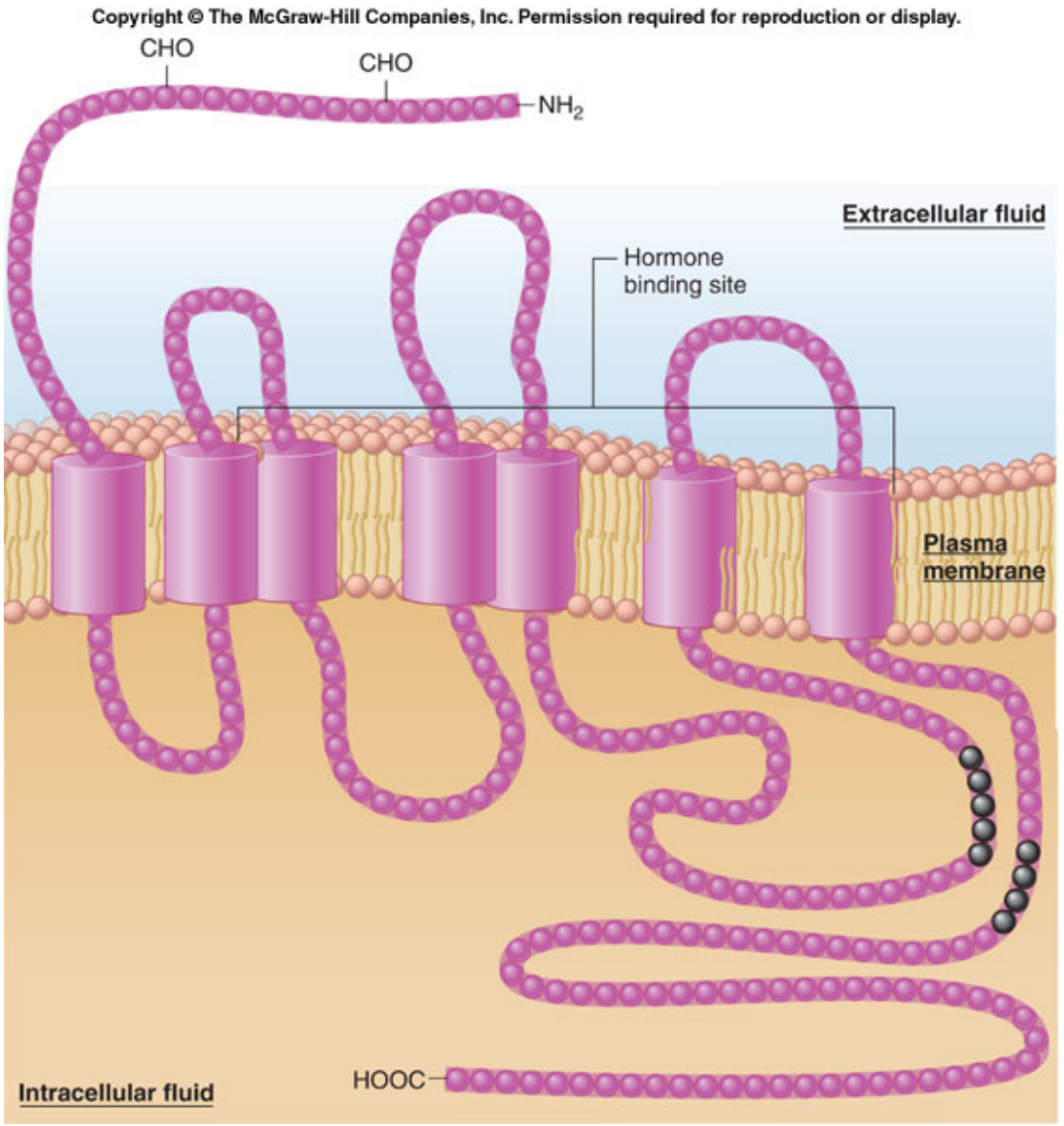


Figure 5-1

TABLE 5–1 A Glossary of Terms Concerning Receptors

Receptor	A specific protein in either the plasma membrane or the interior of a target cell with which a chemical messenger combines, and which then invokes a biologically relevant response in that cell.
Specificity	The ability of a receptor to bind only one type or a limited number of structurally related types of chemical messengers.
Saturation	The degree to which receptors are occupied by a messenger. If all are occupied, the receptors are fully saturated; if half are occupied, the saturation is 50 percent, and so on.
Affinity	The strength with which a chemical messenger binds to its receptor.
Competition	The ability of different molecules very similar in structure to combine with the same receptor.
Antagonist	A molecule that competes for a receptor with a chemical messenger normally present in the body. The antagonist binds to the receptor but does not trigger the cell's response.
Agonist	A chemical messenger that binds to a receptor and triggers the cell's response; often refers to a drug that mimics a normal messenger's action.
Down-regulation	A decrease in the total number of target-cell receptors for a given messenger in response to chronic high extracellular concentration of the messenger.
Up-regulation	An increase in the total number of target-cell receptors for a given messenger in response to a chronic low extracellular concentration of the messenger.
Supersensitivity	The increased responsiveness of a target cell to a given messenger, resulting from up-regulation.

Only Cell A has the matching receptors for this chemical messenger, so it is the only one that responds.

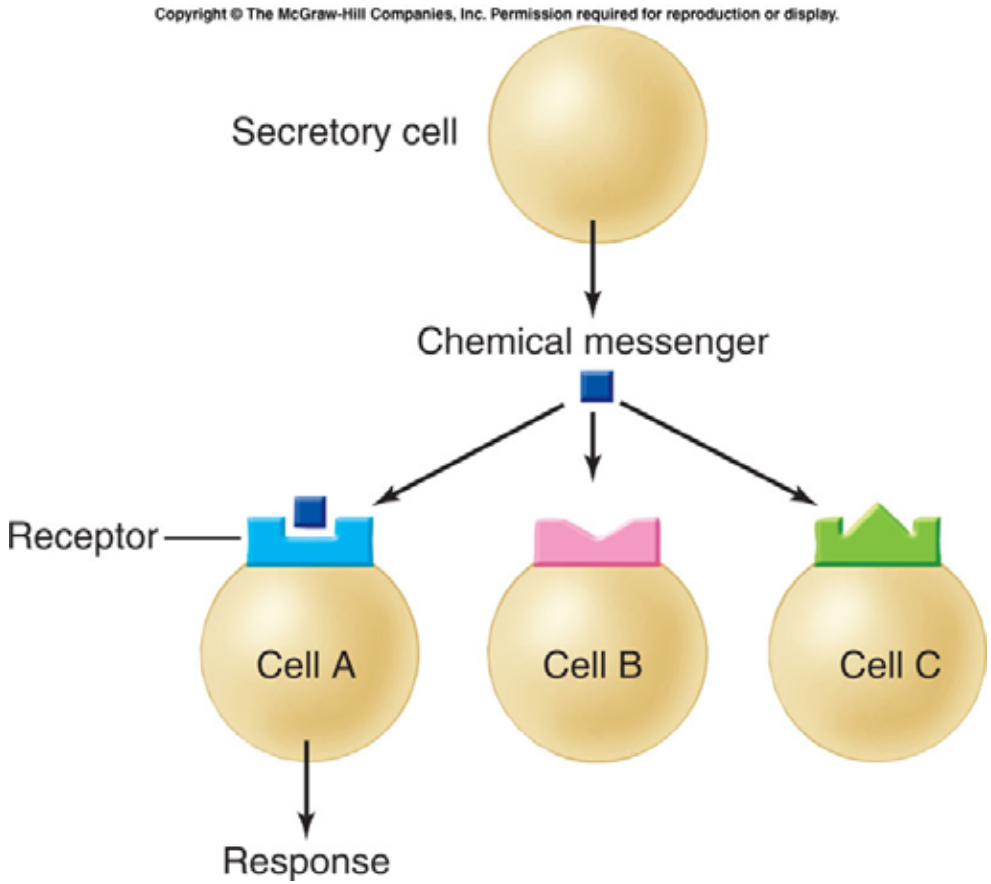


Figure 5-2

Cells B & C lack the matching receptors Therefore are not directly affected by the signal.

Signal transduction pathway

- Pathways initiated by intracellular receptors
- Pathways initiated by plasma membrane receptors

This hydrophobic signal requires a carrier protein while in the plasma …

… but at the target cell the signal moves easily through the membrane and binds to its receptor.

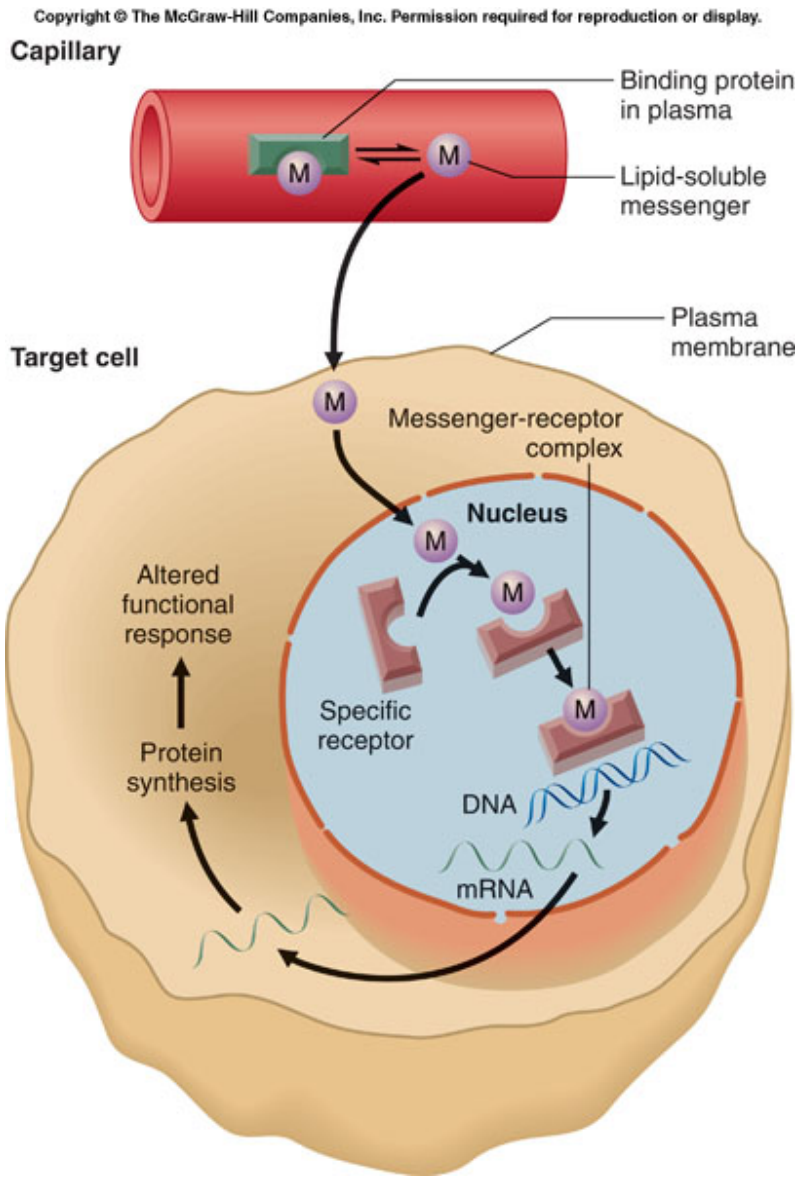


Figure 5-4

Signal transduction pathway

- Pathways initiated by intracellular receptors
- Pathways initiated by plasma membrane receptors
  - Receptors that function as ion channel
  - Receptors that function as enzymes
  - Receptors that interact with cytoplasmic JAK kinase
  - Receptors that interact with G proteins

Figure 5-5

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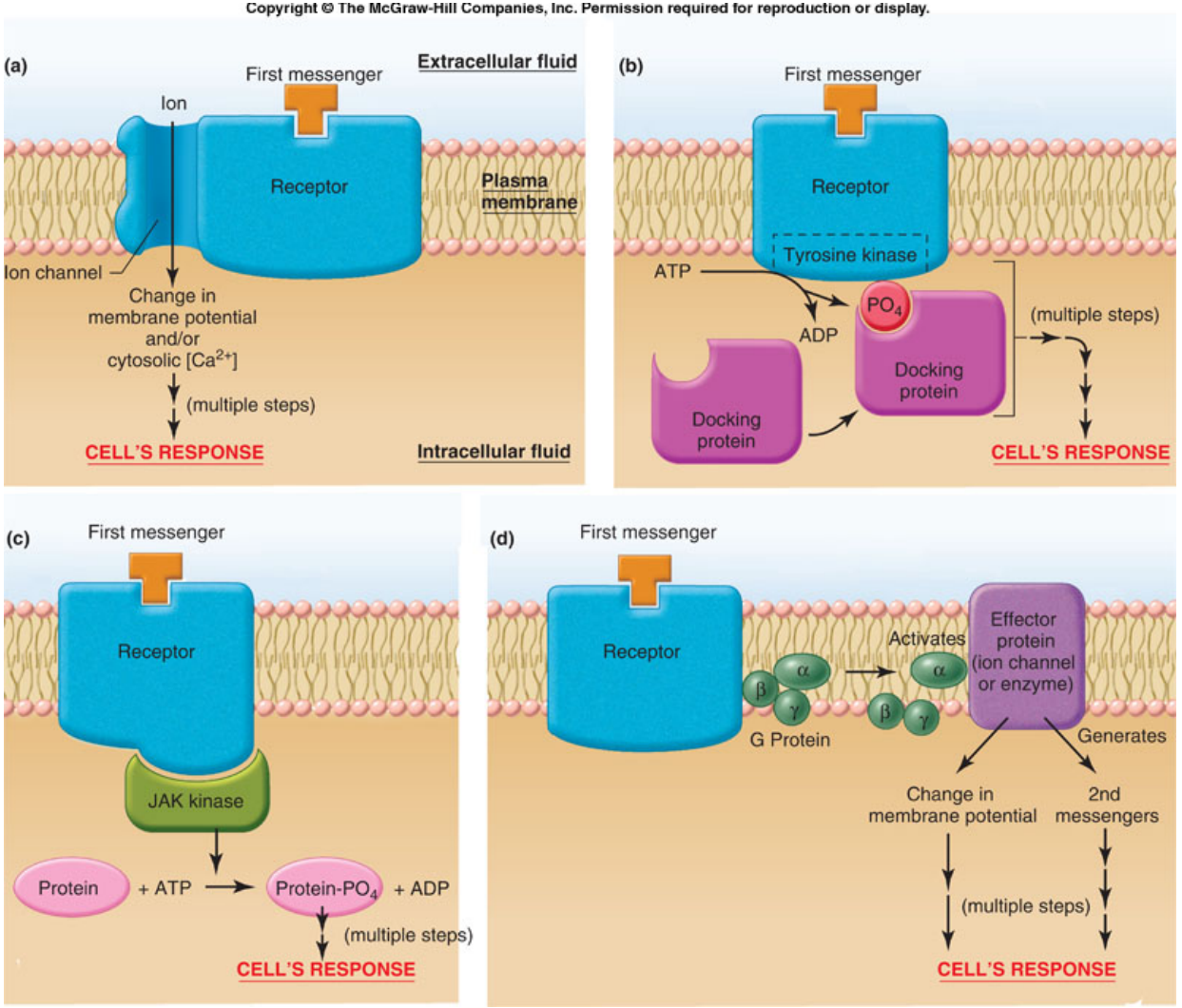

Binding of ligands to membrane-spanning receptors activates diverse response mechanisms.

Figure 5-5a

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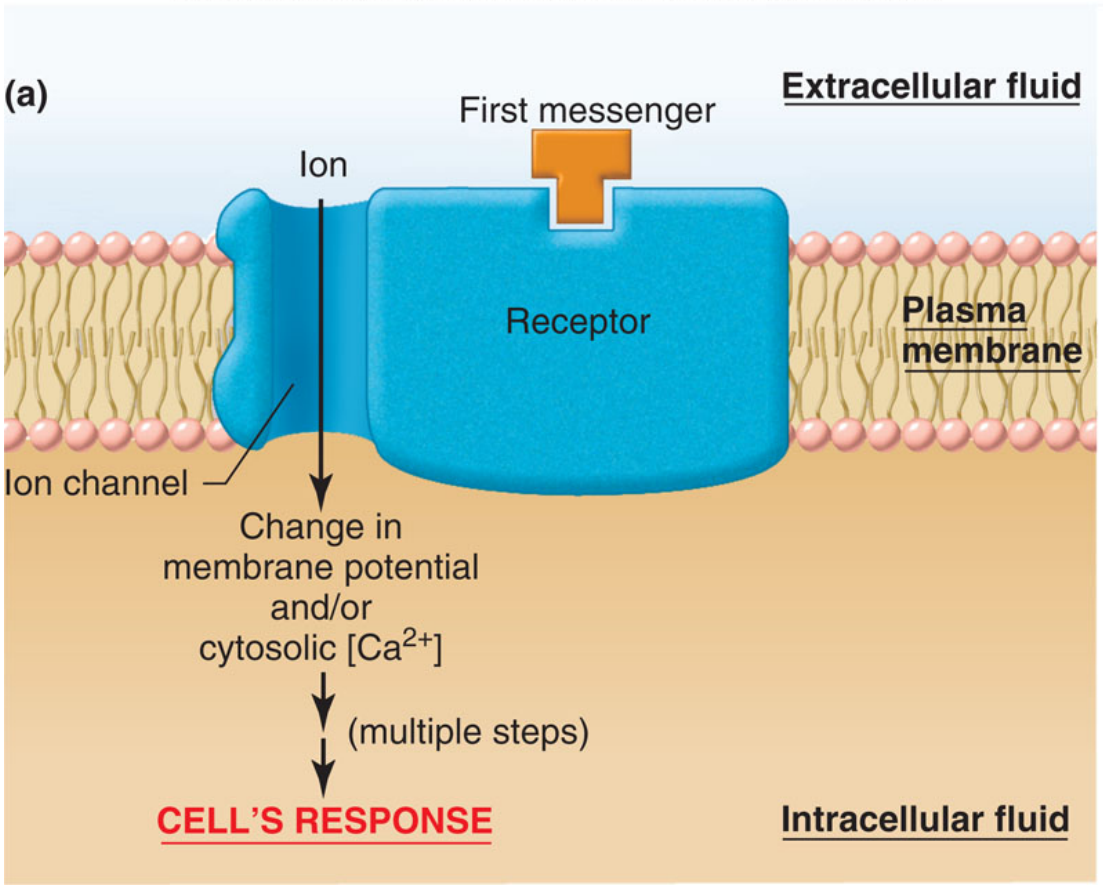

Binding of the ligand to the receptor alters the receptor's shape, which then opens (or closes) an ion channel.

Figure 5-5b

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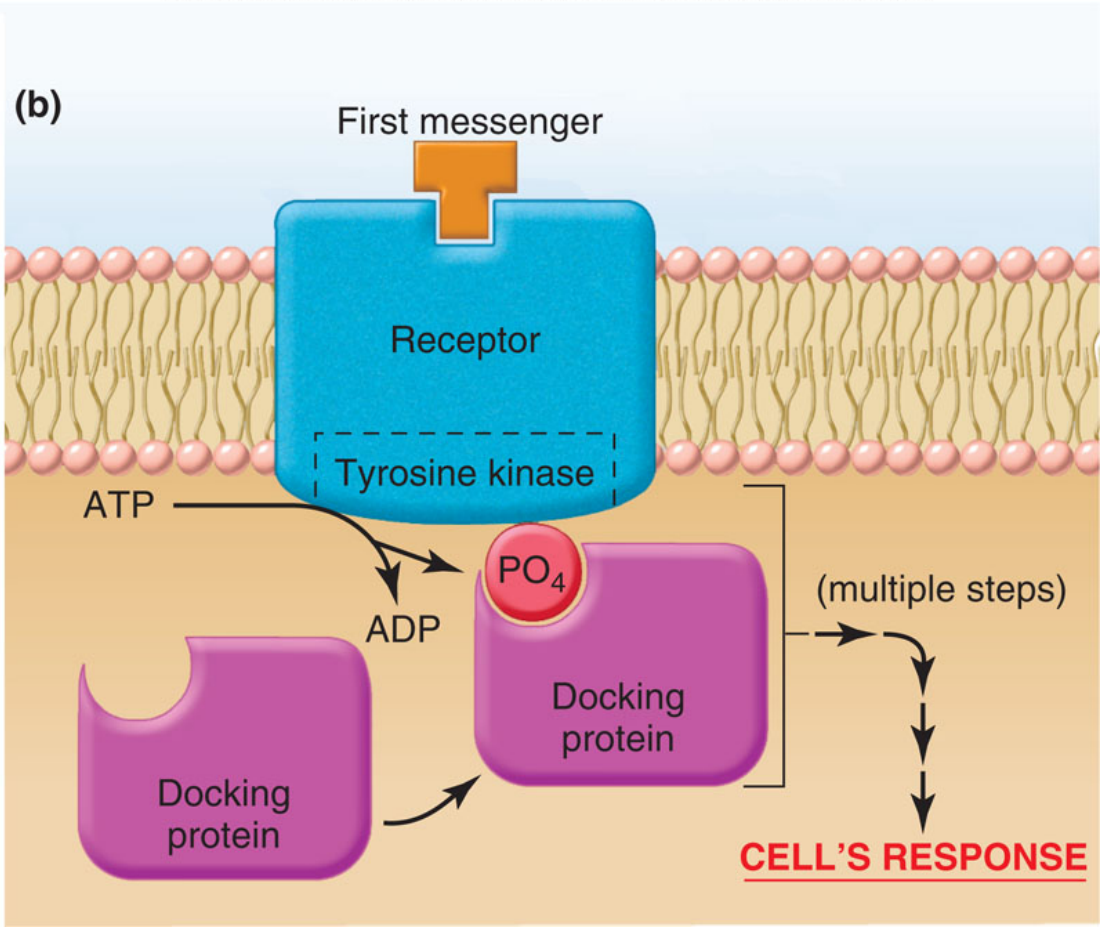

Binding of the ligand to the receptor alters the receptor's shape, which activates its enzyme function, phosphorylating an intracellular protein.

Figure 5-5c

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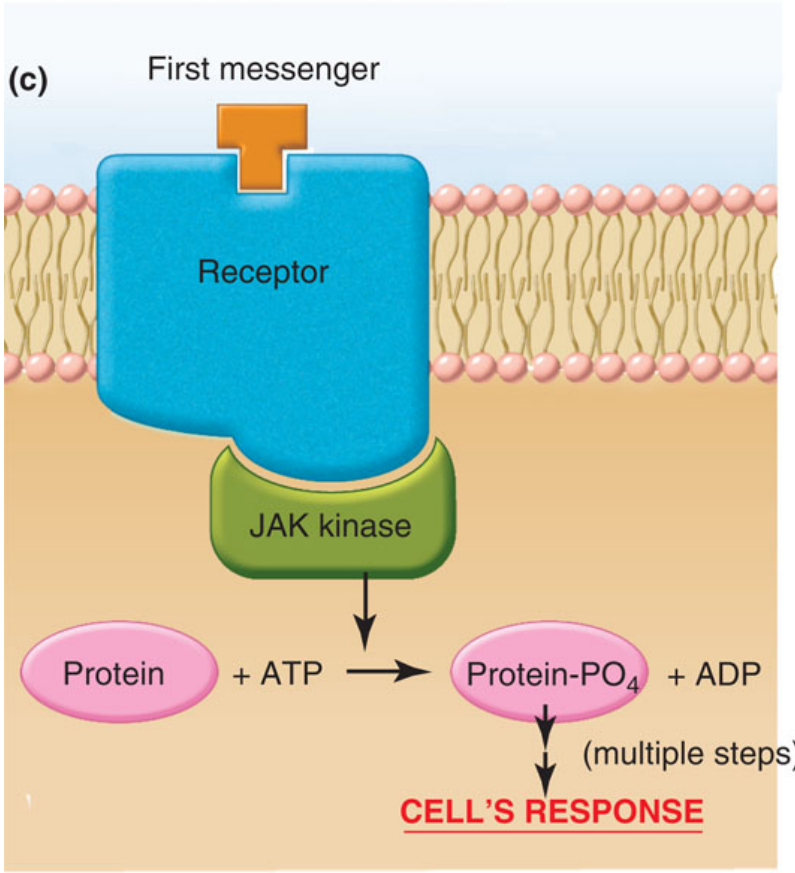

Binding of the ligand to the receptor alters the receptor's shape, which activates an associated enzyme function, phosphorylating an intracellular protein.

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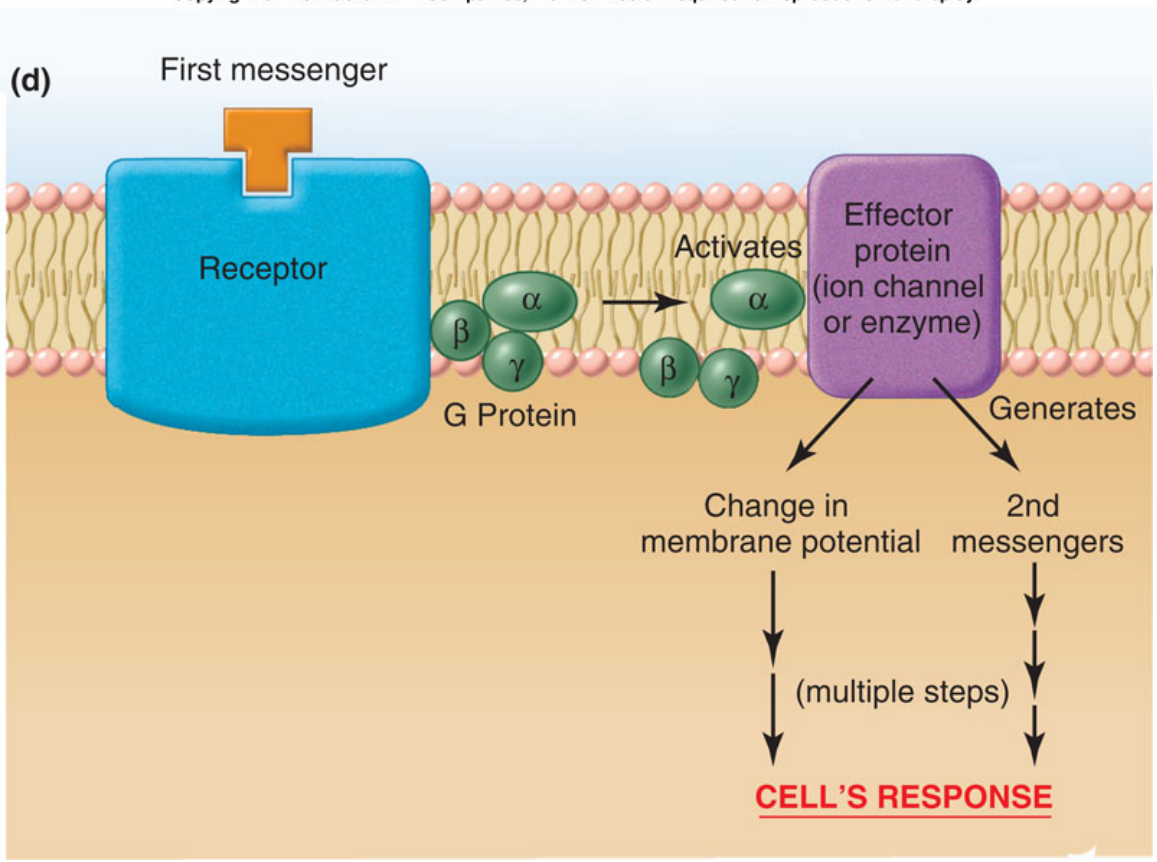

Figure 5-5d

Binding of the ligand to the receptor alters the receptor's shape, which activates an associated G-protein, which then activates effector proteins, i.e., enzyme functions or ion channels.

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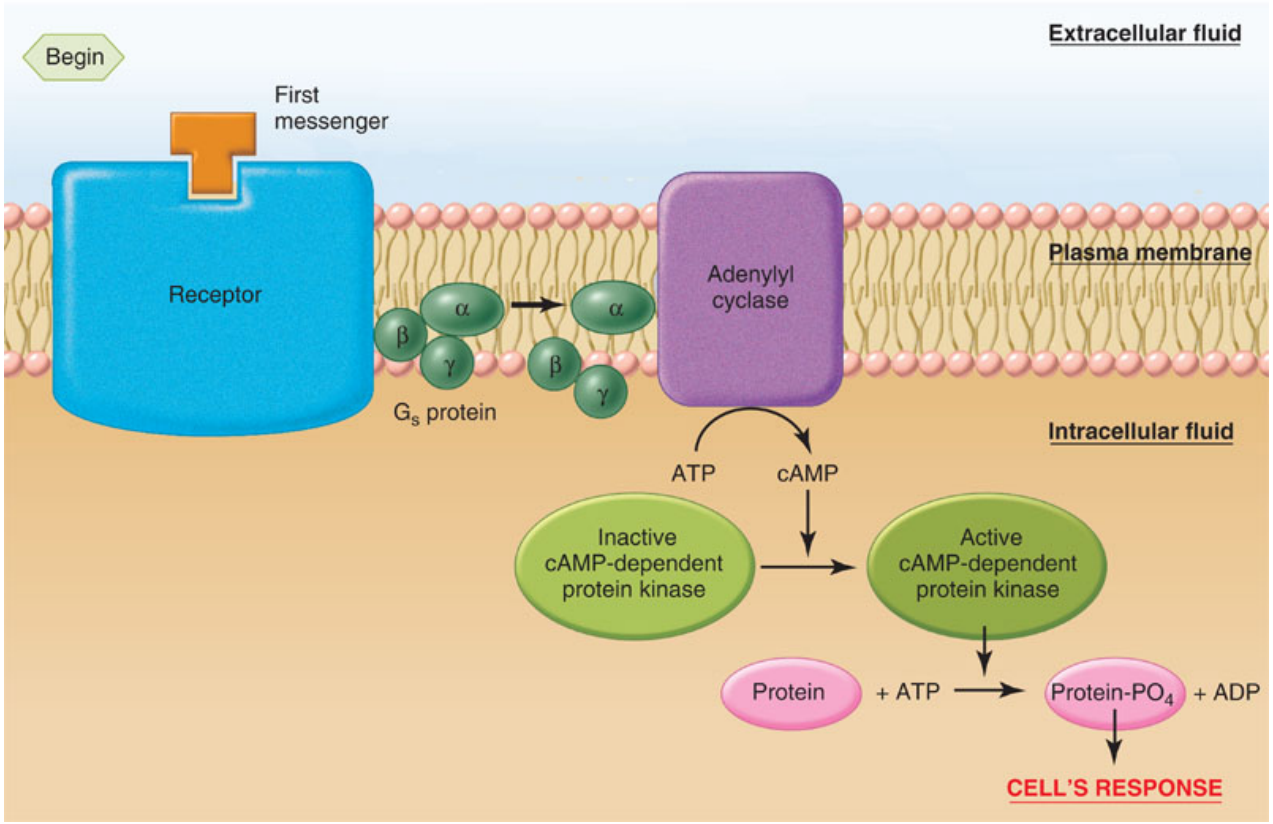


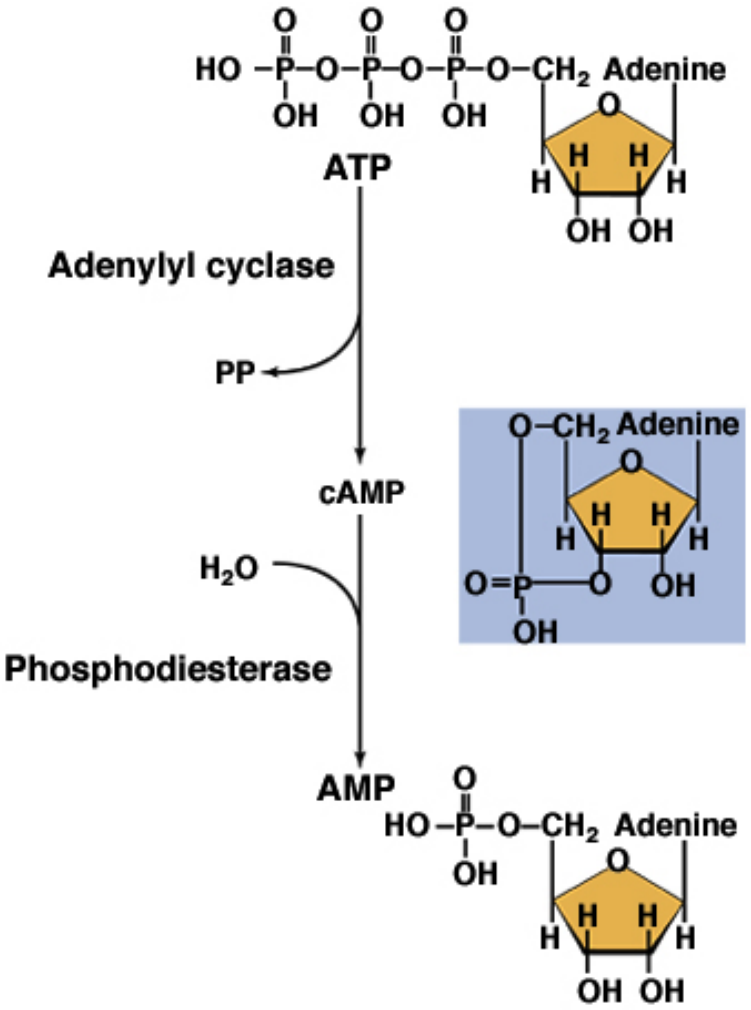
Figure 5-6

The cyclic AMP second messenger system.

Figure 5-7

Adenylyl cyclase forms cAMP, a "second messenger" that activates enzymes used in cellular responses.

The phosphodiesterase enzymes "terminate" the second messenger cAMP.



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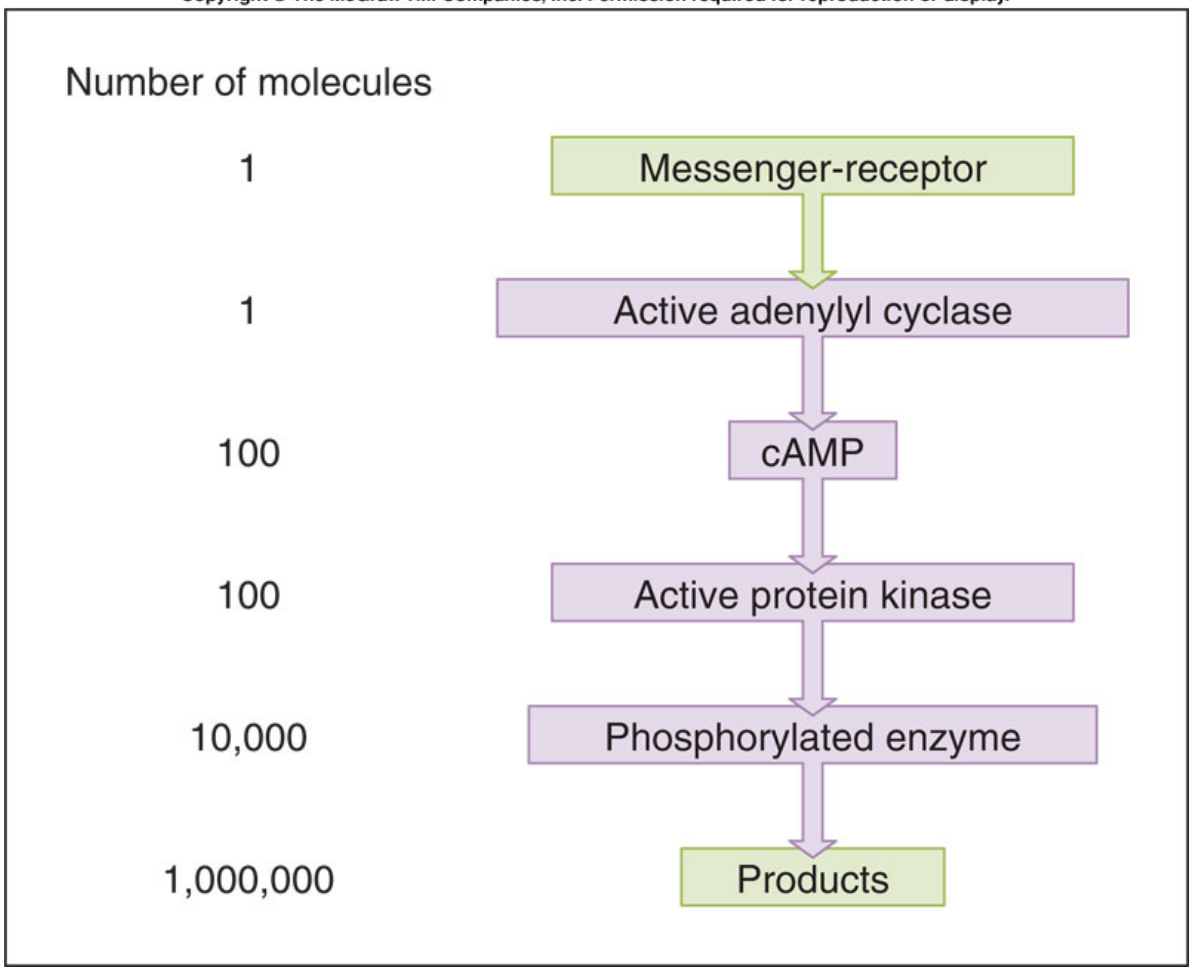

Figure 5-8

The cAMP system rapidly amplifies the response capacity of cells: here, one “first messenger” led to the formation of one million product molecules.

Figure 5-9

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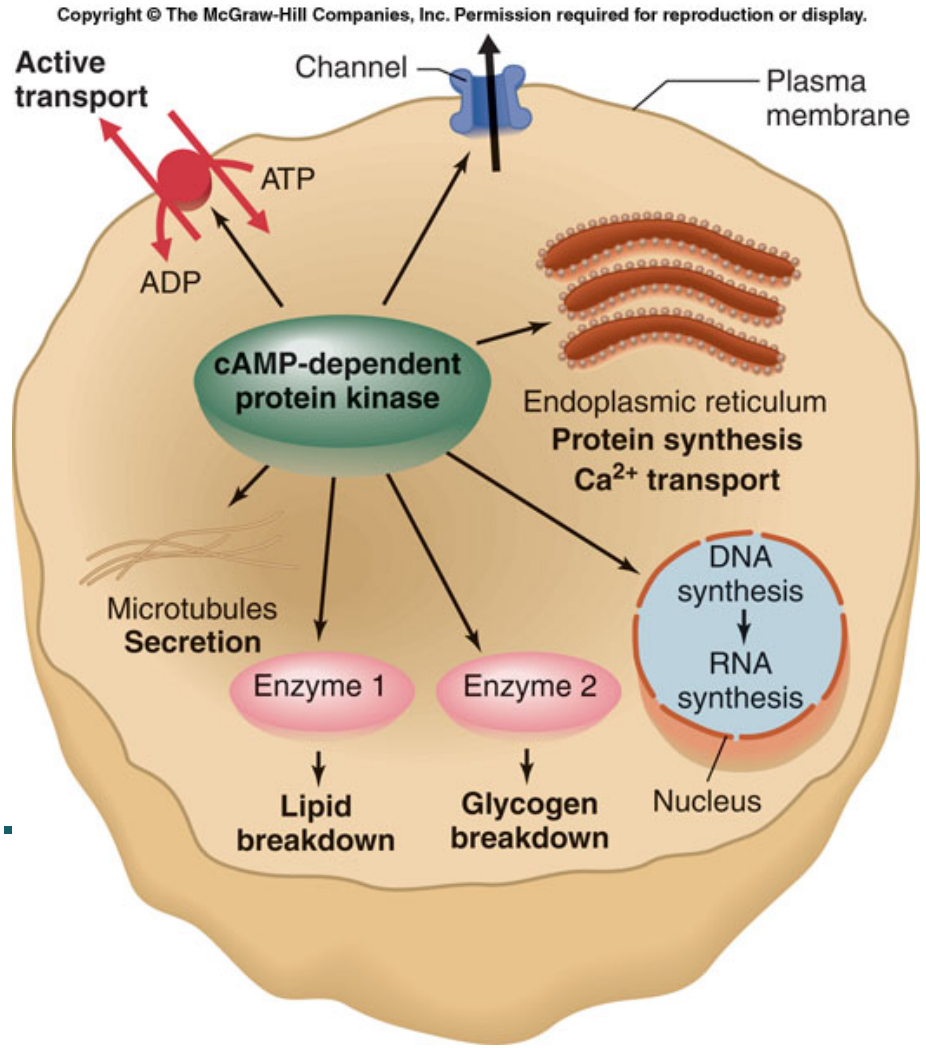

Cells can respond via the cAMP pathways using a diversity of cAMP-dependent enzymes, channels, organelles, contractile filaments, ion pumps, and changes in gene expression.

Figure 5-10

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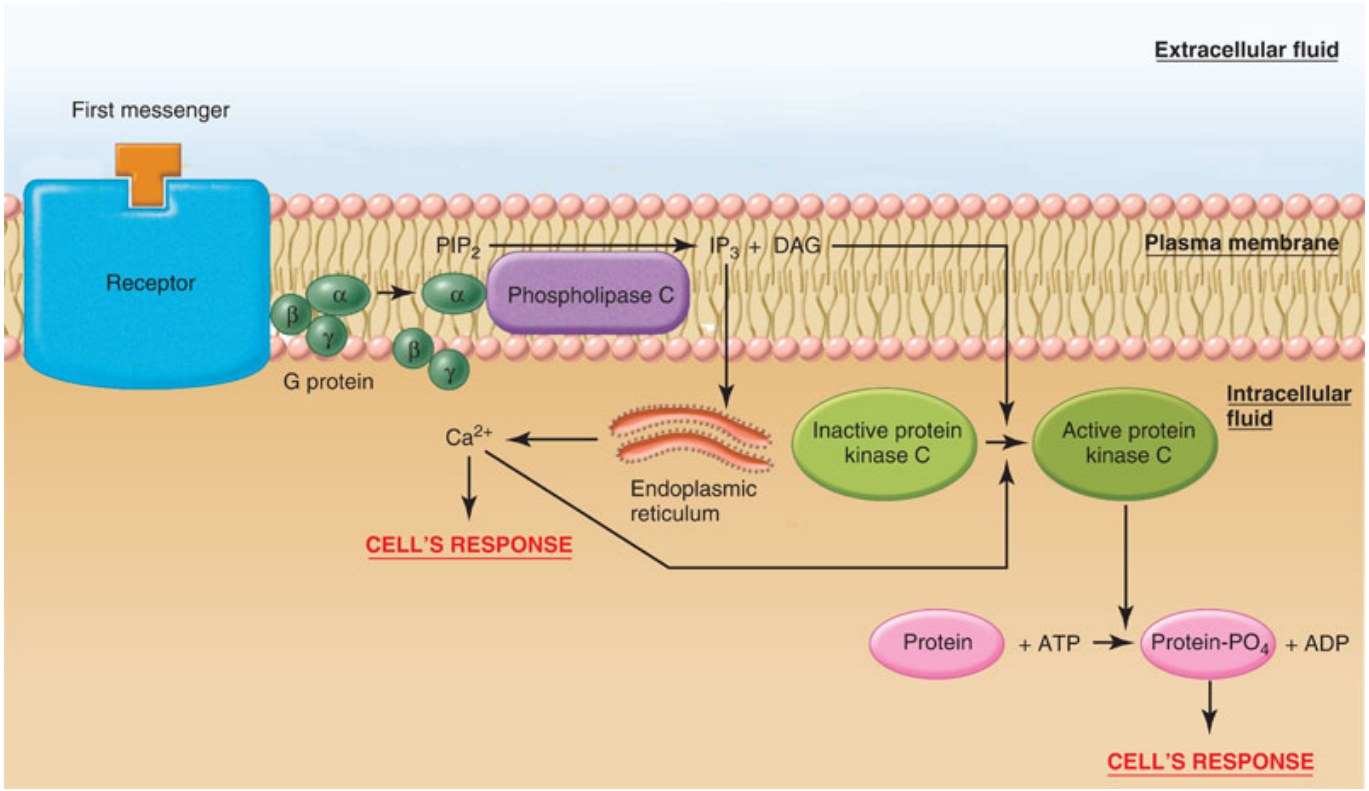

This receptor-G-protein complex is linked to and activates phospholipase C, leading to an increase in IP_3 and DAG, which work together to activate enzymes and to increase intracellular calcium levels.

Click here to play the
Membrane Bound Receptors,
G Proteins,
and Calcium Channels
Flash Animation

TABLE 5–3 Summary of Mechanisms by Which Receptor Activation Influences Ion Channels

1. The ion channel is part of the receptor.
2. A G protein directly gates the channel.
3. A G protein gates the channel indirectly via a second messenger.

TABLE 5–4 Calcium as a Second Messenger

Common mechanisms by which stimulation of a cell leads to an increase in cytosolic Ca^{2+} concentration:

1. Receptor activation
   a. Plasma-membrane calcium channels open in response to a first messenger; the receptor itself may contain the channel, or the receptor may activate a G protein that opens the channel via a second messenger.
   b. Calcium is released from the endoplasmic reticulum; this is mediated by second messengers, particularly IP_3 and calcium entering from the extracellular fluid.
   c. Active calcium transport out of the cell is inhibited by a second messenger.
2. Opening of voltage-gated calcium channels

Major mechanisms by which an increase in cytosolic Ca^{2+} concentration induces the cell's responses:

1. Calcium binds to calmodulin. On binding calcium, the calmodulin changes shape, which allows it to activate or inhibit a large variety of enzymes and other proteins. Many of these enzymes are protein kinases.
2. Calcium combines with calcium-binding intermediary proteins other than calmodulin. These proteins then act in a manner analogous to calmodulin.
3. Calcium combines with and alters response proteins directly, without the intermediation of any specific calcium-binding protein.

Figure 5-11

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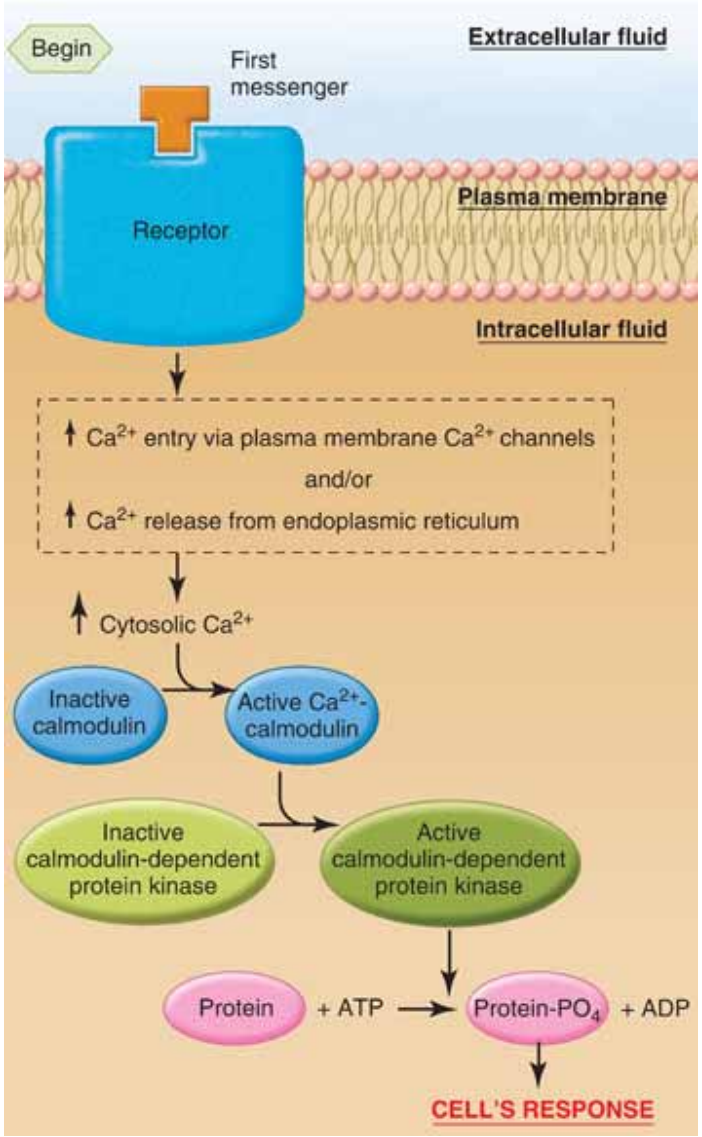

The calcium-calmodulin system is similar to some of the cAMP pathways, because it results in the activation of protein kinases that can phosphorylate key proteins required for cellular responses.

Figure 5-12

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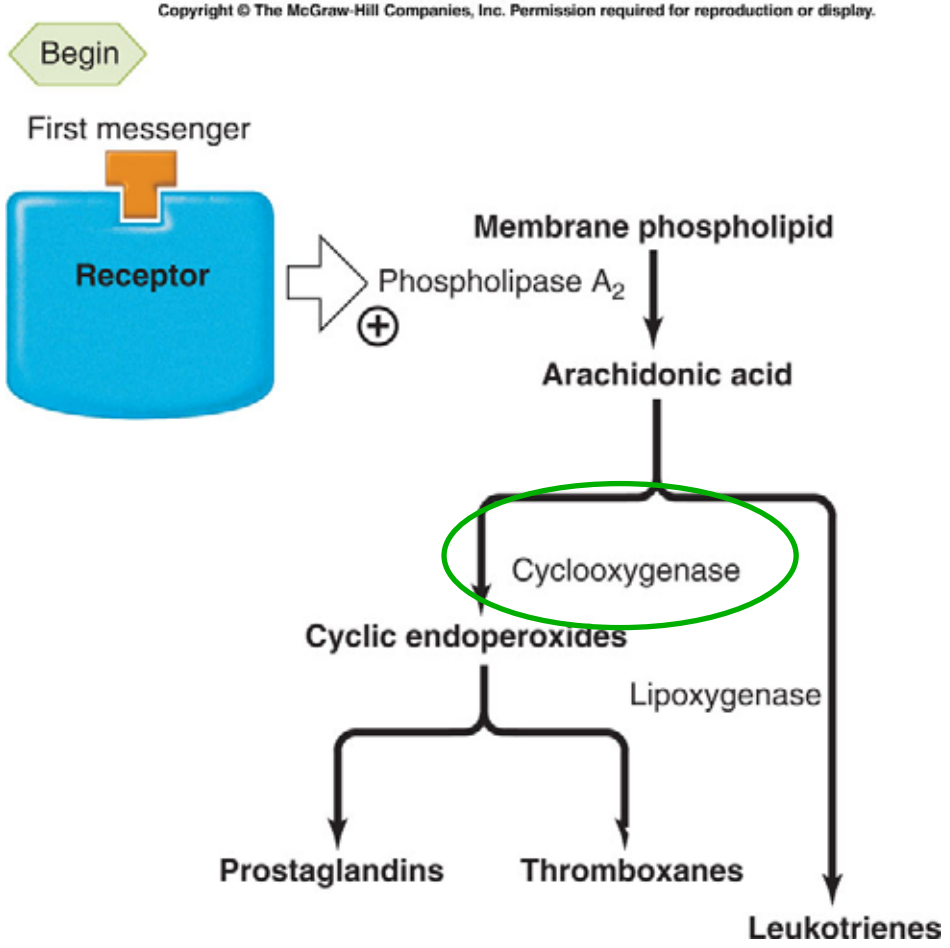
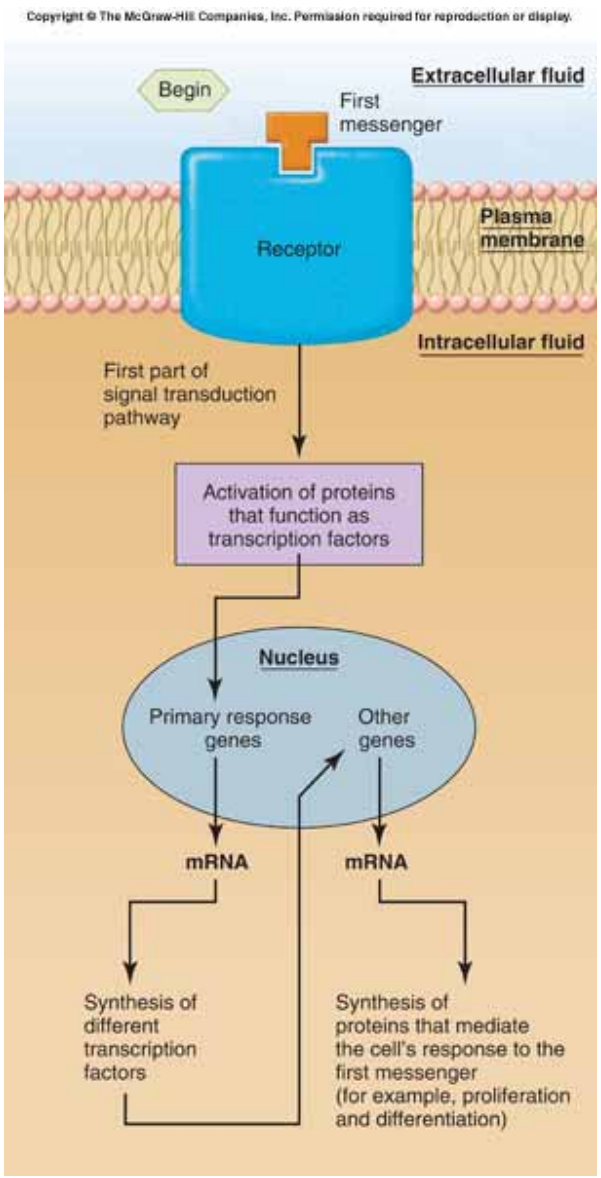


The “arachidonic acid cascade” is activated in inflammation responses; “cox inhibitors” block cyclooxygenase.

Figure 5-13



Not all responses to hydrophilic signals are immediate:

Increases in gene expression can occur, and the resulting proteins can increase the target cells' response.

TABLE 5–5 Reference Table of Important Second Messengers

SUBSTANCE	SOURCE	EFFECTS
Calcium	Enters cell through plasma membrane ion channels or is released from endoplasmic reticulum	Activates calmodulin and other calcium-binding proteins; calcium-calmodulin activates calmodulin-dependent protein kinases. Also activates protein kinase C.
Cyclic AMP (cAMP)	A G protein activates plasma membrane adenylyl cyclase, which catalyzes the formation of cAMP from ATP	Activates cAMP-dependent protein kinase (protein kinase A)
Cyclic GMP (cGMP)	Generated from guanosine triphosphate in a reaction catalyzed by a plasma membrane receptor with guanylyl cyclase activity	Activates cGMP-dependent protein kinase (protein kinase G)
Diacylglycerol (DAG)	A G protein activates plasma membrane phospholipase C, which catalyzes the generation of DAG and IP_3 from plasma membrane phosphatidylinositol bisphosphate (PIP_2)	Activates protein kinase C
Eicosanoids	Generated from arachidonic acid in plasma membrane; arachidonic acid is converted into eicosanoids by cytoplasmic enzymes	Paracrine and autocrine effects, such as smooth muscle relaxation
Inositol trisphosphate (IP_3)	See DAG above	Releases calcium from endoplasmic reticulum

Eicosanoid: A lipid mediator of inflammation derived from the 20-carbon atom arachidonic acid (20 in Greek is "eicosa") or a similar fatty acid. The eicosanoids include the prostaglandins, prostacyclin, thromboxane, and leukotrienes.

The End.