Mechanisms by which chemical messengers control cells


Fundamental role of chemical communication

Intercellular communication by chemical signals

1. Synaptic (nerve cells)
   a) Movement of electric charge along the nerve
   b) Release of a neurotransmitter into synaptic cleft
   c) Response of a postsynaptic cell

2. Endocrine
   Endocrine gland
   Target cell
   Target cell

3. Paracrine: diffusion of a chemical signal in interstitial fluid to the neighbour cells
The most important step in inter-cellular communication:
Interaction (binding) of the chemical messenger molecule to a specialised protein, the RECEPTOR.

1. Specialised proteins which recognize signalling molecules and trigger cellular responses

NOT TO BE CONFUSED WITH:

2. Specialised nerve cells (detectors) which sense for example temperature, pressure etc. and participate in various reflexes

What can activation of a receptor lead to?

- Change properties of the cell membrane, such as its permeability to ions, water or its electrical potential
- Change cellular metabolism (for example adrenalin increases the rate at which many cells consume glucose)
- Change in the rate of cell division and differentiation (special “sex steroid hormones” affect numerous cell types in the body to develop male or female appearance)
- Change in the cell’s contractile activity (adrenalin increases the force of contractions of the heart)
Receptors are found:

- Inside the cell (in the cytoplasm or nucleus)
- Cell surface

Intracellular receptors may be located as free-floating proteins in the cytoplasm or nucleus

SYNOPSIS:

Intracellular receptors for signalling molecules which can pass through the membrane:

1. These are special proteins located in the nucleus or cytoplasm.
2. When activated, these receptors bind to DNA and via activation of specific genes lead to production of specific proteins.
3. These proteins change some of the cell’s functions, for example, making it divide or secrete some chemicals or contract stronger etc.
4. Important examples of intracellular receptors (more detail in later lectures): thyroid hormone receptors and steroid hormone receptors.

In addition:

- Nitric oxide – a gaseous signalling molecule, crosses cellular membranes. Has a different intracellular signalling mechanism: its receptor is an enzyme.
Some signalling molecules cannot cross the cell membrane.

Receptors for these signalling molecules are located at the cell membrane.

RECEPTORS of this kind are characteristic of many SMs, for example acetylcholine (used by many nerve cells) or adrenalin (a hormone).

From "The Cell: A molecular Approach" by G. Cooper
3 main types of receptors found on cell membranes:

1. Receptors which themselves are ion channels (ligand-gated ion channels)

Nerve cells, muscle cells - (e.g. EXCITABLE cells which have membrane potential)

The acetylcholine receptor at the skeletal muscle is an ion channel which opens when acetylcholine binds to it.

Membrane potential becomes more positive (depolarisation occurs)
SYNOPSIS:

✓ In the absence of the signalling molecule (in this example acetylcholine) this ion channel is closed
✓ Binding of acetylcholine changes its shape (conformation) so that it can pass numerous sodium ions
✓ Ions moving through the channel change potential of the cell’s membrane (in this example to more positive values)
✓ Change in membrane potential can:
  - trigger cell contraction (in muscle cells)
  - make a nerve cell generate action potentials

3 main types of receptors found on cell membranes:

2. Receptors which are enzymes or are directly bound to enzymes

PROTEIN KINASES

PHOSPHORYLATION
Target protein must have a "consensus sequence" – a particular pattern of amino-acids recognised by the enzyme.

In most cases there are several reactions which follow each other:

1st
2nd

Changes in cell's proteins

Cell response

3 main types of receptors found on cell membranes:

3. Receptors which act via G-proteins
A G-protein-coupled receptor may modulate an ion channel directly via a G-protein

A G-protein-coupled receptor may activate an enzyme (such as adenylyl cyclase)

SYNOPSIS:
Receptors which are coupled via G-proteins (for example adrenalin receptors)

When activated, these receptors make G-proteins fall into two parts which diffuse away from the receptor.

Activated G-proteins bind to other proteins and change their function. This may lead to activation of some enzymes (for example to mobilise glucose from its storage form glycogen) or modulate ion channels (this will change membrane potential).
WHY DO THE CELLS NEED all THESE COMPLICATED SIGNALLING PATHWAYS?

**Principle of amplification**

A single activated receptor triggers production of many second-order messenger molecules which in turn activate numerous effector proteins.

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**SUMMARY**

<table>
<thead>
<tr>
<th>Located intracellularly</th>
<th>Located at cell membrane</th>
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<tbody>
<tr>
<td>Receptors which operate via gene expression</td>
<td>Receptors which themselves are ion channels (&quot;A&quot;)</td>
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<tr>
<td></td>
<td>Receptors which act as enzymes (for example, the insulin receptor), (&quot;B &amp; C&quot;)</td>
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<tr>
<td></td>
<td>Receptors which are coupled via G-proteins (for example adrenalin receptors) (&quot;D&quot;)</td>
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</table>
Features of binding (1): specificity

Specificity of receptors is not absolute.

Acetylcholine (ACh)

\[ \text{HO-CH}_2\text{CH}_2\text{N-CH}_3 \]

Noradrenaline (NA)

\[ \text{HO-CH}_2\text{CH}_2\text{N-H} \]

Features of binding (2): saturation

Saturation means that the maximal effect of any SM will be limited by the number of available receptors.

Features of binding (3): competitive nature

If several molecules can bind to the same receptor, they will compete and try to displace each other. This principle underlies the mechanism of action of many drugs which interfere with SMs of the body and prevent SMs from interacting with their receptors.
### Signalling Molecule (SM)

<table>
<thead>
<tr>
<th>What it may be called</th>
<th>&quot;Flavour&quot; of the term</th>
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<tbody>
<tr>
<td>Ligand</td>
<td>Signifies the ability of the SM to physically bind (&quot;stick&quot;) to the receptor</td>
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<tr>
<td>Agonist (of a particular receptor)</td>
<td>Signifies the ability of SM to activate the receptor</td>
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<tr>
<td>Transmitter, neurotransmitter</td>
<td>Usually applied to the SMs released by nerve cells in synapses</td>
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<tr>
<td>Hormone</td>
<td>SM which is released from cells remote from the target and travels with blood</td>
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#### The key points:

1. Fundamentally, cells communicate using CHEMICAL MESSENGERS.
2. Ways of inter-cellular communication: paracrine, synaptic and endocrine.
3. Chemical messengers bind to specialised proteins, the RECEPTORS.
4. Receptors are found: a) In the cytoplasm of the cell b) On the cell surface.
5. Intracellular receptors usually work via a change in gene expression.
6. Cell membrane receptors come in 3 flavours:
   a) Receptor- ion channels (ACh receptors in skeletal muscle)
   b) Receptor-enzymes which usually phosphorylate other proteins (insulin receptor)
   c) Receptors which are coupled to G-proteins (adrenaline receptors)
7. Receptors-enzymes and GPCRs amplify the initial signal using second- and third order intermediates.

END