Mechanisms of cell communication

Biology

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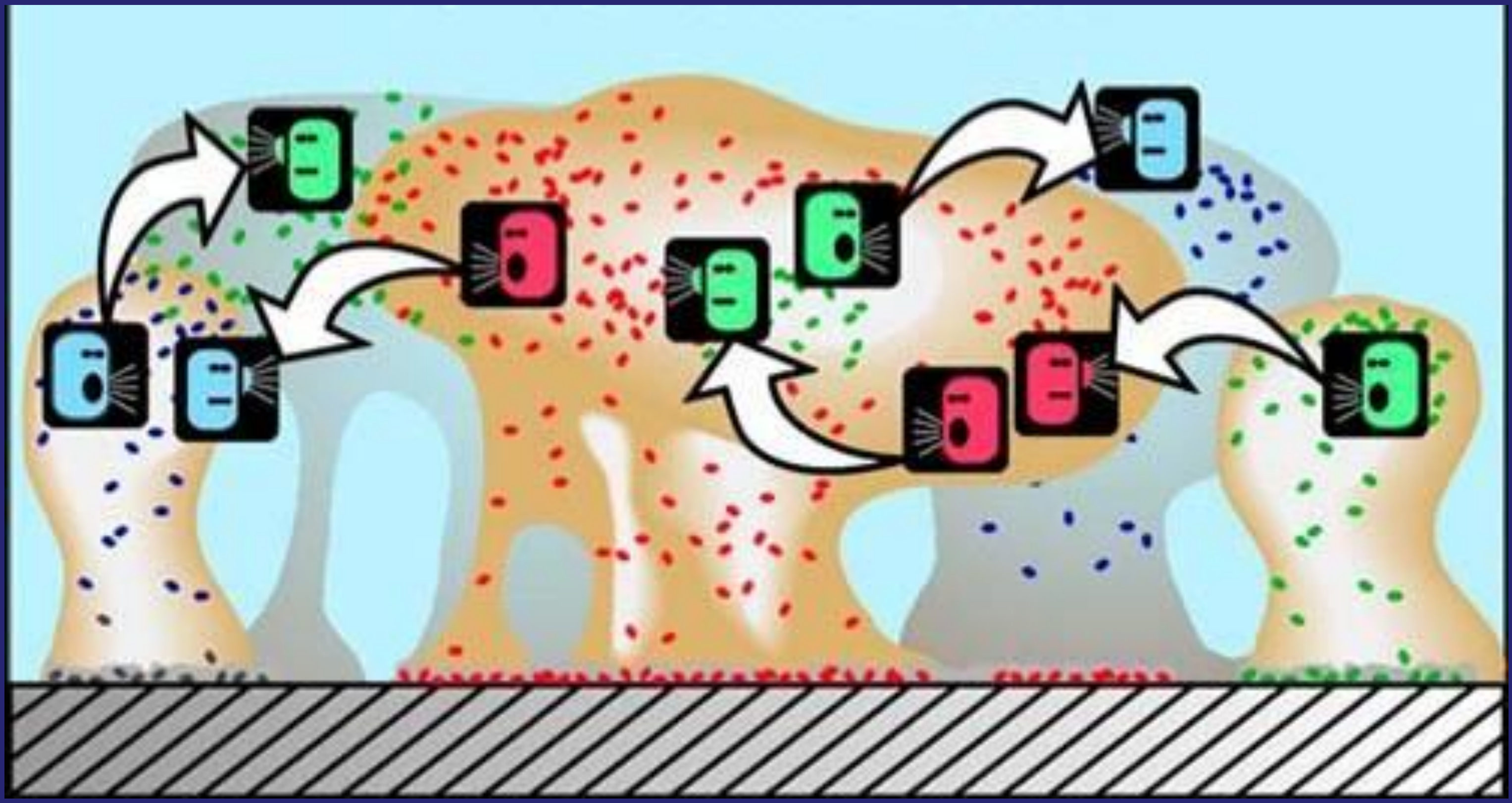
Communication between cells is important for the growth, daily physiology and behavior of the organism.

We are talking about **CELL SIGNALING**.



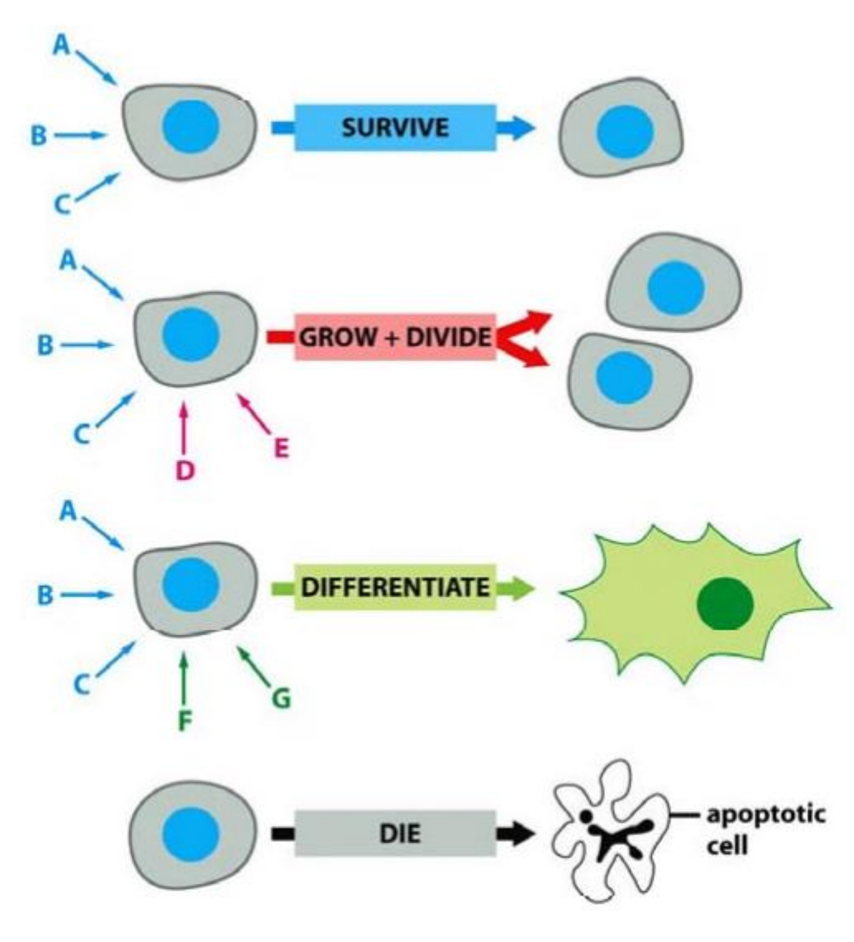
Intercellular communication

To make a multicellular organisms, cell must communicate, just as human must communicate if they are to recognize themselves into a complex society

Intercellular mechanisms of cell must

- control which signals are emitted
- control at what time they are emitted
- enable the signal-receiving cell to interpret those signals
- use the signals to guide its behaviour

- A cell in a multicellular organism may be exposed to hundreds of signals. exposed to hundreds of signals.
- Different types of cells respond differently to the same type of signals to the same type of signals.
- A major challenge is to understand how the cells process such information and the cells process such information and make decisions.



A cell needs signals from surrounding cells to survive. If it does not have a sufficient number of the right signals (by means of which it recognizes that it is in the right place at the right time), it commits suicide (apoptosis).
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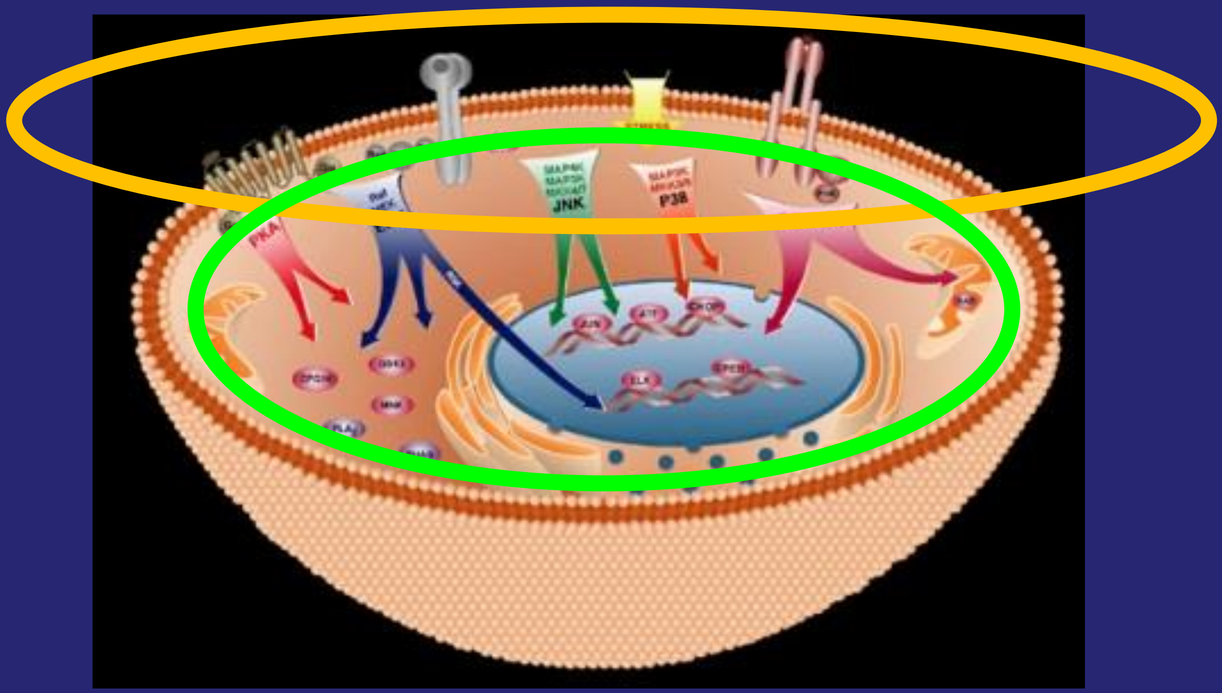
Signal molecules

Extracellular signal molecules

Intracellular signal molecules



Extracellular signal molecules

Organisms emit and receive the signals

- **communication <u>between</u> cells**
- **mostly operate over <u>long distances </u>or to <u>immediate neighbours</u>**
- **reception of the signals depends on <u>receptor proteins</u> (usually at the cell surface)**

Binding signal molecules to receptor activates it, which in turn activates one or more <u>intracellular signalling pathways</u>

Intracellular signal molecules

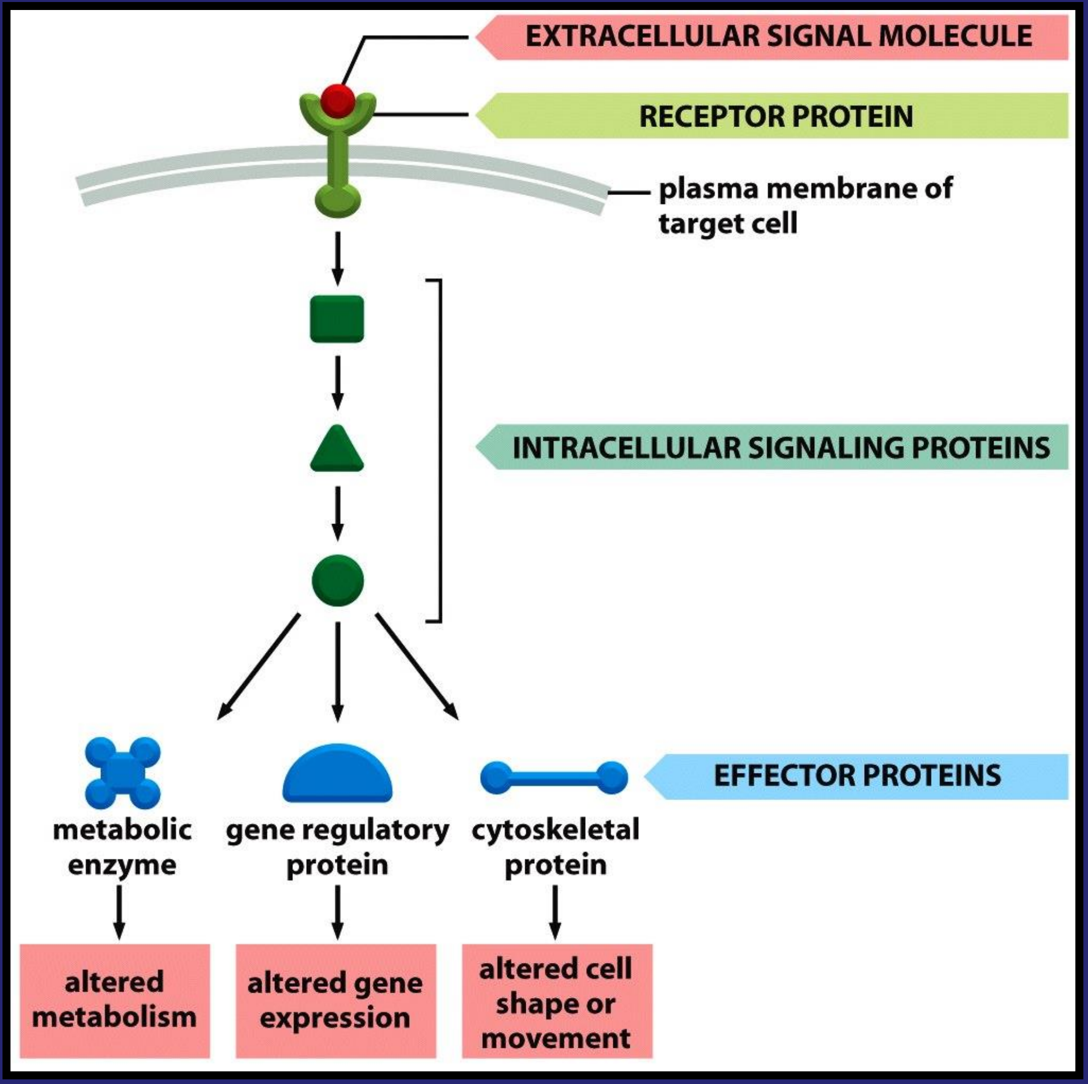
- they are building units of the intracellular signalling pathways
- they process the signal inside the receiving cell and
- distribute it to the appropriate intracellular targets – effector proteins

Effector proteins

Depending on the signal and the nature and state of the receiving cells

- **gene regulatory proteins,**
- **ion channels,**
- **components of a metabolic pathway,**
- **parts of the cytoskeleton,**
- **etc.**

General scheme



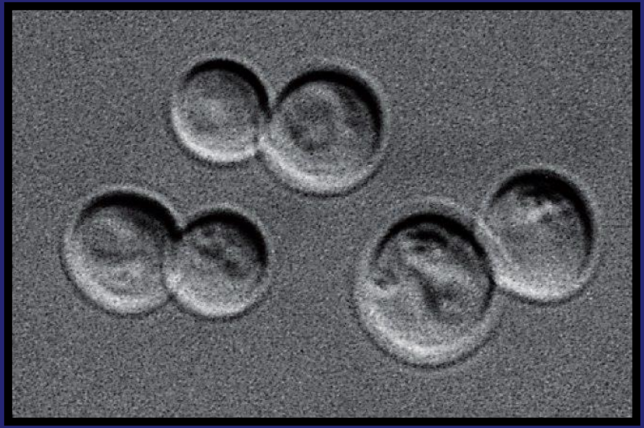
Communication of unicellular organisms

Although bacteria and yeasts largely lead independent lives, they communicate and influence one another's behaviour

- **respond to chemical signals that are secreted by their neighbours**
- **regulate density = *Quorum sensing***
- **coordinate motility, antibiotic production, spore formation, and sexual conjugation**

Mating factor in yeast

When *Saccharomyces cerevisiae* haplotype individual is ready to mate, it secrets a peptide mating factor that signals cell of the opposite mating type to stop proliferating and prepare to mate



Normally spherical cells

Cells put out a protrusion toward the source of the mating factor

Extracellular signals

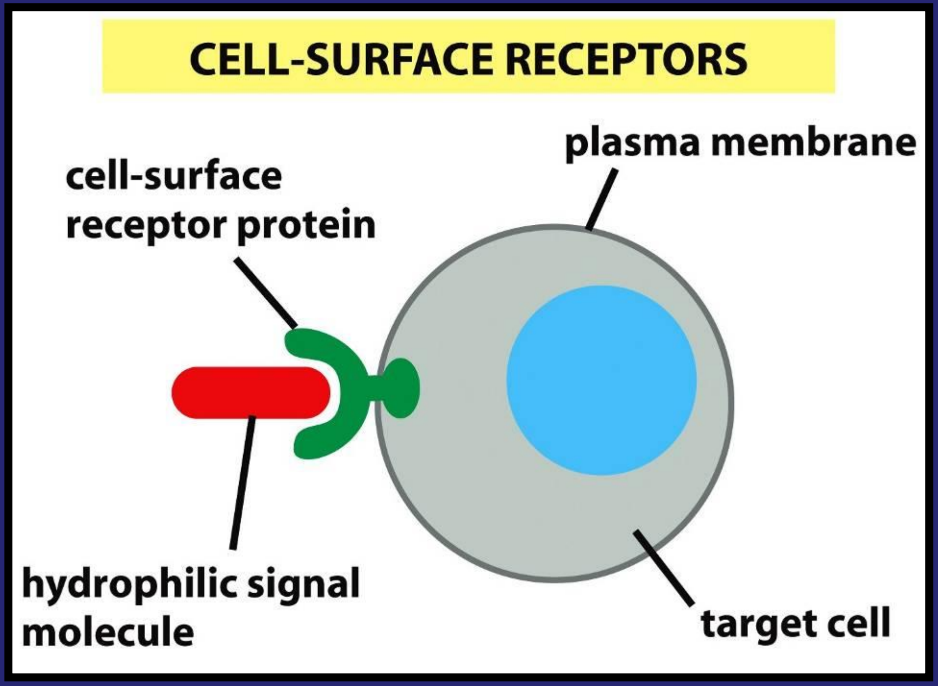
Signal molecules include proteins, small peptides, amino acids, nucleotides, steroids, retinoids, fatty acid derivates, and even dissolved gass such as nitric oxide and carbon dioxide

Regardless of the nature of the signal, the target cell respond by means of a receptor, which specifically binds the signal molecule and then initiates a response in the target cell.

The cell receptors are CELL-SURFACE and INTRACELLULAR

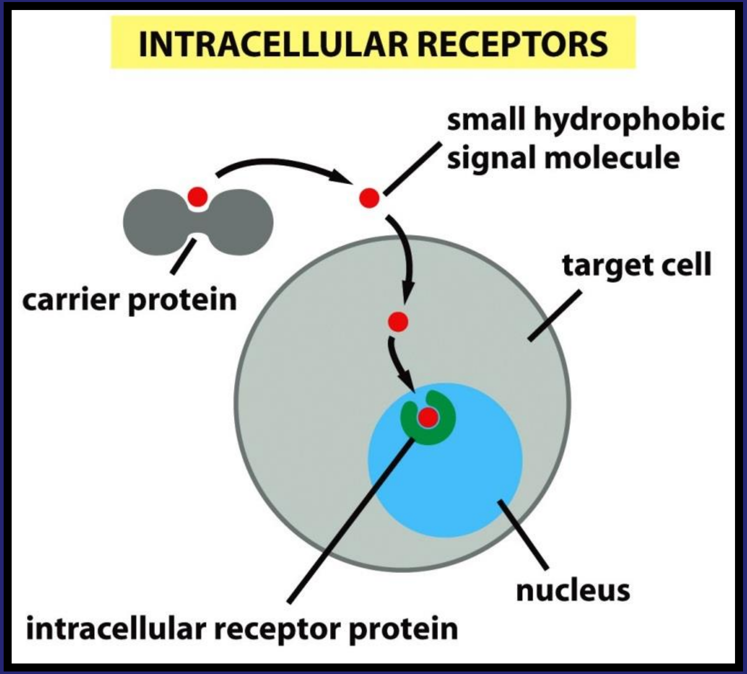
Extracellular signals binding 1/2

- hydrophilic signal molecules are unable to cross plasma membrane directly
- they bind to cell-surface receptors
- In turn the signal inside the target cell is generated

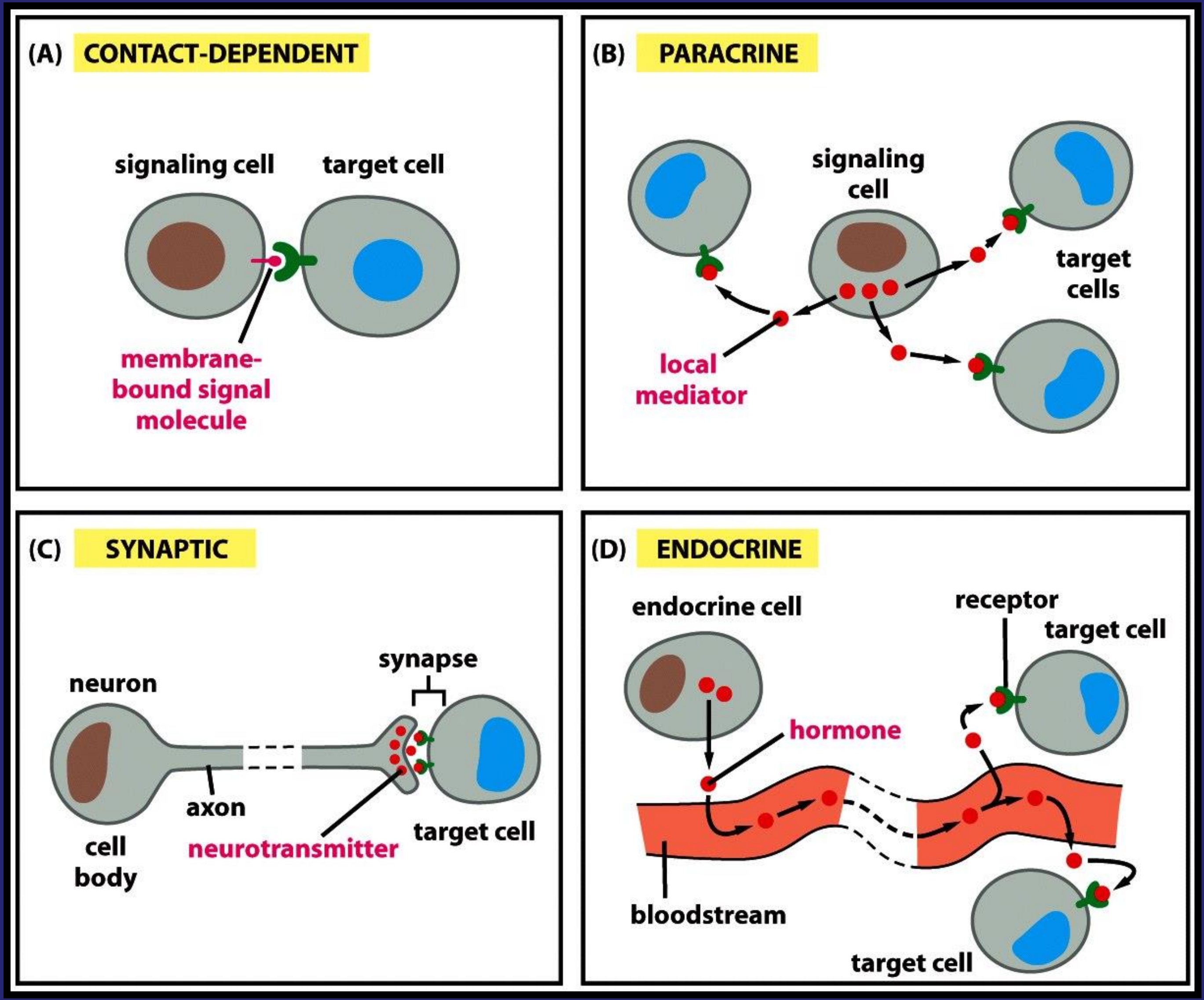


Extracellular signals binding 2/2

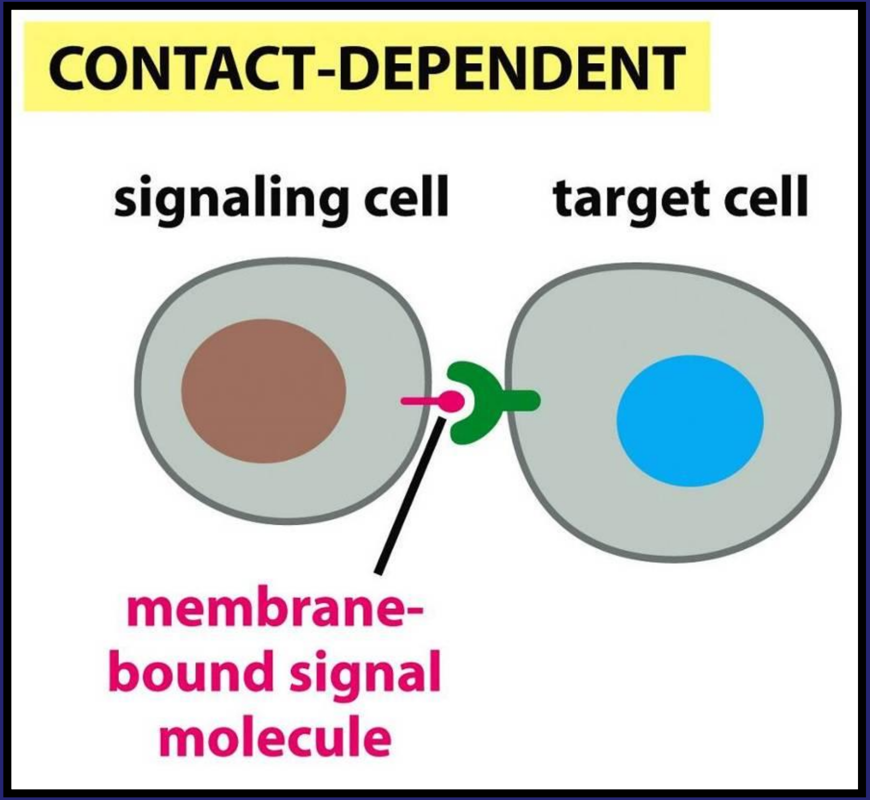
- some small signal molecules diffuse across the plasma membrane and bind to receptor inside the cell
- the molecules are mostly hydrophobic and insoluble in water = they need carrier proteins



Four forms of intercellular signalling

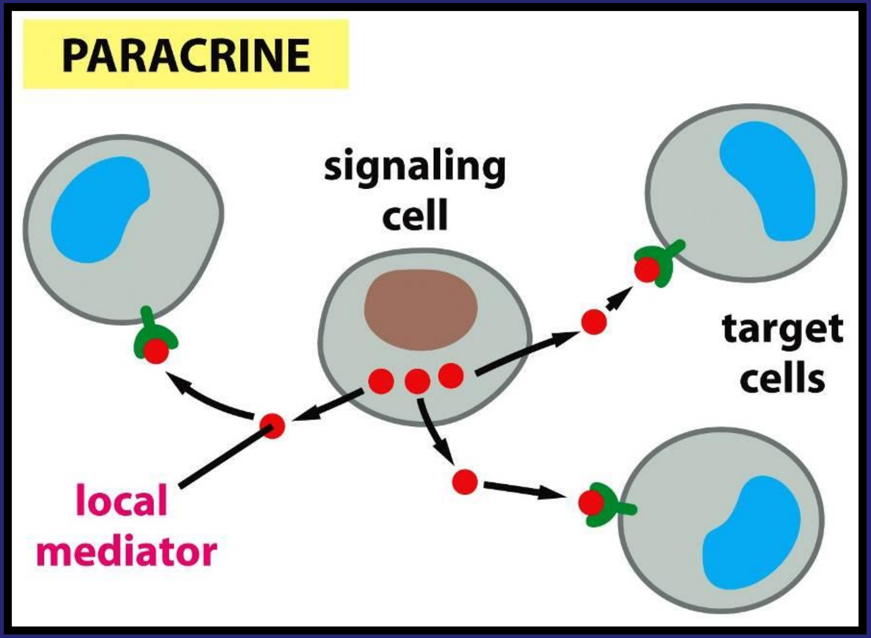


Contact-dependent signalling



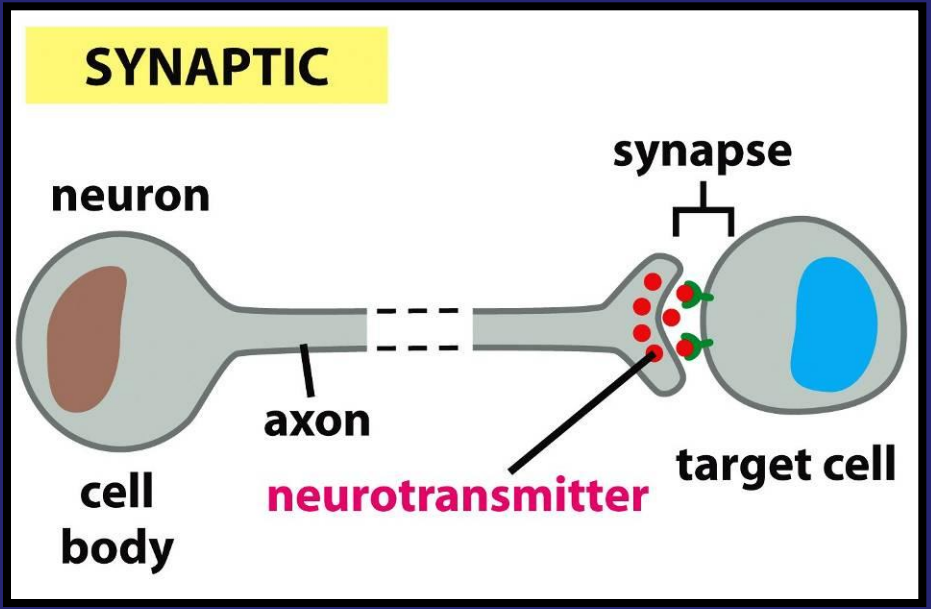
- cells must be in direct membrane-membrane contact
- important during development and immune responses

Paracrine signalling



- depends on signals that are released into the extracellular space and act <u>locally on neighbouring cells</u>
- target cells are different types
- if cells themselves respond to the signal we refer to as <u>autocrine signalling</u>
- this strategy is used by cancer cells – stimulate their own survival and proliferation

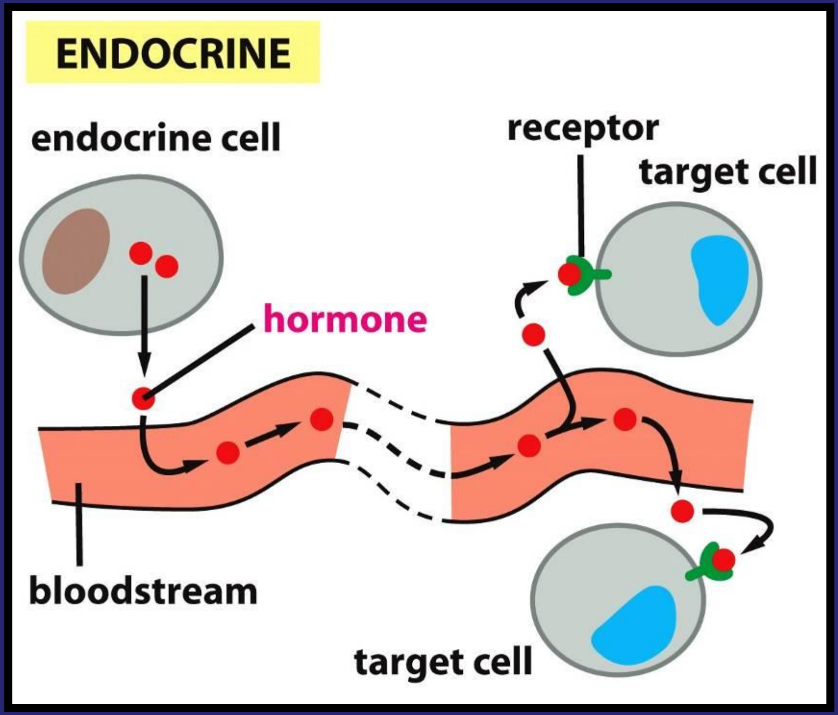
Synaptic signalling



- **<u>long-range</u> signalling mechanism**
- **axons enable to contact <u>target cells far away</u>, where processes terminate at the specialized sites – <u>chemical synapses</u>**

- **signals are transmitted electrically along the axons and release neurotransmitters at synapses**

Endocrine signalling



- <u>long-range</u> signalling mechanism
- endocrine cells secrete their signal molecules, called <u>hormones</u>, into the <u>bloodstream</u>

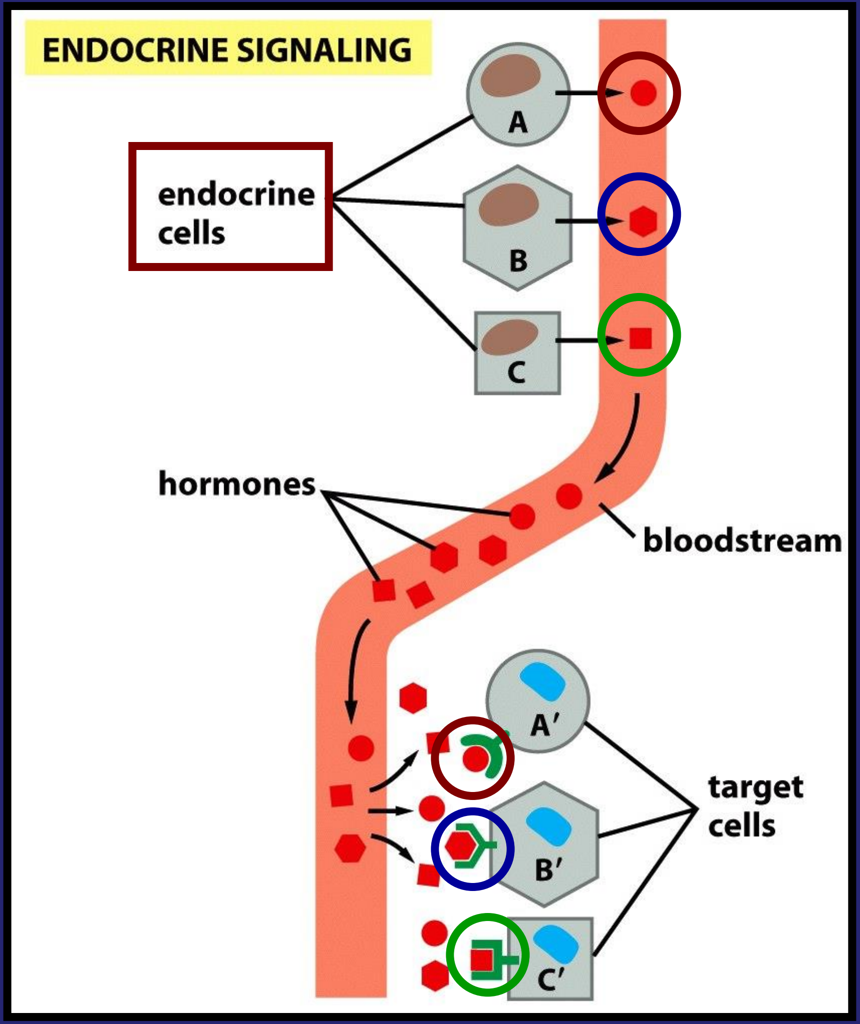
- bloodstream carries the molecules far and wide, allowing them to act on target cells that may lie anywhere in the body

Endocrine versus neuronal strategies

In complex animals, endocrine cells and nerve cells work together to coordinate the activities of cells in widely separated parts of the body

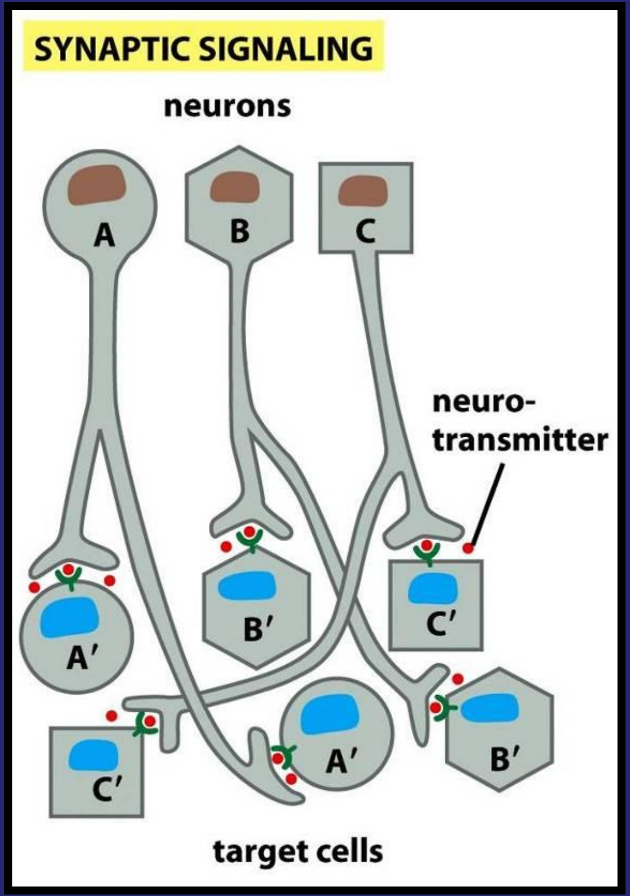
- **different endocrine cells must use different hormones to communicate specifically with their target cells**
- **different nerve cells can use the same neurotransmitter and still communicate in a highly specific manner**

Endocrine signalling



- cells secrete hormones into the blood
- act only on those target cells that carry the <u>appropriate receptors</u>

Synaptic signalling



- specificity arises from the <u>synaptic contacts</u> between a nerve cell and the specific target cells it signals
- usually, only a target cell that is in synaptic communication with a nerve cells is exposed to the neurotransmitter released from the nerve terminal

! Some neurotransmitters act in a paracrine mode – local mediators that influence multiple target cells in the area

Other differences

Endocrine signalling

- is relatively slow
- hormones are greatly diluted, must be able to act at very low concentrations (typically < 10^{-8} M)
- high affinity to target cells

Synaptic signalling

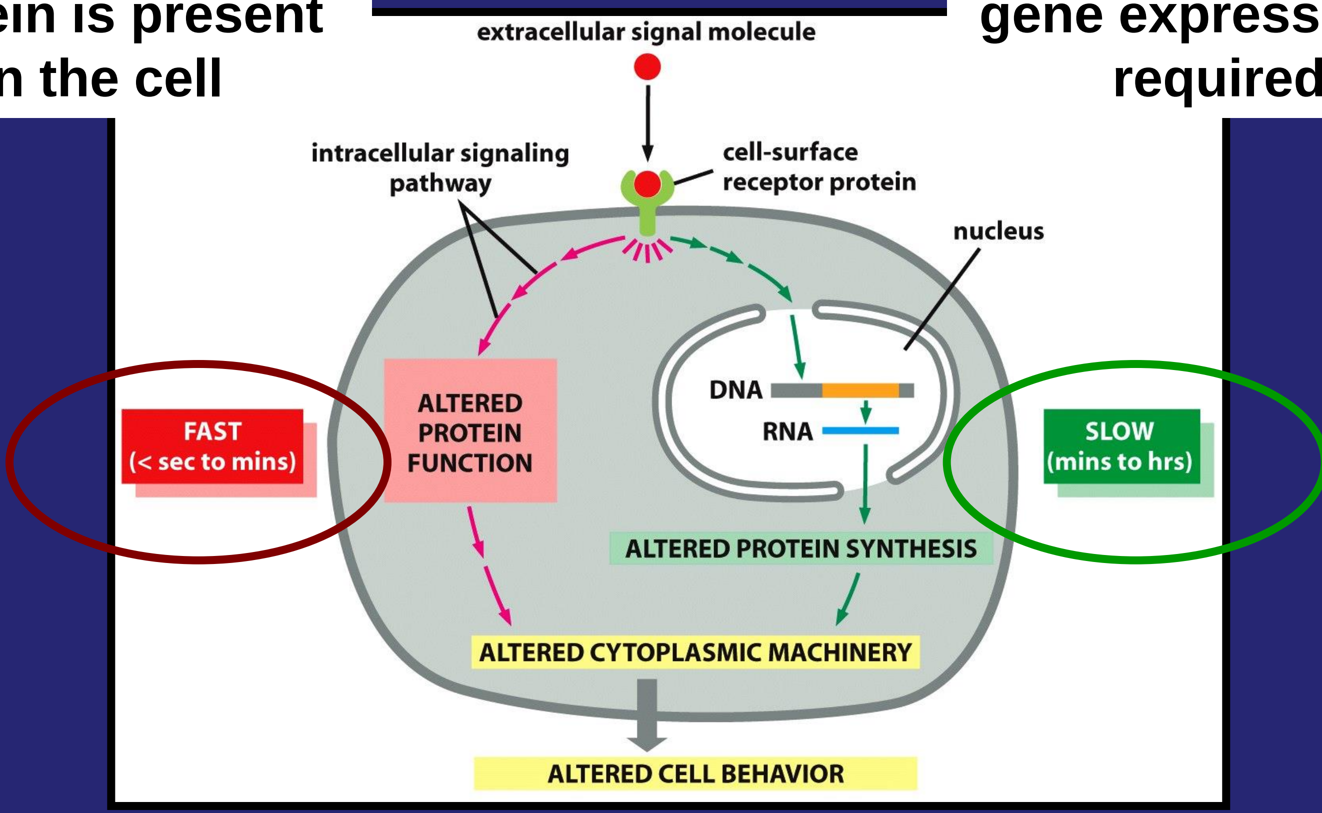
- is faster and more precise
- neurotransmitters are diluted much less and can achieve high local concentrations (5×10^{-4} M)
- low affinity to target cells, can rapidly dissociate

The speed of response

Depends not only on the mechanism of signal delivery, but also on the nature of the target cell´s response

protein is present in the cell

gene expression is required

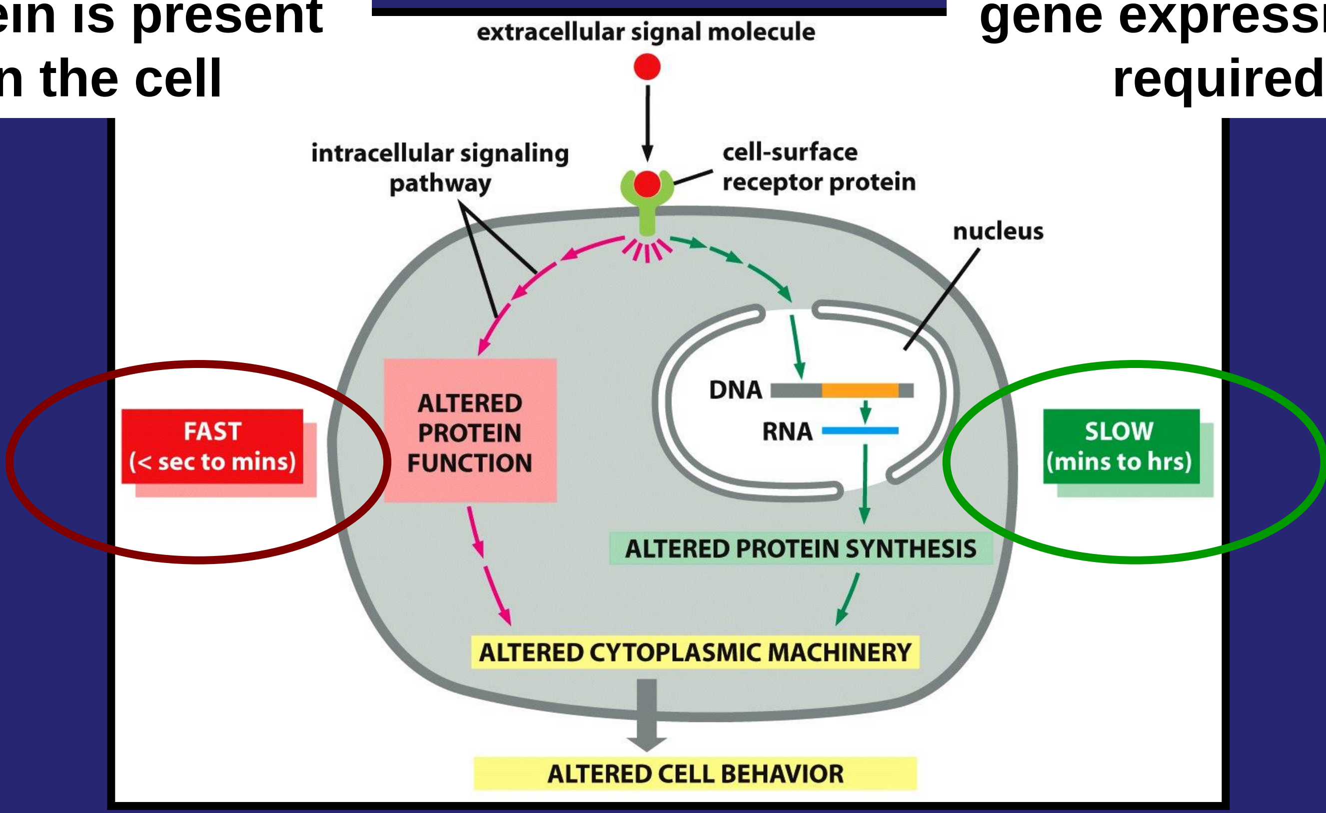


The speed of response – example 1

Changes in cell movement or secretion need not involve changes in gene expression and occur much more quickly (seconds or minutes)

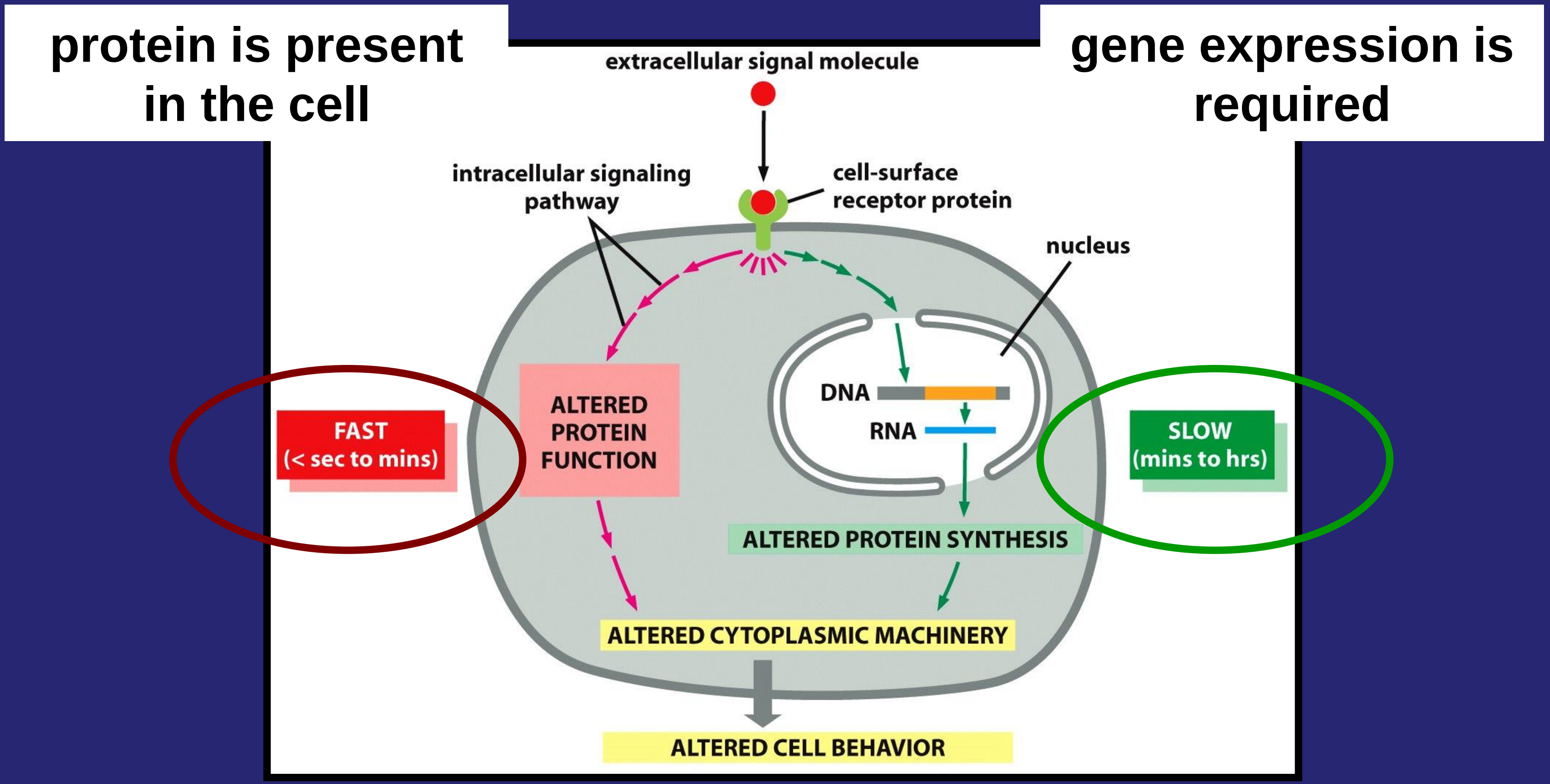
protein is present in the cell

gene expression is required

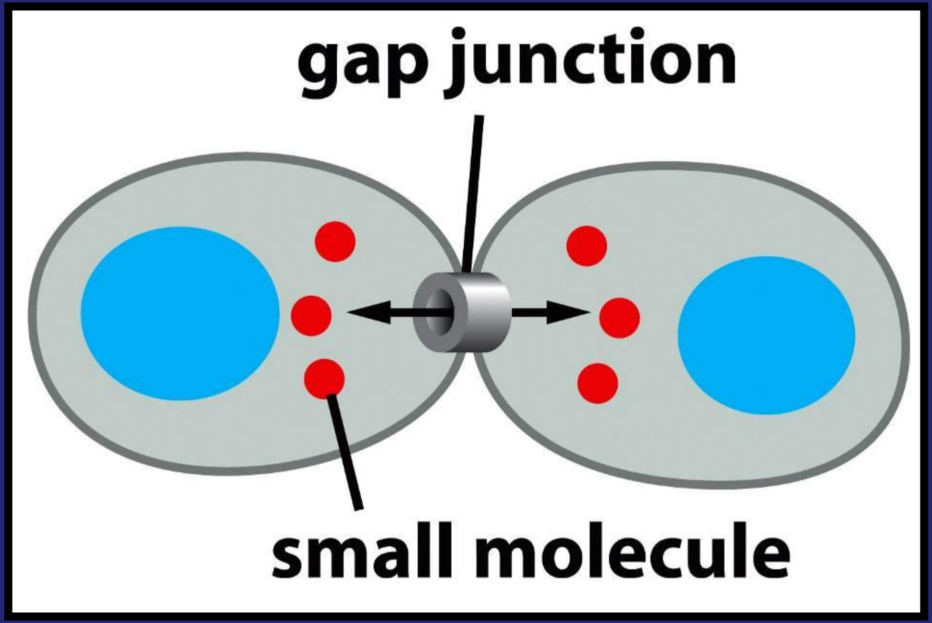


The speed of response – example 2

Synaptic responses mediated by changes in membrane potential can occur in milliseconds



Gap junctions



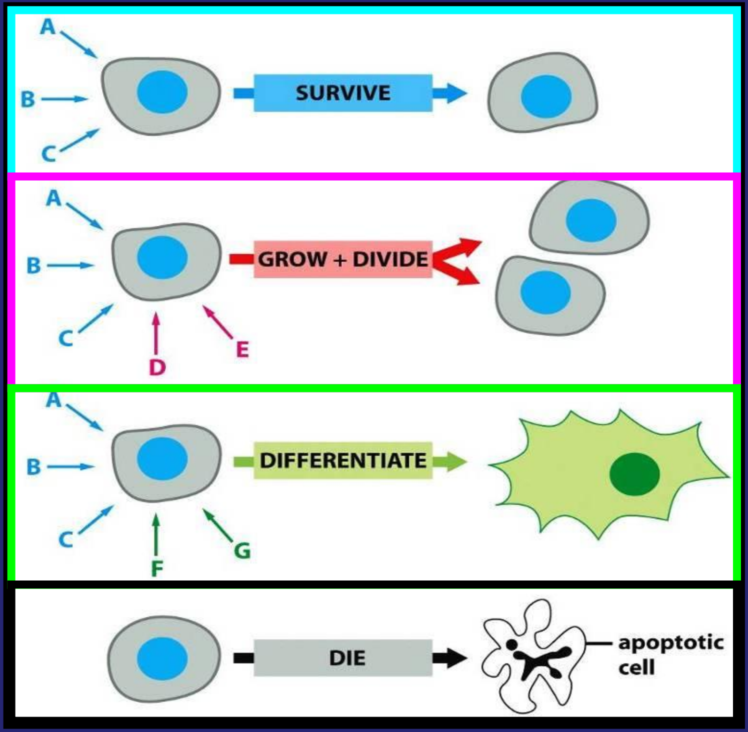
- allow neighbouring cells to share signalling information
- is a narrow water-filled channel
- direct connect the cytoplasm of adjacent cells
- allow the exchange of inorganic ions and other small water-soluble molecules, NO MACROMOLECULES
- allow respond to extracellular signals in a coordinated way

Example of gap junctions

- A fall in blood glucose levels release noradrenaline from sympatic nerve endings
- The noradrenaline stimulates hepatocytes in the liver to increase glycogen breakdown and to release glucose into the blood
- Not all the hepatocytes are innervated by nerves
- The innervated hepatocytes transmit the signal through gap junctions

Multiple signals

- cells display a set of receptors
- cells respond to set of signals in combinations

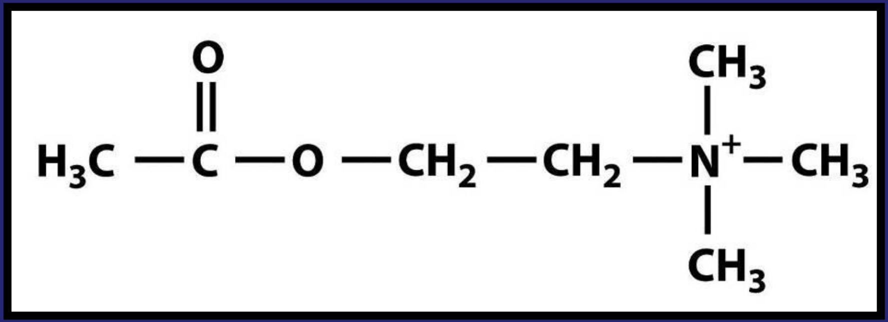


- several signals to survive
- and additional signals to grow and divide
- and other additional signals to differentiate
- if deprived of appropriate survival signals, a cell undergo apoptosis

Various responses

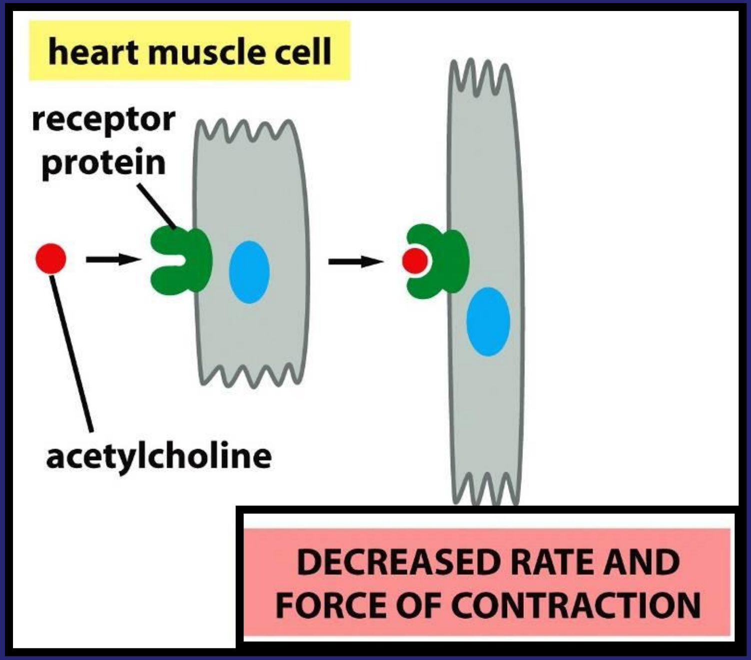
A cell´s response to extracellular signals depends not only on the receptor proteins but also on the intracellular machinery by which it interprets the signals

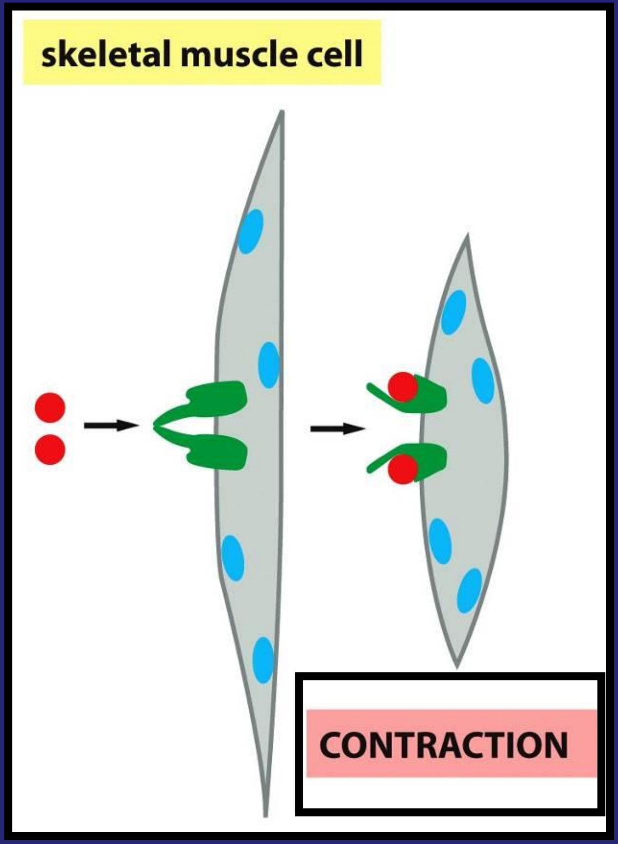
Neurotransmitter acetylcholine



1) decrease the rate and force of contraction in heart muscle cells
2) stimulates skeletal muscle cells to contract
3) stimulate secretion in salivary gland cells

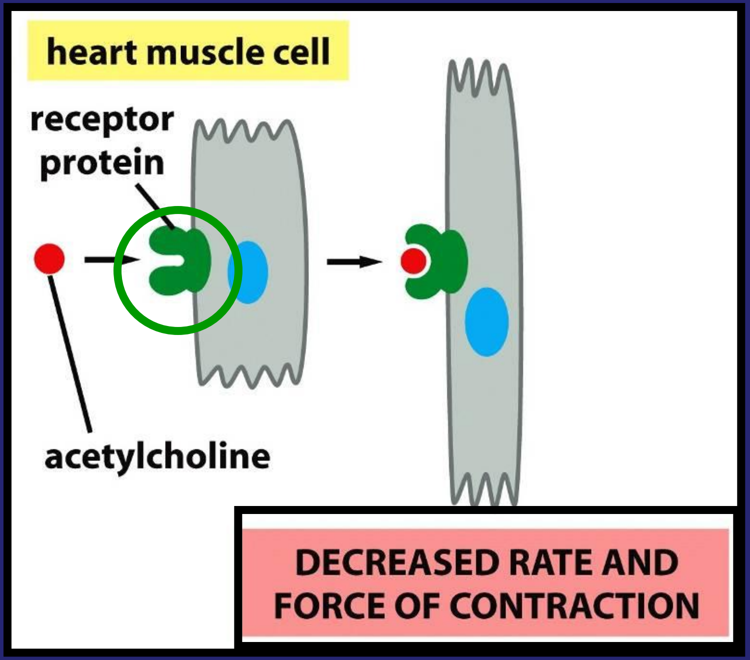
Different receptors

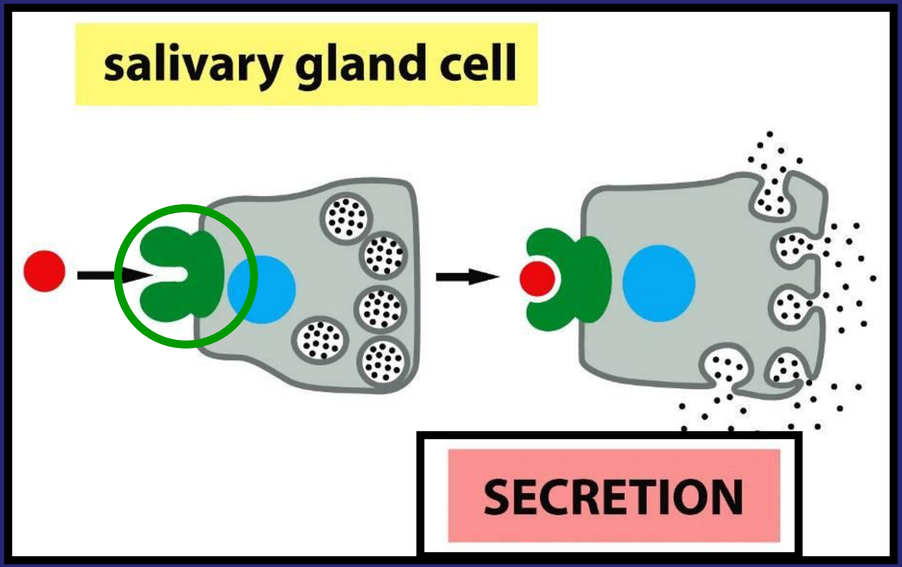




Different receptors = different action of the similar cells

Different cell types





Different cells

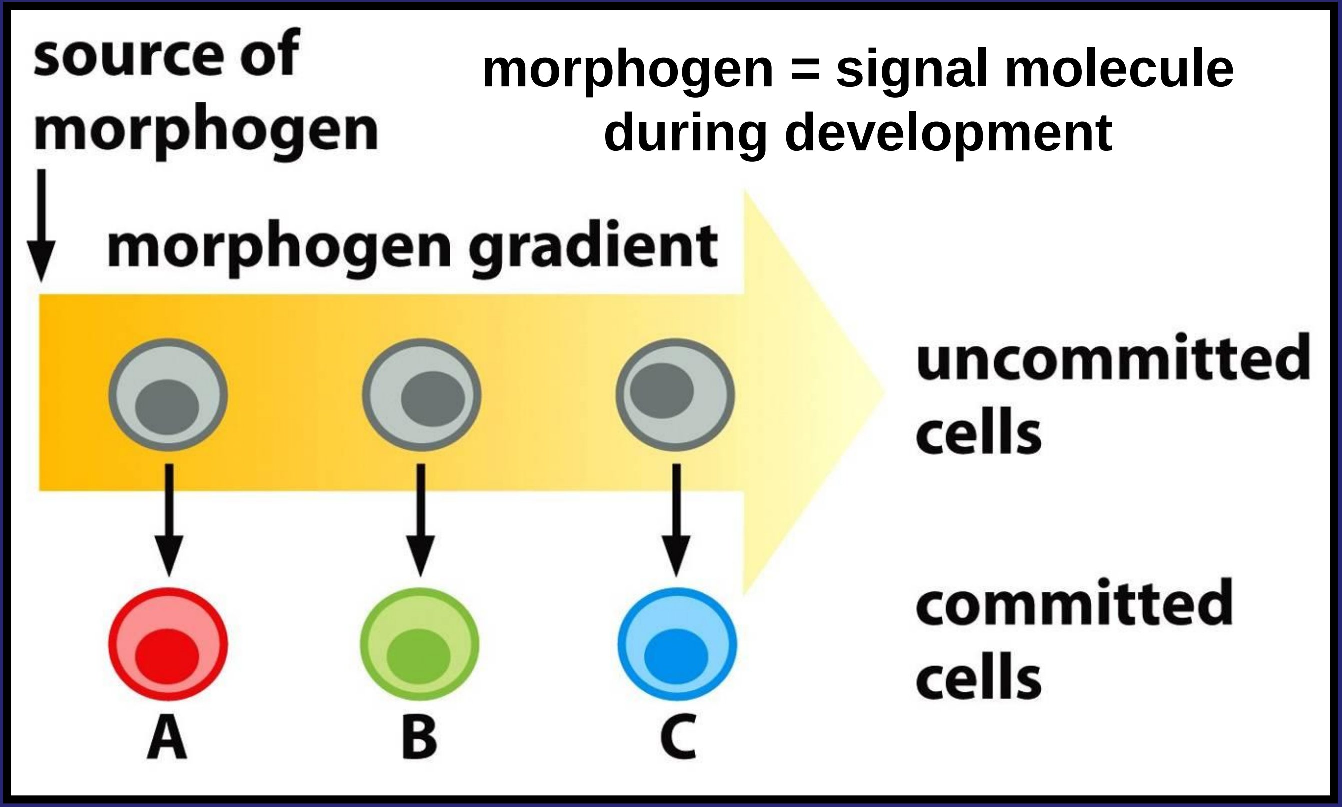
The same receptors

Different action

- **signals are interpreted differently in different cells**

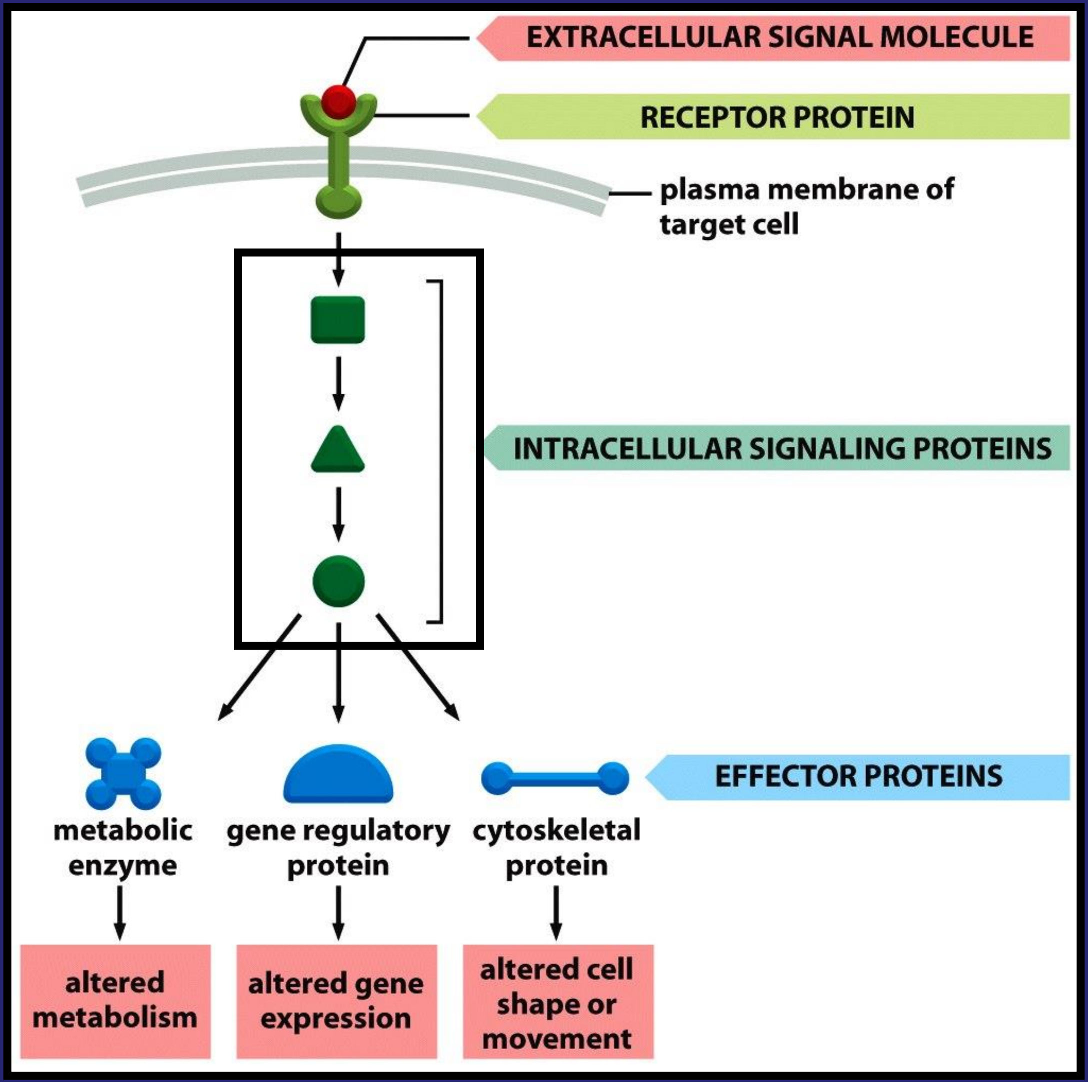
Morphogen gradients

The same signal acting on the same cell type can have quantitatively different effects depending on the signal's concentration



expression of different sets of genes

Activation of intracellular proteins



Nitric oxide

Steroid hormones

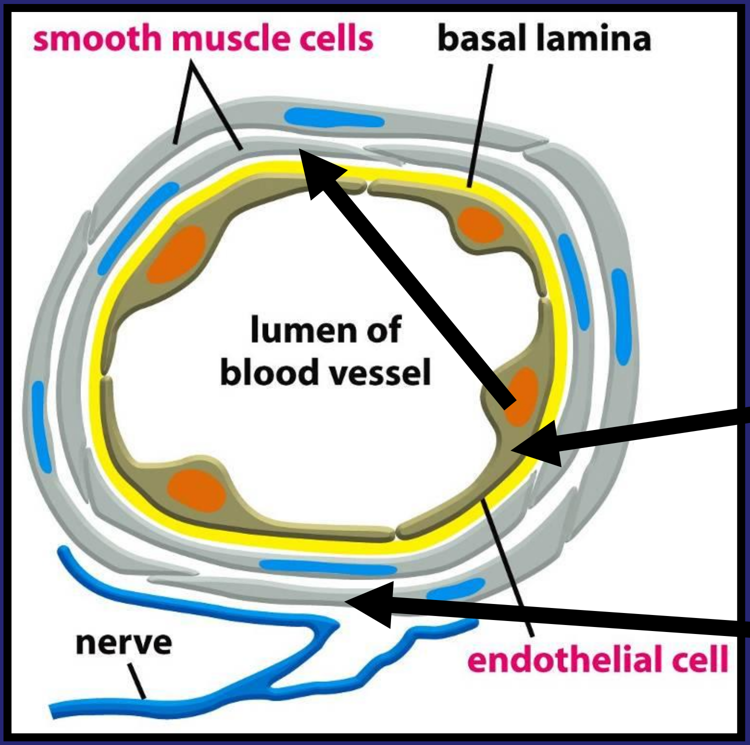
Nitric oxide

One of the important signal molecules that activate intracellular receptors

- **is able to pass readily across the target cell´s plasma membrane**
- **acts as a signal molecule in both animals and plants**
- **one of many functions is muscle relaxation**

Nitric oxide role in muscle relax

Blood vessel with autonomous nerve



the vessel dilate

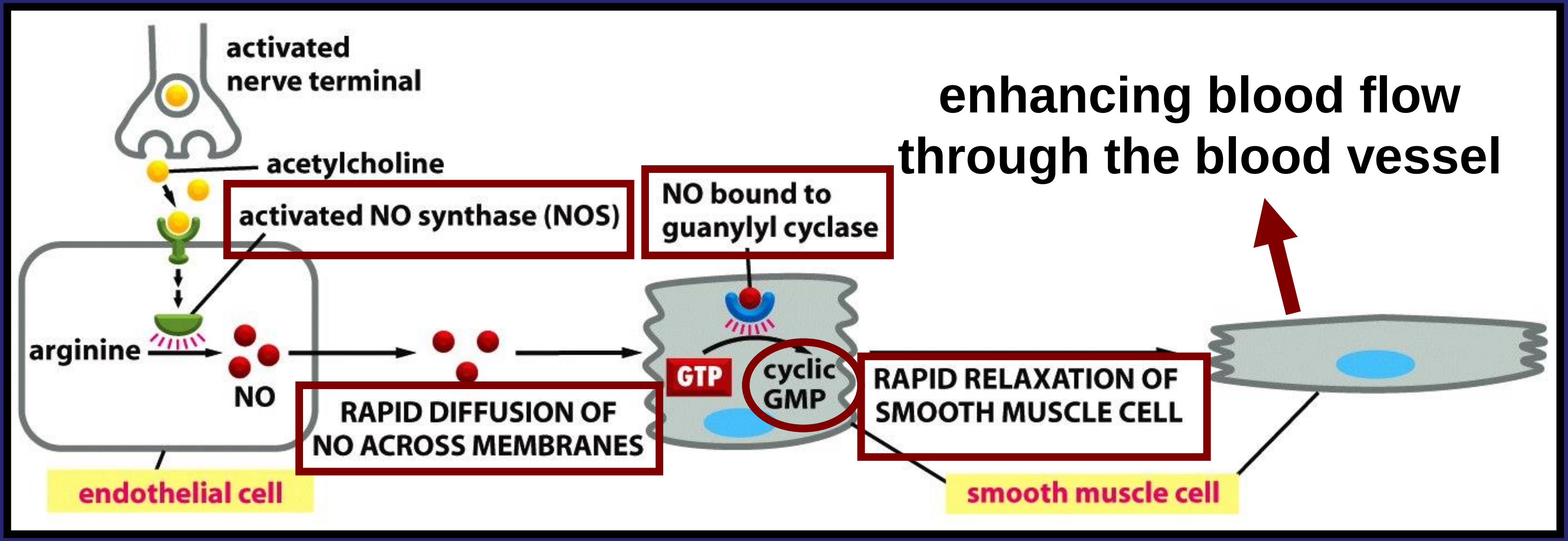
smooth muscle relax in the wall

endothelia release NO

acetylcholine acts on the endothelium

the nerve release acetylcholine

Nitric oxide role mechanism



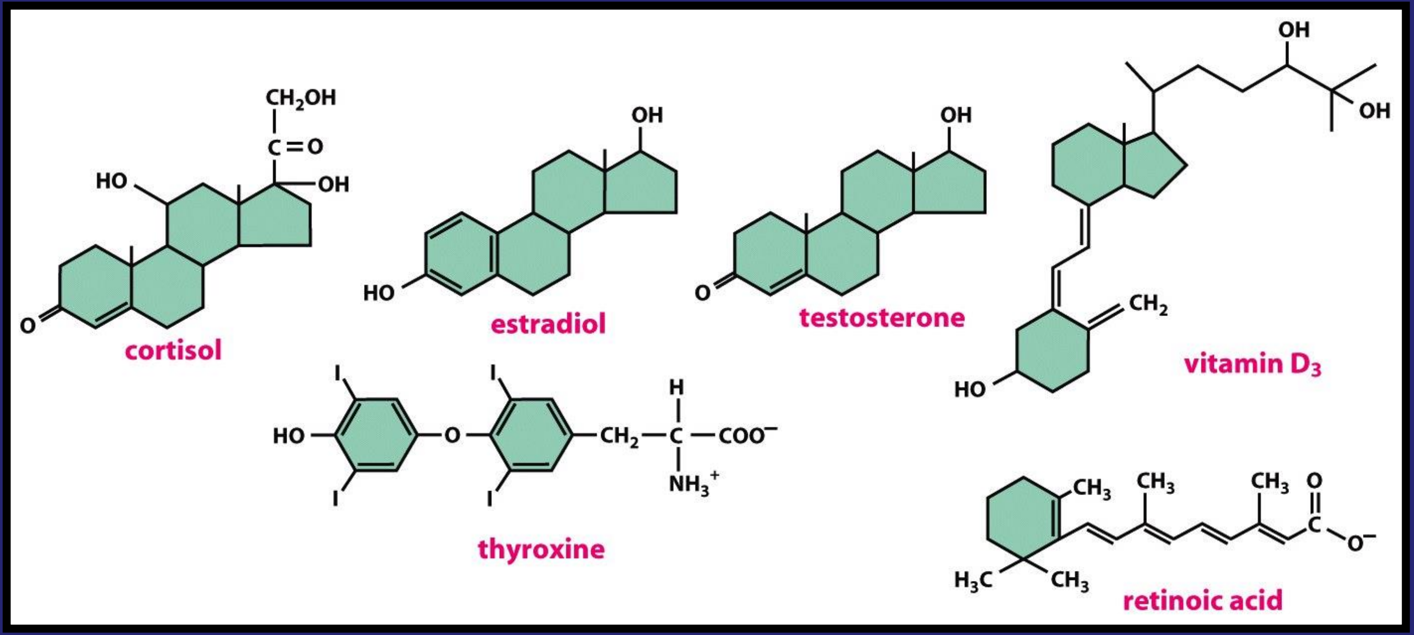
- released acetylcholine activates NO synthase in endothelial cells
- NO diffuses into neighbouring smooth muscle cells
- NO binds and activates guanylyl cyclase to produce cGMP
- cGMP triggers a response that cause relax

Hydrophobic signal molecules

Diffuse directly across the plasma membrane and bind to gene regulatory proteins

- **Steroid hormones**
- **Thyroid hormones**
- **Retinoids**
- **Vitamin D**

Examples



- different structures
- act by similar mechanism
- bind to their respective intracellular receptor proteins and alter ability of these proteins <u>to control the transcription of specific genes</u>

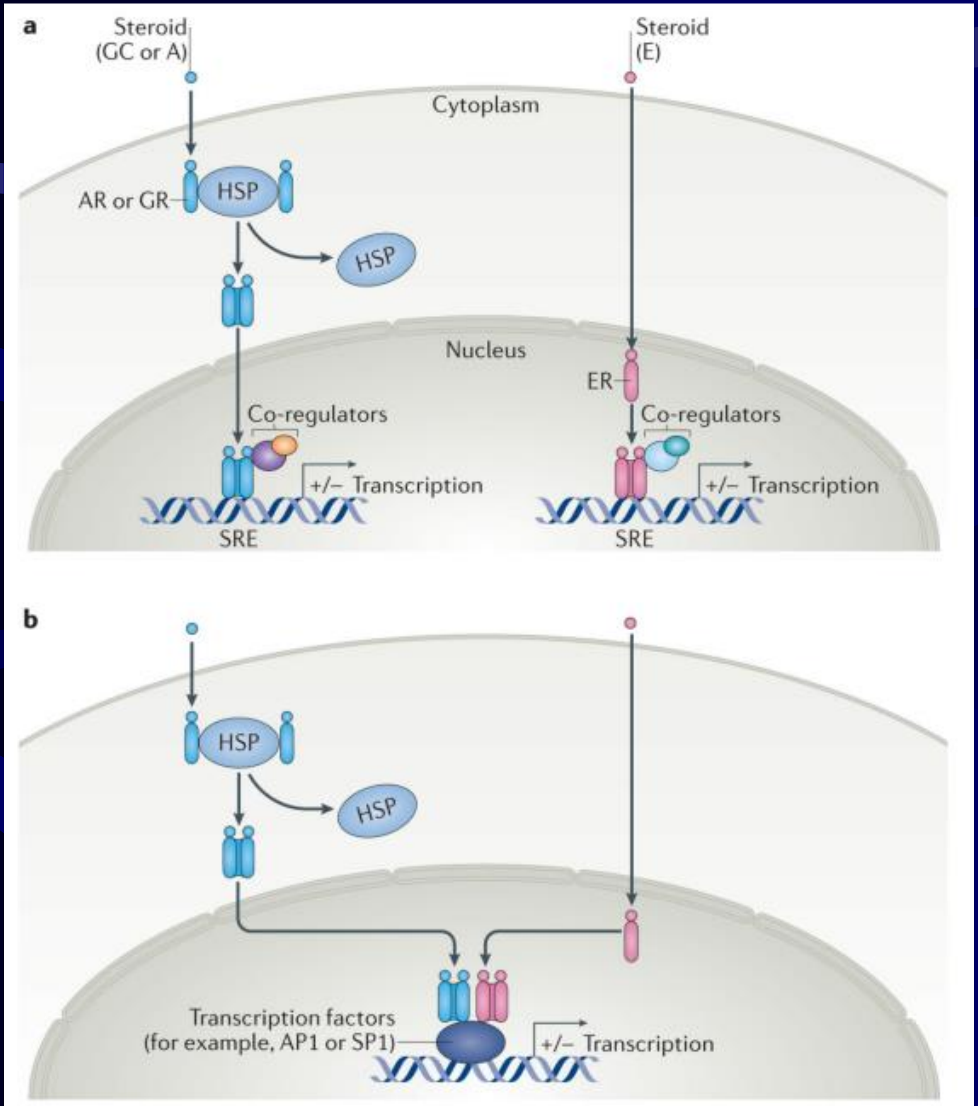
Intracellular receptors and effectors

Above mentioned proteins serve both as intracellular receptors and as intracellular effectors of the signal

They are structurally related, being part of the very large nuclear receptor family

All nuclear receptors bind to DNA as either homodimers or heterodimers

Intracellular receptors and effectors



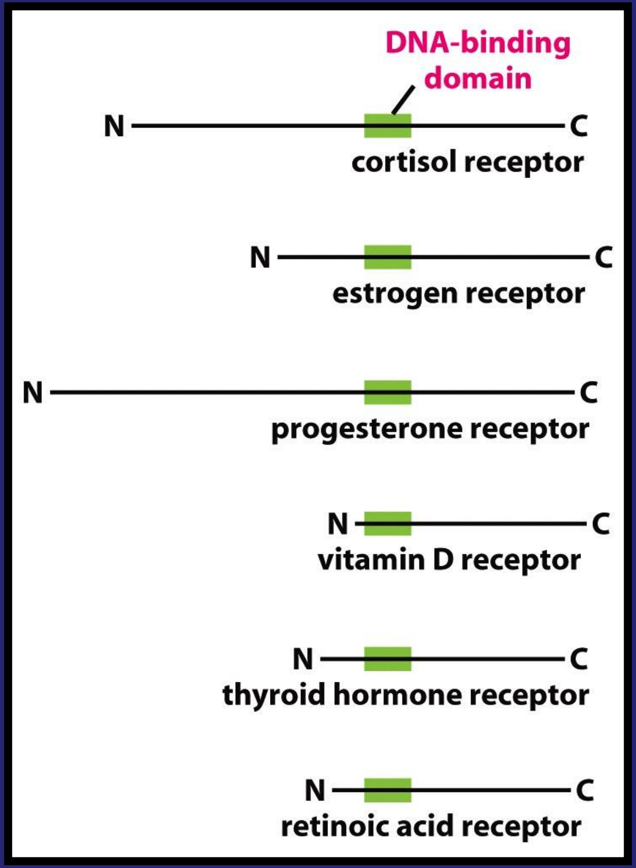
https://doi.org/10.1038/nrm.2016.122

Figure 1. Nuclear steroid signalling

a | Classic steroid sinalling pathway. Steroids enter cells through mechanisms that are still not understood. Some steroid receptors, such as glucocorticoid (GC) and androgen (A) receptors (GR and AR, respectively), are primarily in the cytoplasm as monomers bound to heat shock proteins (HSPs). Others, such as the oestrogen (E) receptor (ER), are located as monomers primarily in the nucleus, although a small percentage may also be bound to HSPs in the cytoplasm (not shown). In the case of GC and A, steroid binding to cytoplasmic receptors triggers release from the HSPs, receptor dimerization, alterations in receptor conformation and nuclear localization. In the case of E, the sex steroid binds to nuclear receptors to promote dimerization and changes in receptor conformation. In all cases, nuclear dimerized receptors then bind to specific steroid-response elements (SREs) and interact with various co-regulators to modulate gene transcription through either repression or activation. **b** | Tethered steroid signalling. Nuclear steroid receptors can also modulate gene expression without direct DNA binding. In this case, they bind to other transcription factors, such as AP1 or SP1, to either repress or activate transcription.

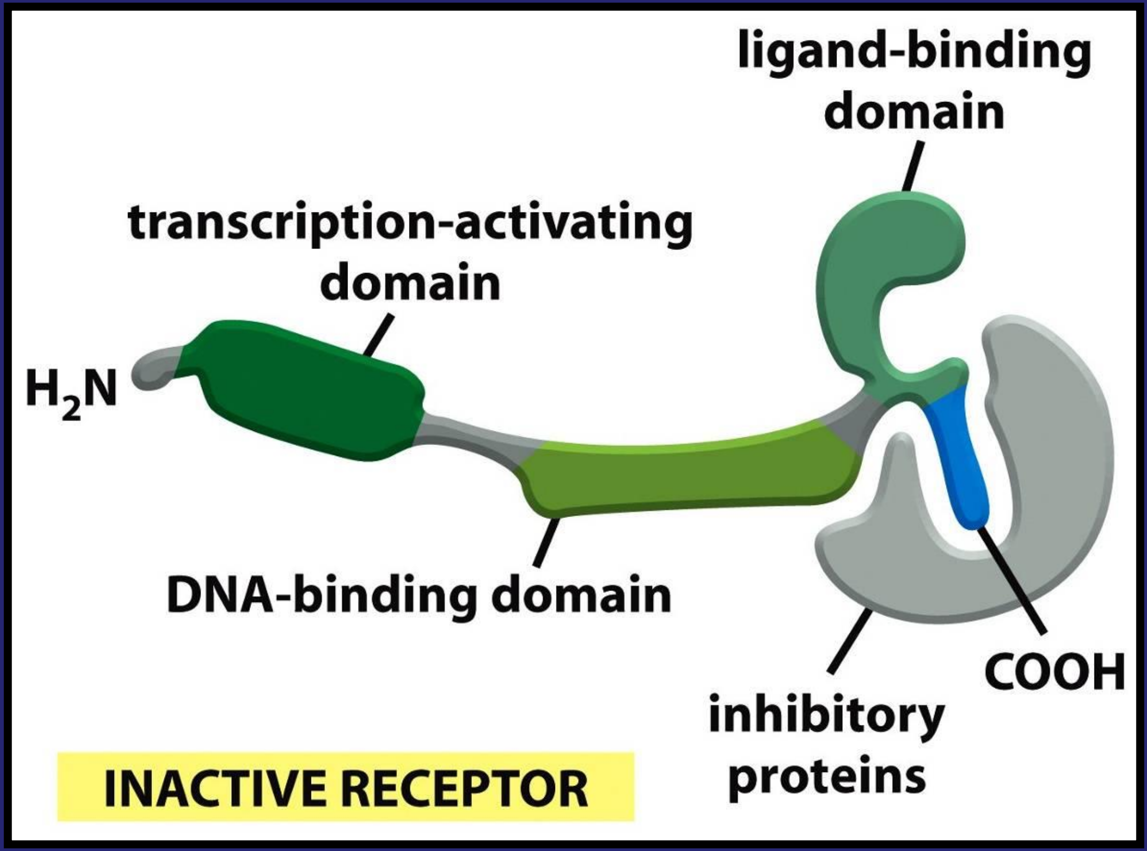
DNA-binding domains

All have a related structure



Inactive receptor

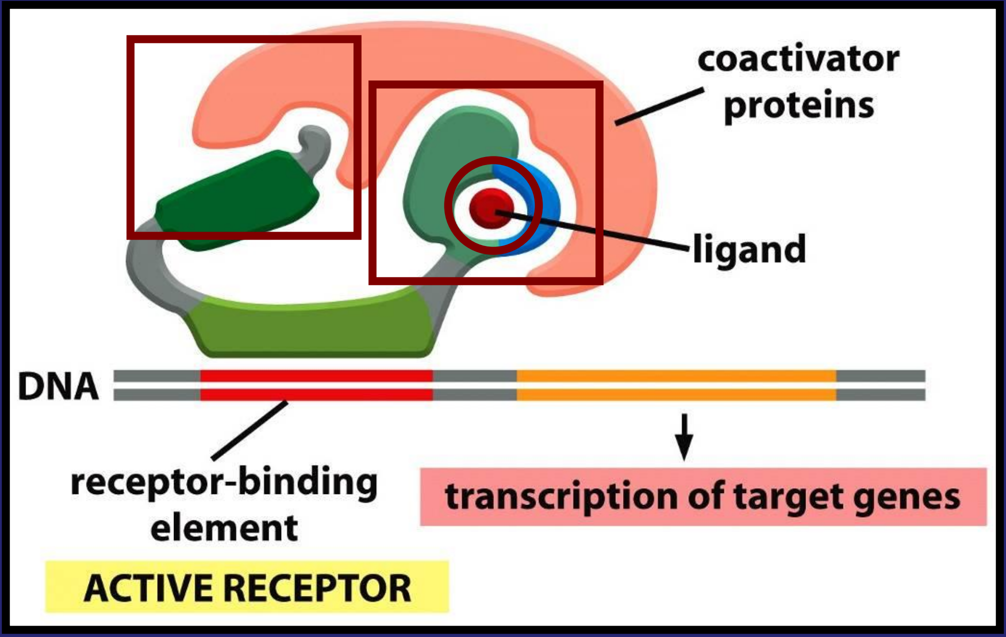
Inactive receptor protein is bound to inhibitory proteins



Active receptor

Binding of ligand to the receptor causes

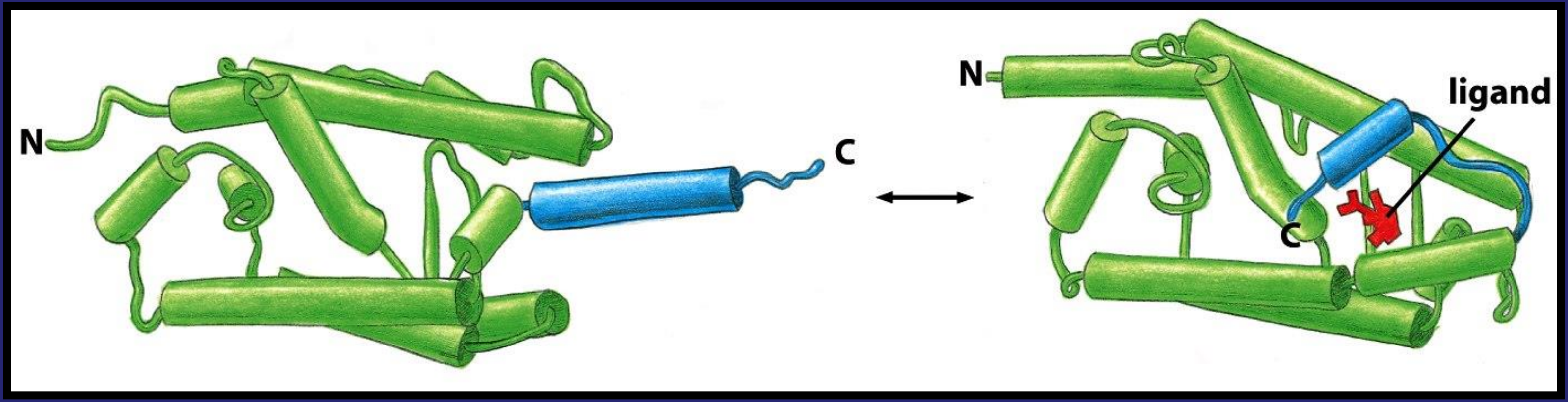
- **the ligand-binding domain of the receptor to clamp shut around the ligand**
- **the inhibitory proteins to dissociate, and**
- **coactivator proteins to bind to the receptor's transcription activating domain = gene expression**



The three-dimensional structure …

… of a ligand-binding domain with and without ligand bound

Blue alpha helix acts as a lid that snaps shut when the ligand (red) binds, trapping the ligand in place

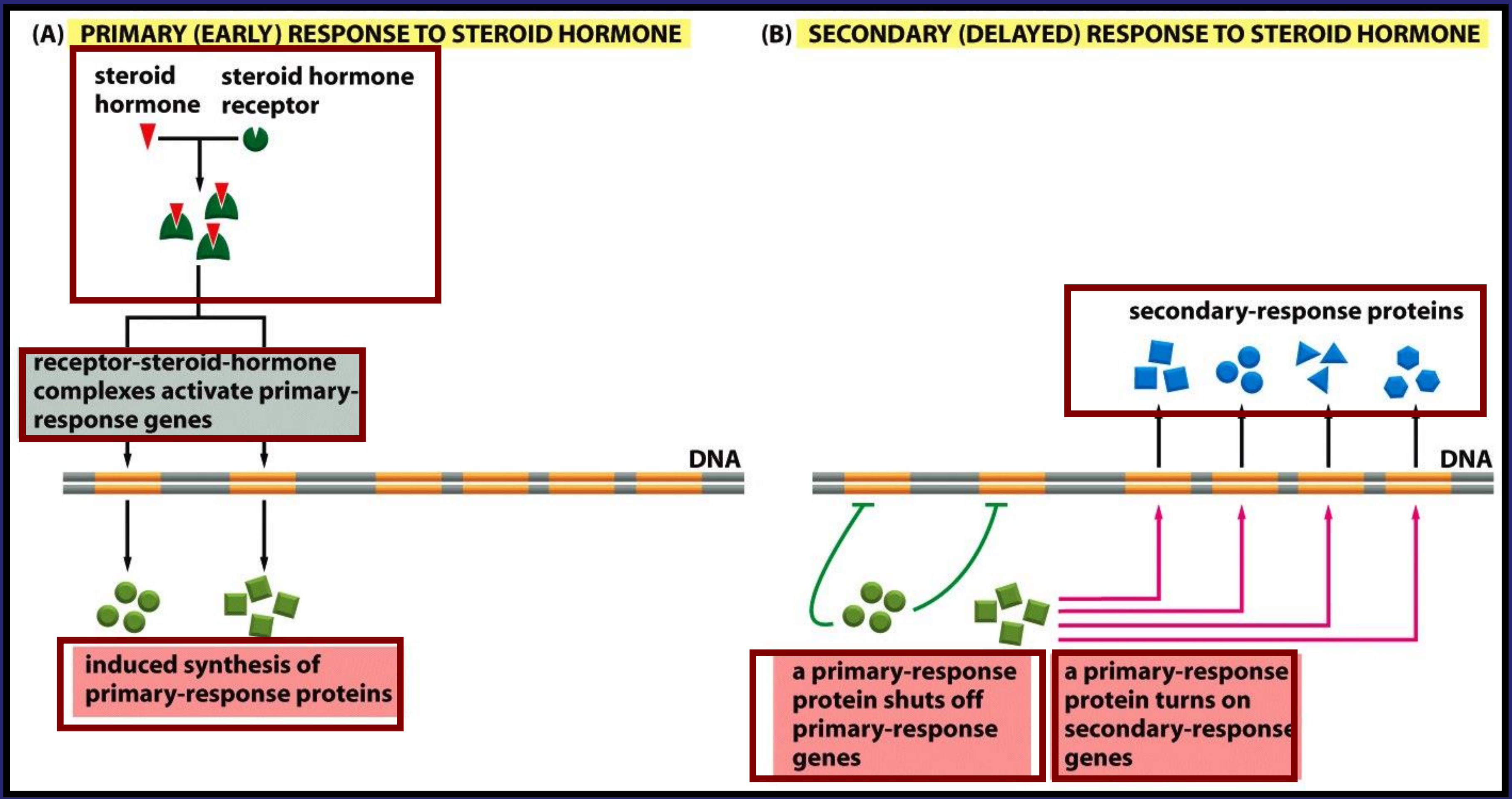


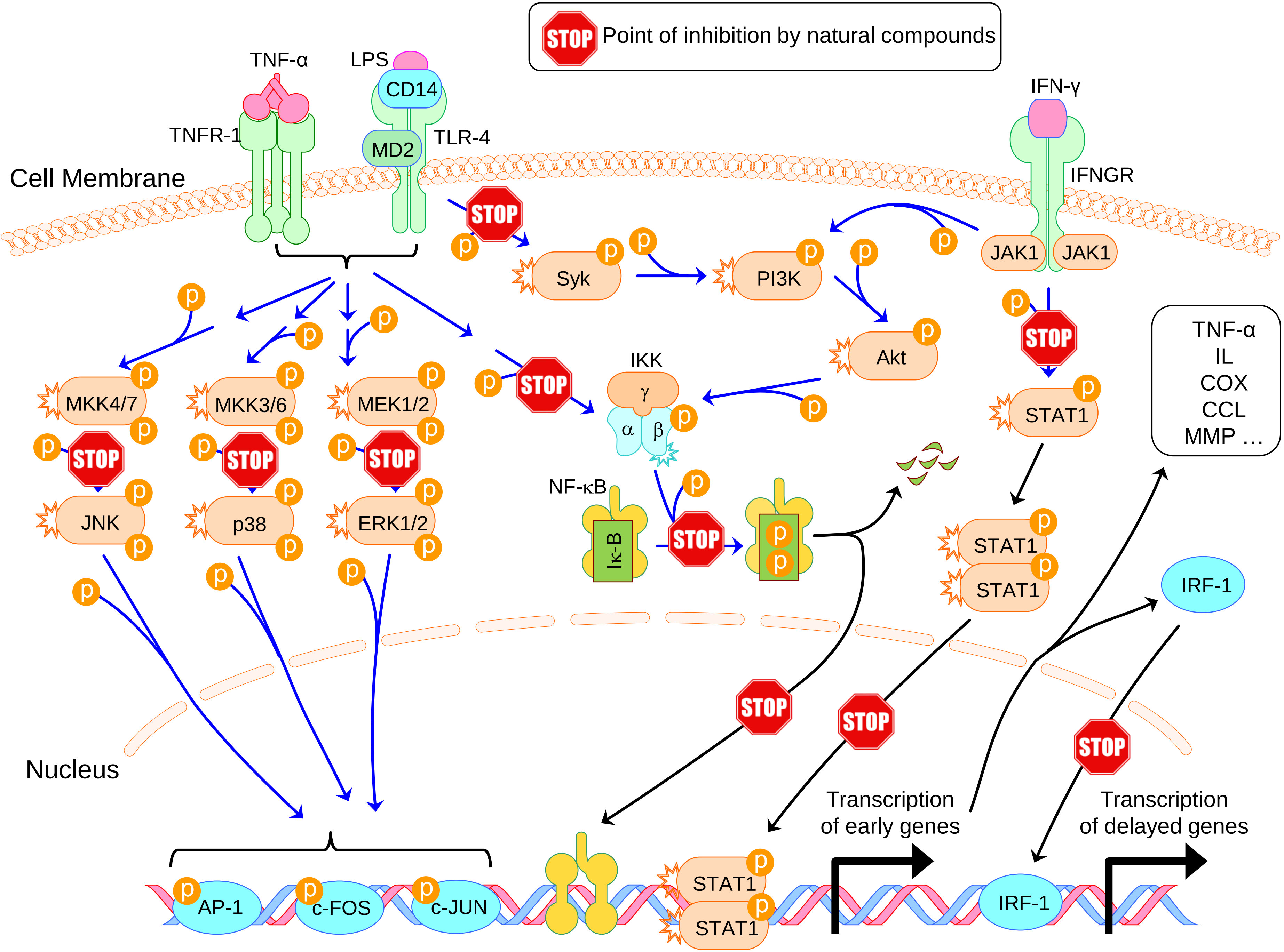
Responses to the steroid hormones

- **The transcriptional response usually takes place in multiple steps**
- **In the cases in which ligand binding activates transcription, for example, the direct stimulation of a small number of specific genes occurs within about 30 minutes = <u>the primary response</u>**
- **The protein products of these genes turn in activate other genes to produces delayed, <u>secondary response</u>**

- **In addition, some of the proteins produced in the primary response may act back to inhibit the transcription of primary response genes = <u>negative feedback</u>**

Primary and secondary response





Point of inhibition by natural compounds
STOP
TNF-α
LPS
CD14
TNFR-1
TLR-4
MD2
IFN-γ
IFNGR
Cell Membrane
Syk
PI3K
Akt
JAK1
JAK1
IKK
γ
α
β
NF-κB
Iκ-B
MKK4/7
MKK3/6
MEK1/2
JNK
p38
ERK1/2
STAT1
STAT1
STAT1
TNF-α
IL
COX
CCL
MMP …
IRF-1
Nucleus
Transcription of early genes
Transcription of delayed genes
AP-1
c-FOS
c-JUN
STAT1
STAT1
IRF-1
p

The three largest classes of cell-surface receptor proteins

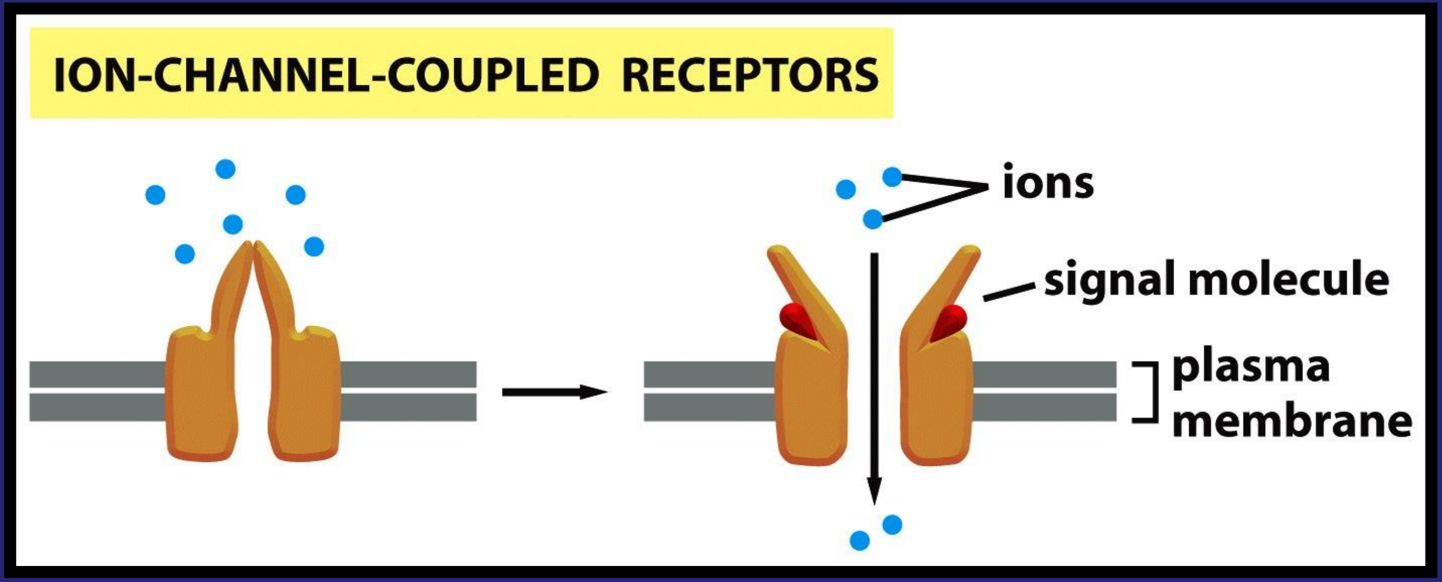
Ion-channel-coupled

G-protein-coupled

Enzyme-coupled

Ion-channel-coupled receptors

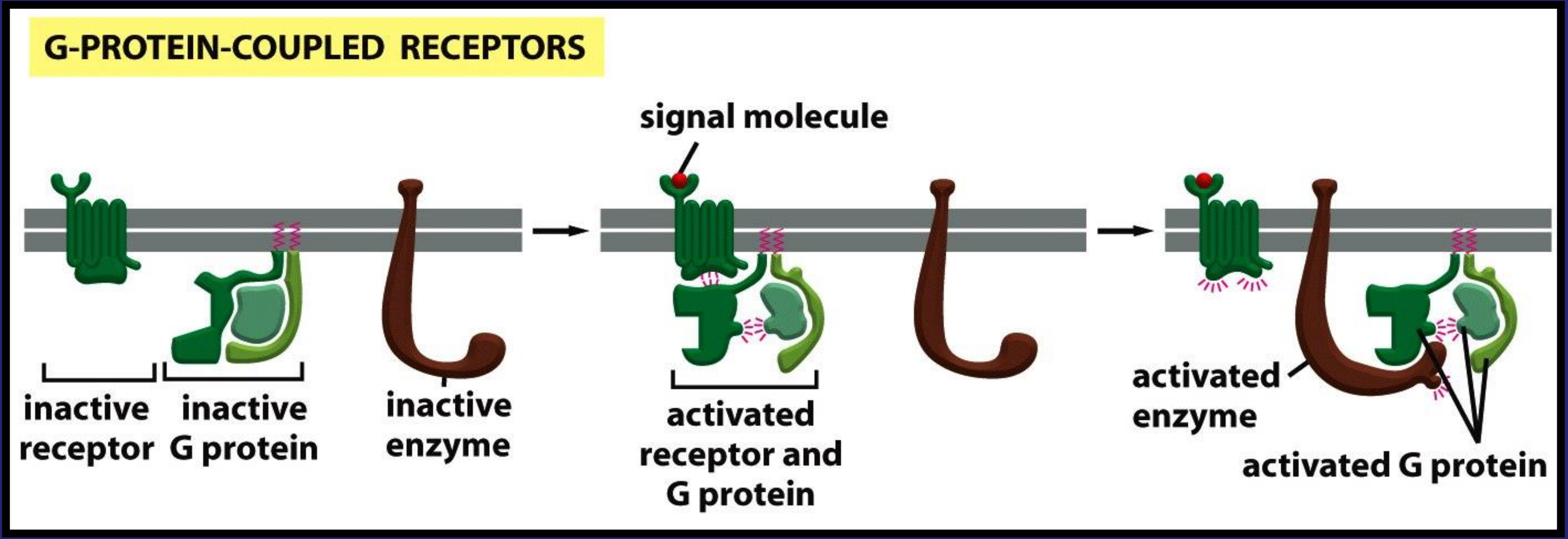
Allow <u>rapid synaptic signalling</u> between nerve cells and other electrically excitable target cells (nerve, muscle)



- **mediated by a small number of <u>neurotransmitters</u> that transiently open or close an ion channel formed by protein to which they bind, briefly changing the ion permeability**

G-protein-coupled receptors

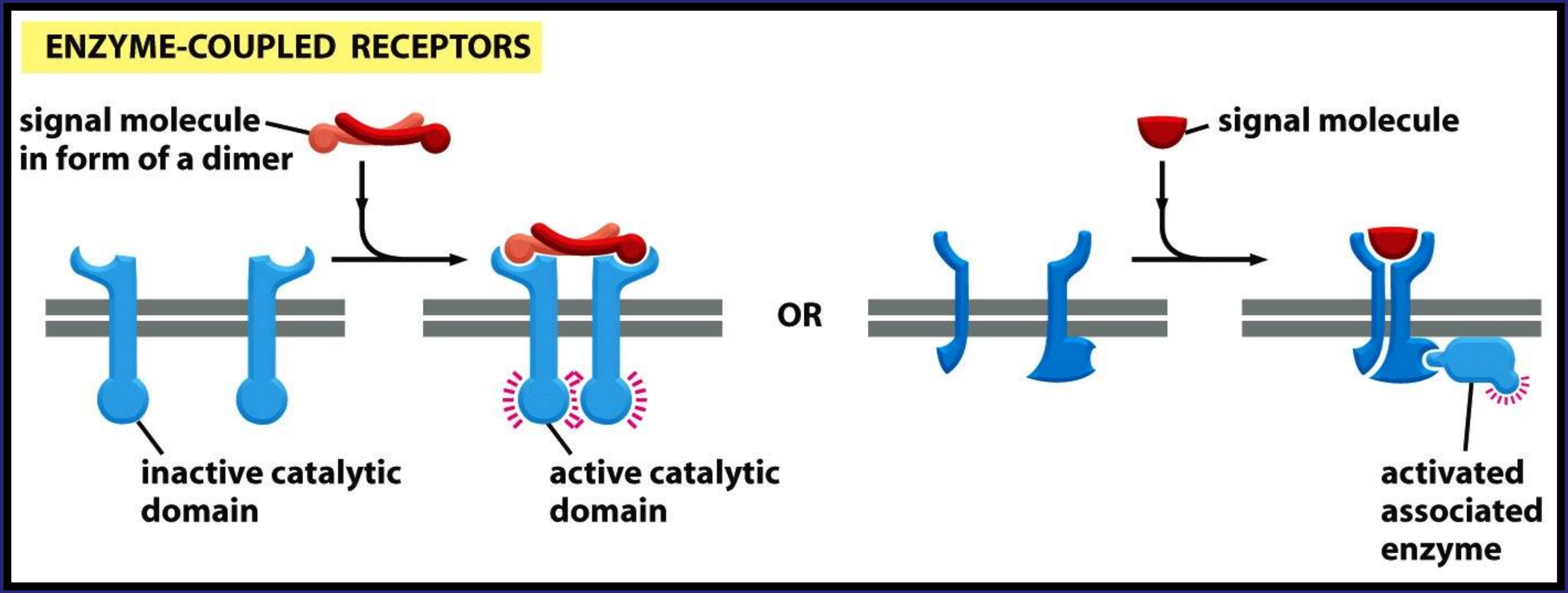
Act by indirect regulating the activity of a separate plasma-membrane-bond target protein (enzyme or channel)



- a trimeric GTP-binding protein (G protein) mediates interaction between <u>the activated receptor</u> and <u>this target protein</u>
- the activation change concentration of intracellular mediators or ion permeability

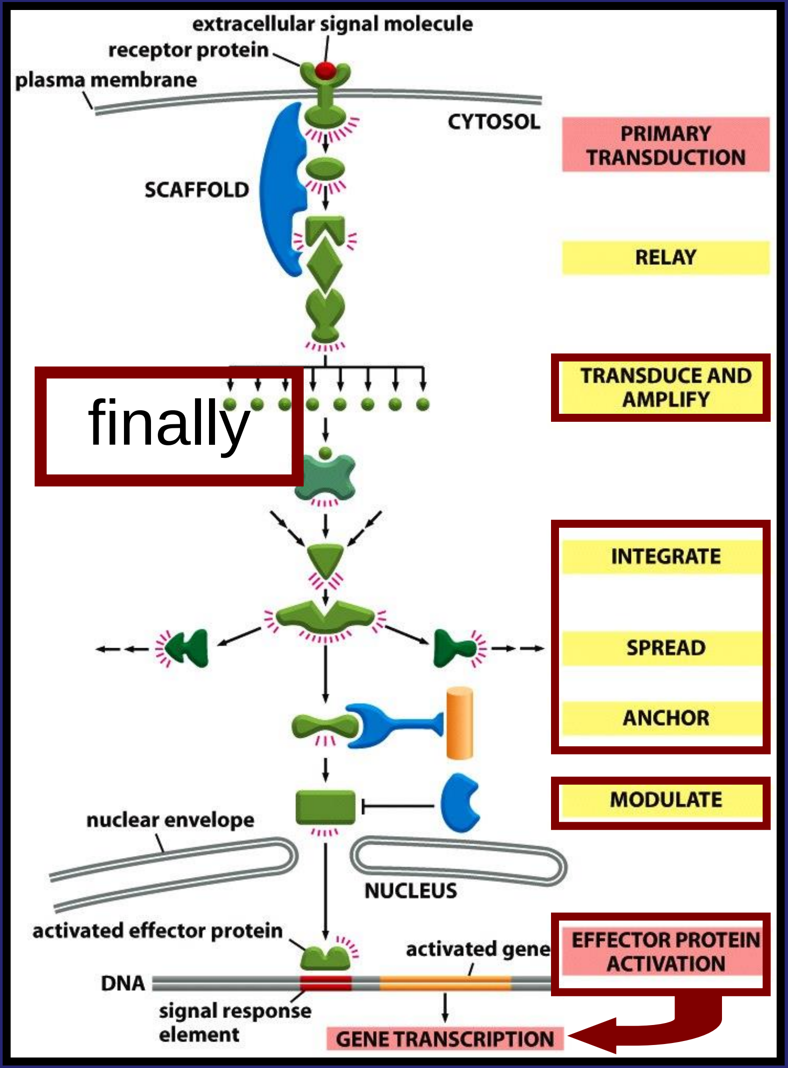
Enzyme-coupled receptors

Either function directly as enzymes or associate with enzymes that they activate



- usually single-pass transmembrane proteins that have their ligand-binding site outside the cell and their catalytic or enzyme-binding site inside
- they are either protein kinase or associated with them

Intracellular signaling pathway



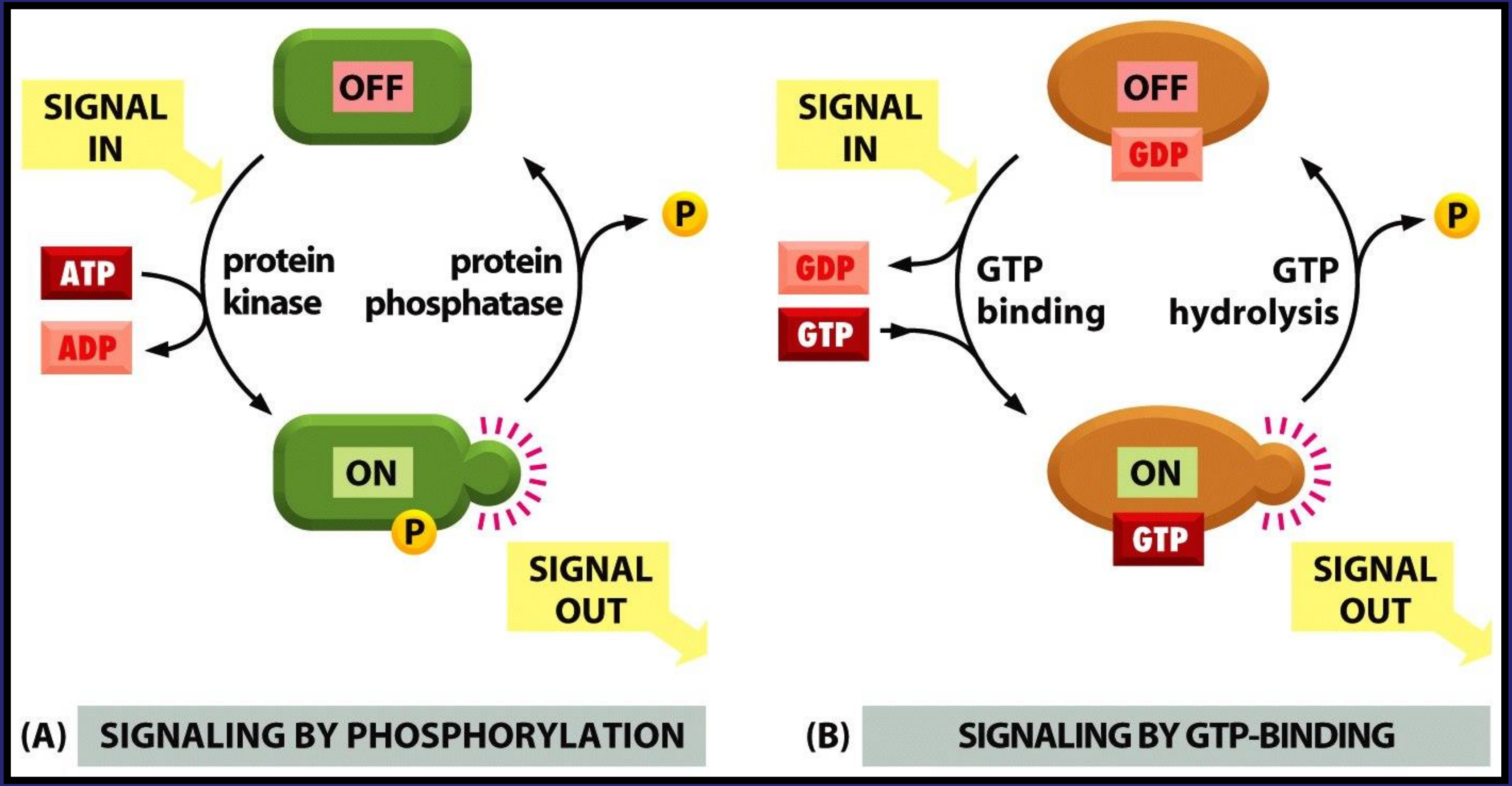
- a series of signaling proteins and small intracellular mediators relay the extracellular signal into the nucleus

The signal is

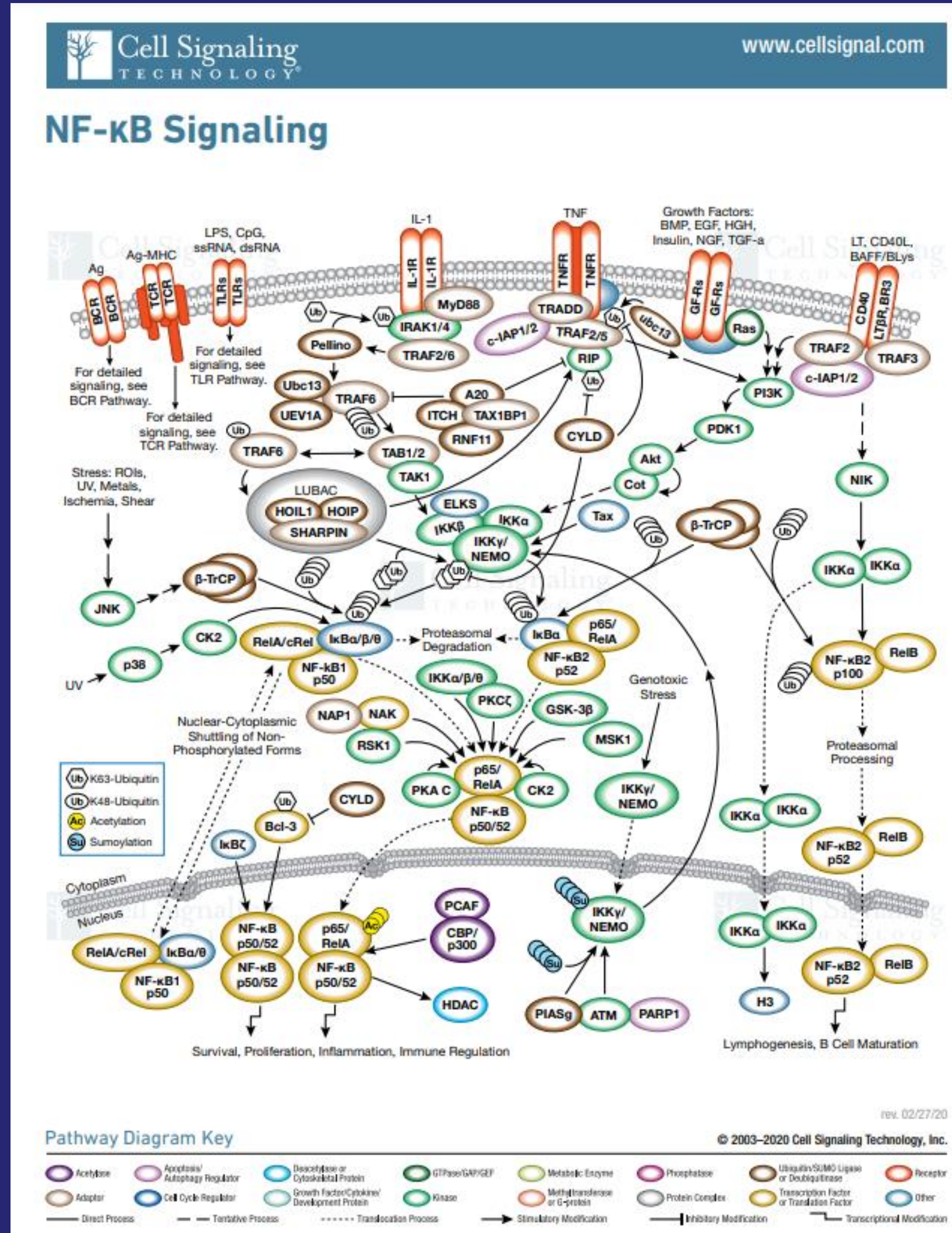
- altered (transduced)
- amplified
- distributed
- modulated

The final effect of one signal depends on multiple factors

Two types of intracellular signaling proteins



Intracellular signalling net – NF-κB example



Cell signalling feedback

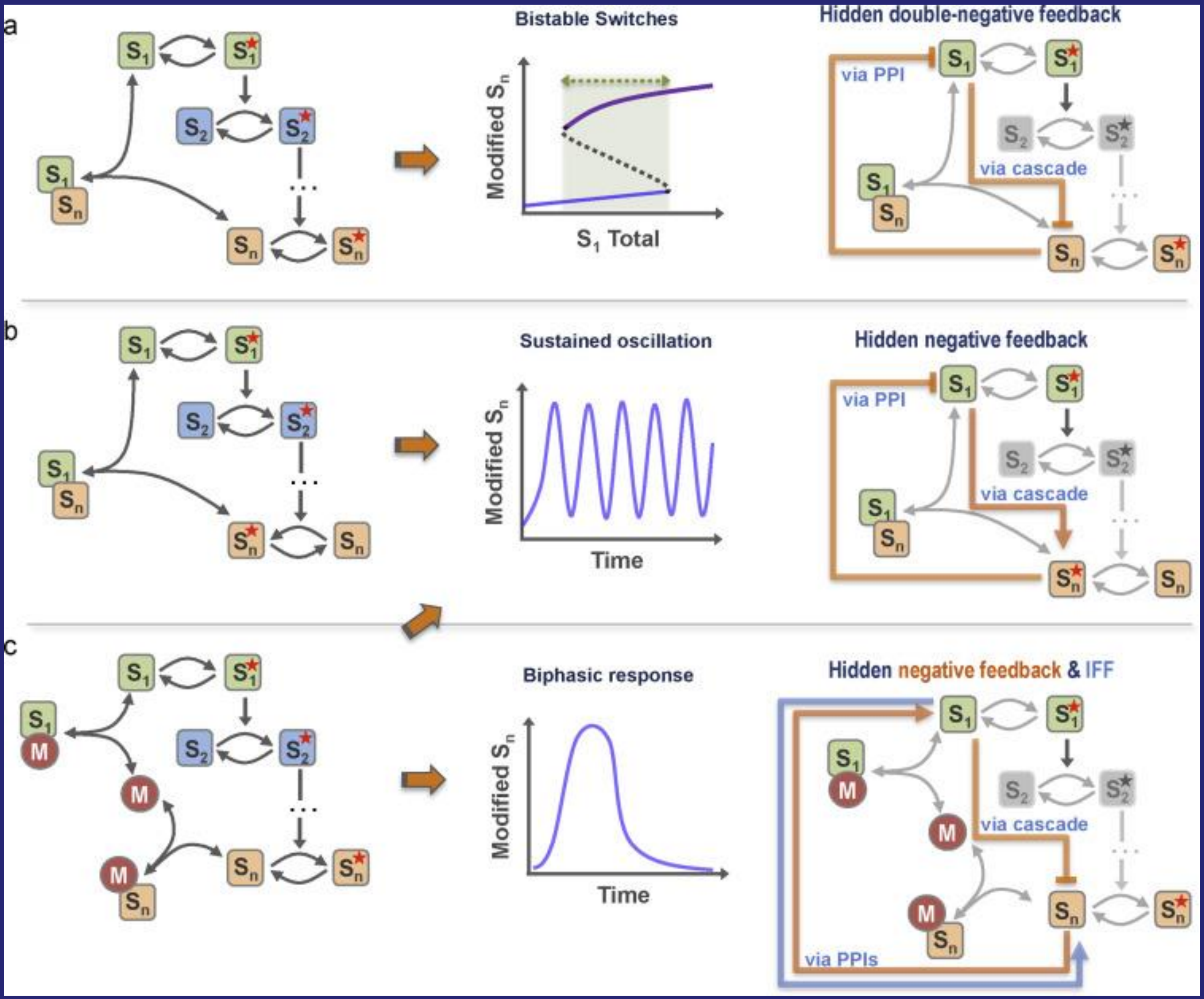


Fig. 2. PPIs generate hidden feedback/feed-forward loops and complex behaviours. (a) A single PPI linking unmodified components belonging to different layers of a cascade could induce bistable switches (modified moieties are denoted with a star, hereafter), caused by a hidden double-negative feedback illustrated in the right panel. (b) A PPI linking unmodified/modified cascade components could induce sustained oscillation, triggered by a hidden negative feedback depicted in the right panel. (c) Coupled PPIs motif linking unmodified forms of the cascade components could generate oscillation and biphasic dose-response, brought about by a hidden negative feedback or a incoherent feed-forward (IFF) loop (right panel).

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