5. Some dissolved gases cross the plasma membrane and activate intracellular enzymes directly.

Nitric oxide (NO) triggers smooth muscle relaxation in a blood vessel wall.
Nitric Oxide (NO), a local mediator

Characteristics
(1) Dissolved gas (diffuses readily out of the cell)
(2) Quickly converted to nitrate and nitrite (half life of 5-10s).
(3) NO synthase (NOS): Arginine (substrate) \(\rightarrow\) NO + Citrulline (products).

Action mechanism
(1) Smooth muscle cells relaxation (blood-vessel dilation)
(2) 'Nitroglycerin' (In the body, it is converted to NO, which rapidly relaxes coronary blood vessels and increases blood flow to the heart)
(3) Binds to 'Guanylyl cyclase (GC)' to produce cGMP, a second messenger.

Viagra: an impotence drug that enhances penile erection by blocking the degradation of cGMP, prolonging the NO signal.

Cell surface Receptor: the vast majority of signal molecules are too large or hydrophilic (proteins, peptides, and small, highly water-soluble molecules) and bind to cell surface receptors.

Primary signal transduction step (Binds to extracellular signal)
Generates new intracellular signals
A molecular relay race (the message is passed downstream from one intracellular signaling molecule to another).
Response of the cell (a metabolic enzyme is kicked into action; the cytoskeleton is tweaked into a new configuration, or a gene is switched on or off).

Functions of Intracellular signaling proteins
Relay (relay the signal onward and thereby help spread it through the cell)
Transduce and amplify (transduce the signal into a different form and makes it stronger, so that a few extracellular signal molecules are enough to evoke a large response)
Integrate (receive signals from more than one pathway and integrate them before relaying a signal)
Distribute (create branches in the information flow diagram and evokes a complex response)
Functions of Intracellular signaling proteins (continued)

- **Scaffold** (act as a scaffold to bring two or more signaling component in the chain)
- **Anchor** (anchor one or more signaling proteins in a pathway to a particular structure in the cell where the signaling proteins are needed)
- **Modulate** (modulate the activity of other signaling proteins and thereby regulate the strength of signaling along a pathway)

7. Some intracellular signalling proteins act as molecular switches

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**Protein kinase** (+: phosphatase)

**GTP-binding proteins**

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Figure 15-18 Molecular Biology of the Cell (© Garland Science 2008)

Figure 15-19 Molecular Biology of the Cell (© Garland Science 2008)
The importance of switching-off process (Activation and inactivation steps are both important for the signaling).

**Molecular switch**: receipt of a signal causes them to toggle from an inactive to an active state.

1. **Protein kinase**
   By far the largest class.
   Tacks a phosphate group onto the switch protein.
   **Protein phosphatase**: plucks the phosphate off again.
   The activity of any protein that is regulated by phosphorylation depends of the balance between the activities of kinases and the phosphatases.
   **Phosphorylation cascades**: many of the switch proteins controlled by P are themselves protein kinase.
   **Serine / threonine kinases and Tyrosine kinases**.

2. **GTP-binding proteins**
   Active / inactive state = GTP / GDP bound.
   **GTPase activity**: Once activated by GTP binding, they have intrinsic GTP-hydrolyzing activity, and shut themselves off.
   **G proteins**:
   The large trimeric GTP-binding proteins Relay messages from G-protein-coupled receptors.

8. **Cell surface receptors** fall into three main classes

   **Cell-surface receptors**
   1. **Ion-channel-coupled receptors**
   2. **G-protein-coupled receptors**
   3. **Enzyme-coupled receptors**

   ![Figure 15-16a Molecular Biology of the Cell (© Garland Science 2008)](image)

   allow a flow of ions across the plasma membrane, which changes the membrane potential and produces an electrical current.
activate membrane-bound, trimeric GTP-binding proteins (G proteins, which then activate either an enzyme or an ion channel in the plasma membrane, initiating a cascade of other effects.

1. **Receptors > Extracellular signals**
   Many extracellular signal molecules have more than one type of receptor.
   Some signal molecules bind to receptors in more than one class (e.g., Ach on skeletal muscle cells / heart muscle cells)

2. **Cell surface receptors - targets for many foreign substances**
   From heroin, nicotine to tranquilizers, chili peppers.
   Either mimic the natural ligand, occupying the normal ligand-binding site or bind to the receptor at some other site, either blocking or overstimulating the receptor's natural activity.
   Many drugs and poisons.
   A large part of the pharmaceutical industry.

| TABLE 16-2 SOME FOREIGN SUBSTANCES THAT ACT ON CELL-SURFACE RECEPTORS |
|---------------------------------|---------------------|-----------------|-----------------|
| SUBSTANCE                        | SIGNAL MOLECULE     | RECEPTOR ACTION | EFFECT           |
| Valium and barbiturates          | γ-aminobutyric acid (GABA) | stimulates GABA-activated ion-channel-coupled receptors | relief of anxiety: sedation |
| Nicotine                         | acetylcholine       | stimulates acetylcholine-activated ion-channel-coupled receptors | constriction of blood vessels; elevation of blood pressure |
| Morphine and heroin              | endorphins and enkephalins | stimulate G-protein-coupled opiate receptors | analgesia (relief of pain); euphoria |
| Curare                            | acetylcholine       | blocks acetylcholine-activated ion-channel-coupled receptors | blockage of neuromuscular transmission, resulting in paralysis |
| Strychnine                       | glycine             | blocks glycine-activated ion-channel-coupled receptors | blockage of inhibitory synapses in spinal cord and brain, resulting in seizures and muscle spasm |

Table 16-2: Essential Cell Biology 3/e (© Garland Science 2010)
9. **Ion-channel-couple receptors** convert chemical signals into **electrical** ones

- **Transmitter-gated ion channels**
  - **Simplest and most direct way**
  - Rapid transmission of signals across synapses in the nervous system
  - **Transduce** a chemical signal into an electrical signal
  - Neurotransmitter binding > **Conformation change** (open or close a channel for the flow of specific types of ions (Na⁺, K⁺, Ca²⁺, or Cl⁻))
  - A change in the **membrane potential** within a millisecond
  - Trigger a **nerve impulse**, or alter the ability of other signals (Chapter 12)

- **Ion-channel-linked receptors**
  - Used for induction of anesthesia
  - Also used for sedation
  - Michael Jackson
  - Potentiation of GABA<sub>A</sub> receptor activity (slowing the channel-closing time)
  - Acting as a sodium channel blocker
10. Intracellular signaling complexes enhance the speed, efficiency, and specificity of the response

How does an individual cell manage to make specific responses to so many different combinations of extracellular signals?

How is it possible to achieve specificity and avoid cross-talk?
ASSEMBLY OF SIGNALING COMPLEX ON PHOSPHOINOSITIDE DOCKING SITES

inactive receptor
specific phospholipid molecules (phosphoinositides)
signal molecule
activated receptor
hyperphosphorylated phosphoinositides

inactive intracellular signaling proteins
activated intracellular signaling proteins
downstream signals

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