# Medicine and Surgery

**A.Y. 2025/2026 - Programme Code: 6734**

**84284-Signaling pathways in health and disease I.C.**

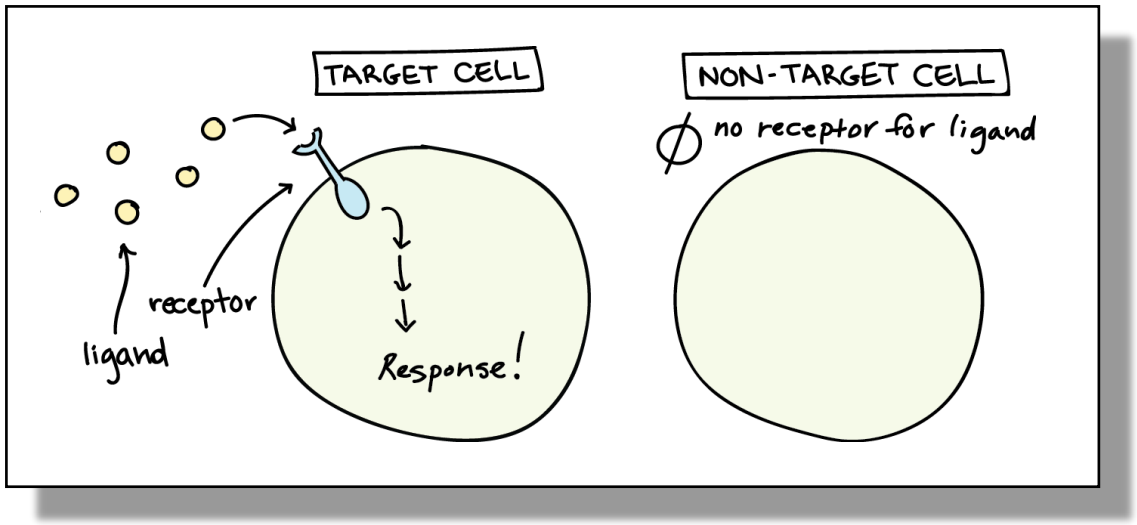
Module A – 84285 **Cell signaling** 4 CFU

## *Lecture A.01*
## *General features of cell signal transduction: physical and chemical signals*

ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

Maria Luisa Genova
Email: marialuisa.genova@unibo.it

March 9, 2026

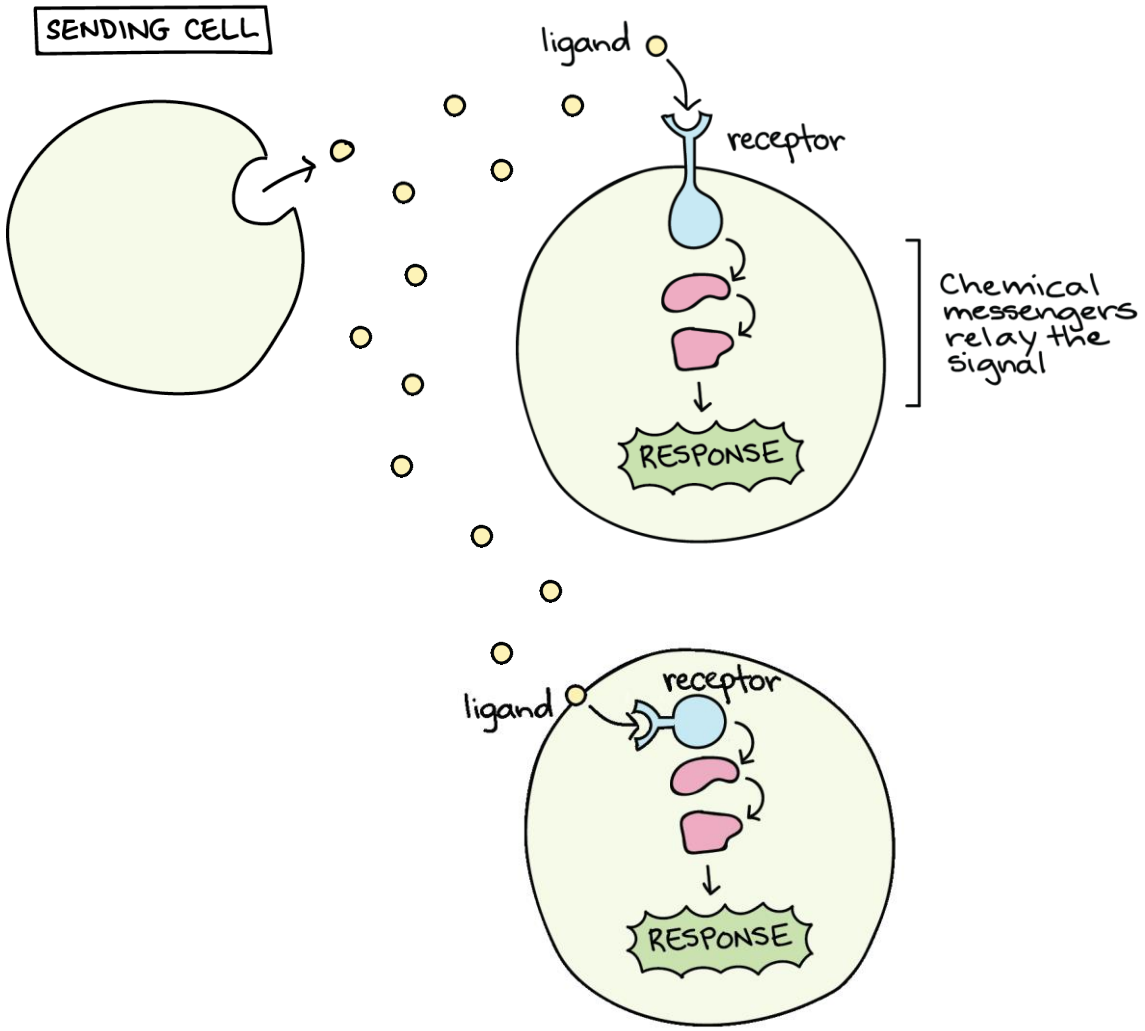



**At any very moment, living cells are sending and receiving millions of messages in the form of physical signals or chemical signaling molecules.**

In order to detect a chemical signal, a cell (**target cell**) must have the right **receptor** for that signal (**ligand**).

When a ligand specifically binds to its receptor, it alters the shape or activity of the receptor, triggering a change (**response**) inside of the cell.
Not all cells can sense a particular chemical message.
Physical signals are generally converted to chemical signals at the level of the receptor (photo-receptors; pressure-sensing channels).

The signals are often relayed through a chain of chemical messengers inside the cell. Ultimately, this phenomenon leads to a change in the cell (e.g. alteration in the activity of a gene/metabolic pathway; the induction of a whole process such as cell division). Thus, the original extra-cellular signal is converted into an intra-cellular signal that triggers a response.




Ligands produced by signaling cells come in many different varieties and interact with receptors either on the outside of target cells or inside.

# Basic categories of chemical signaling in multicellular organisms:

## PARACRINE SIGNALING

Released ligands diffuse through the space between the cells. Cells communicate over relatively short distances (immediate surrounding area) to locally coordinate activities with nearby target cells (e.g. tissue development; synaptic signaling).

## AUTOCRINE SIGNALING

A cell signals to itself, releasing ligands that bind to receptors on its own surface (or to receptors inside of the same cell). In many cases, a signal may have both autocrine and paracrine effects.

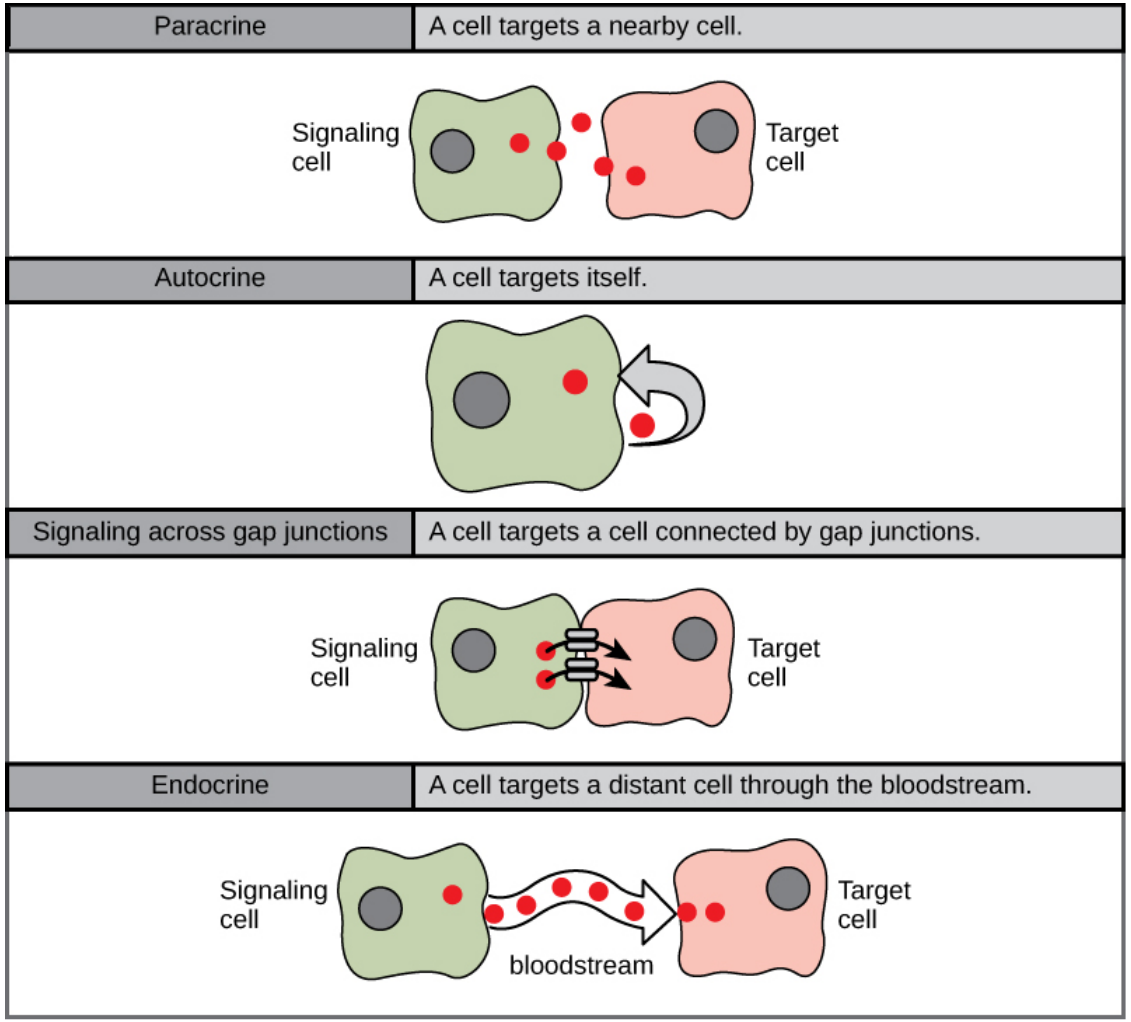
## CELL-CELL CONTACT SIGNALING

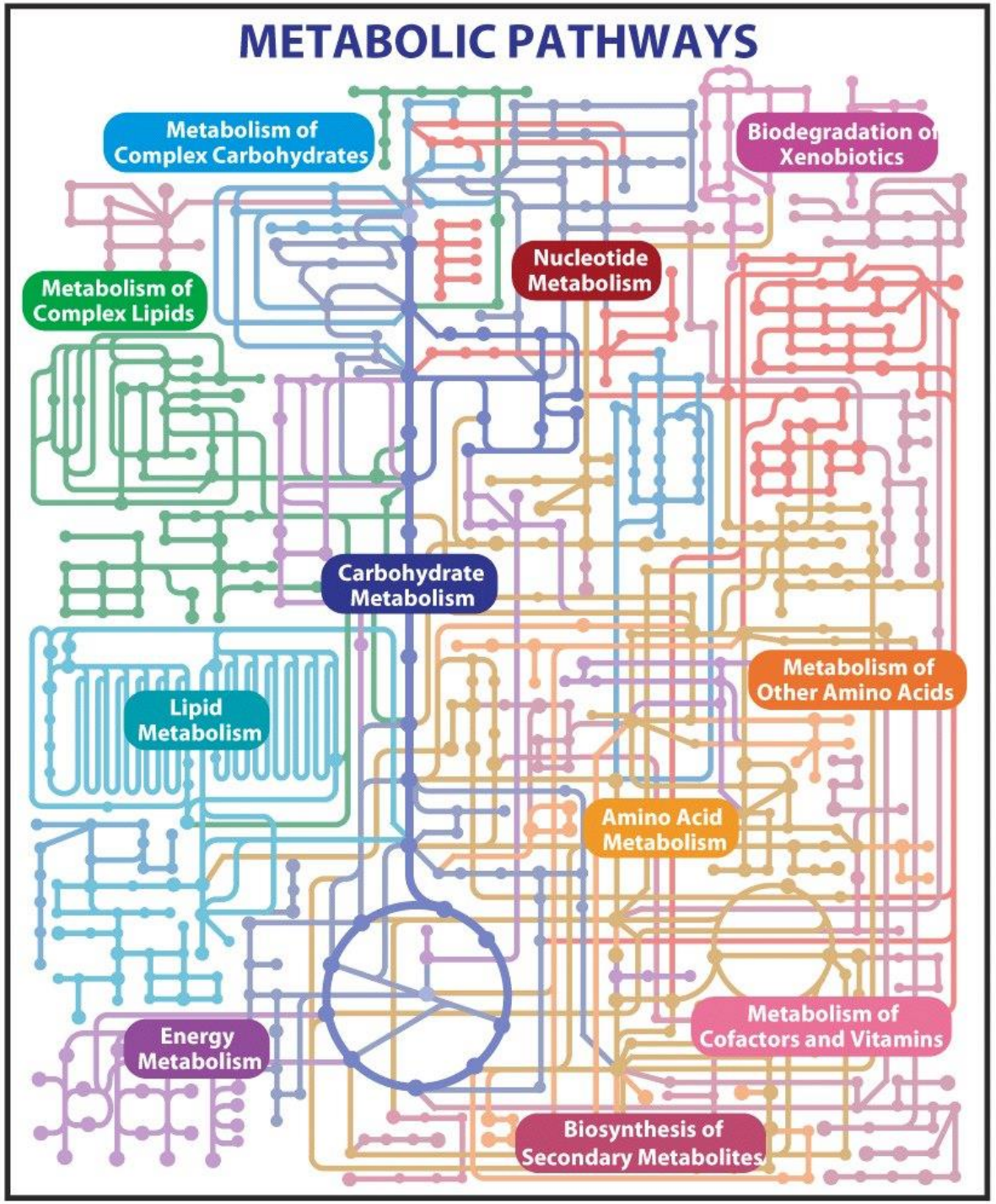
Small signaling molecules (intracellular mediators) diffuse between two neighbouring cells directly connected by water-filled channels (e.g. gap junctions in animals and plasmodesmata in plants). This allows a group of cells to coordinate their response to a signal that only one of them may have received.

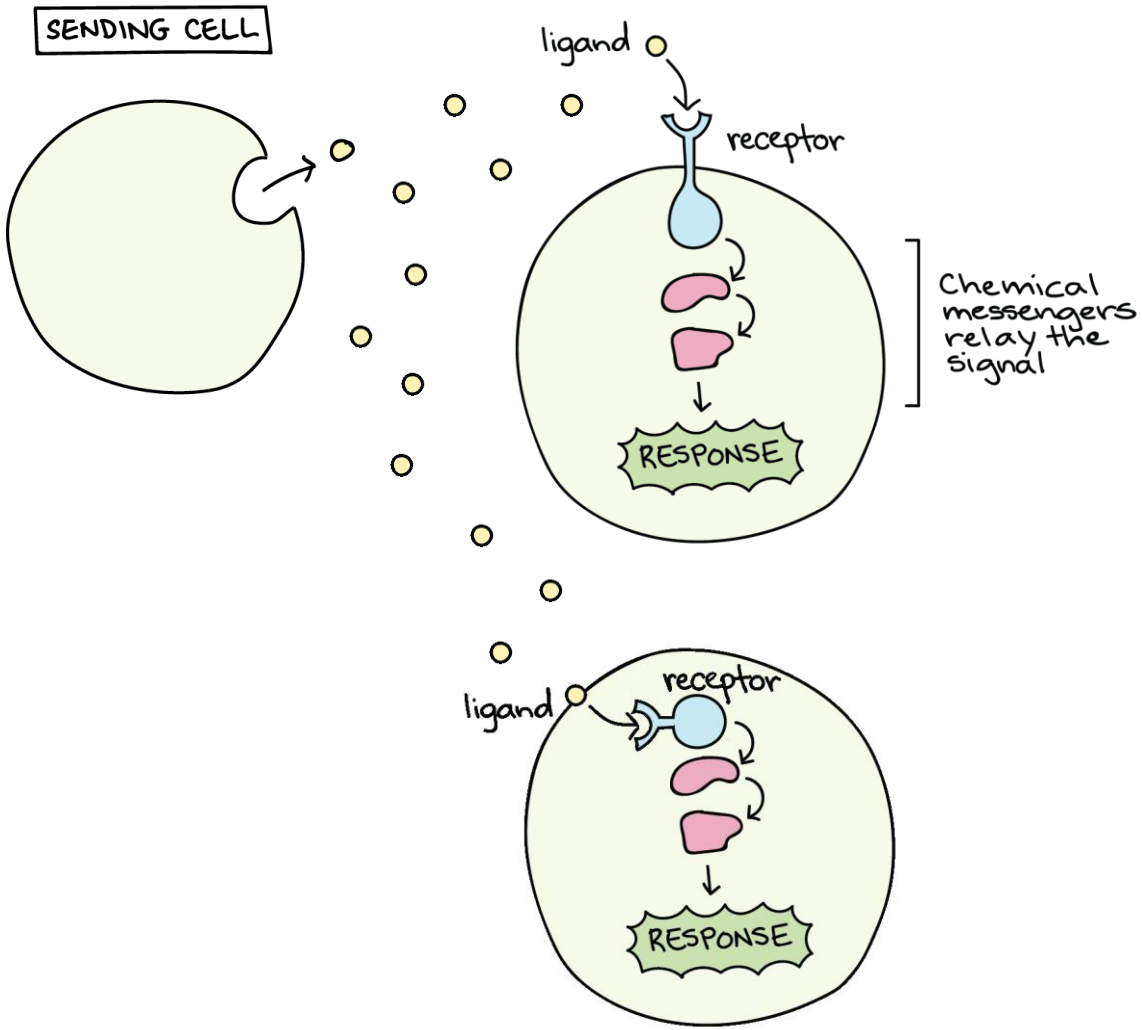
## ENDOCRINE SIGNALING

Signaling molecules produced in one part of the body (in endocrine glands) can affect other body regions some distance away. Ligands (hormones) travel the large distances between endocrine cells and their target cells via the bloodstream (a relatively slow way to move throughout the body). At difference from paracrine signaling, in which local concentrations of ligands can be very high, hormones get diluted because of their form of transport and are present in low concentrations when they act on their target cells.

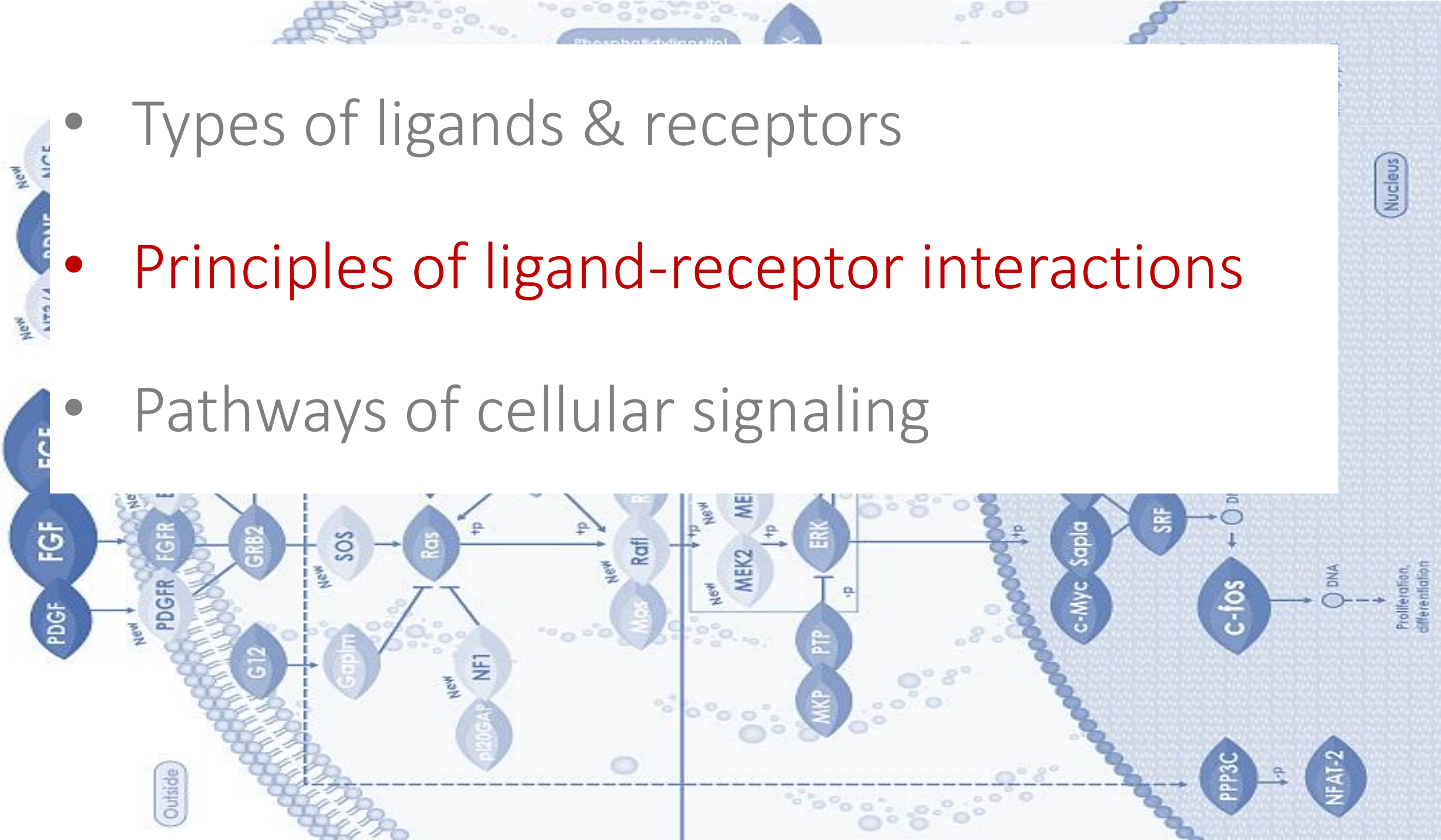
The main difference between the various categories of signaling is the distance that the signal travels through the organism to reach the target cell.




METABOLIC PATHWAYS
Metabolism of Complex Carbohydrates
Biodegradation of Xenobiotics
Nucleotide Metabolism
Metabolism of Complex Lipids
Carbohydrate Metabolism
Metabolism of Other Amino Acids
Lipid Metabolism
Amino Acid Metabolism
Energy Metabolism
Metabolism of Cofactors and Vitamins
Biosynthesis of Secondary Metabolites


SENDING CELL
ligand
receptor
RESPONSE
Chemical messengers relay the signal
ligand
receptor
RESPONSE

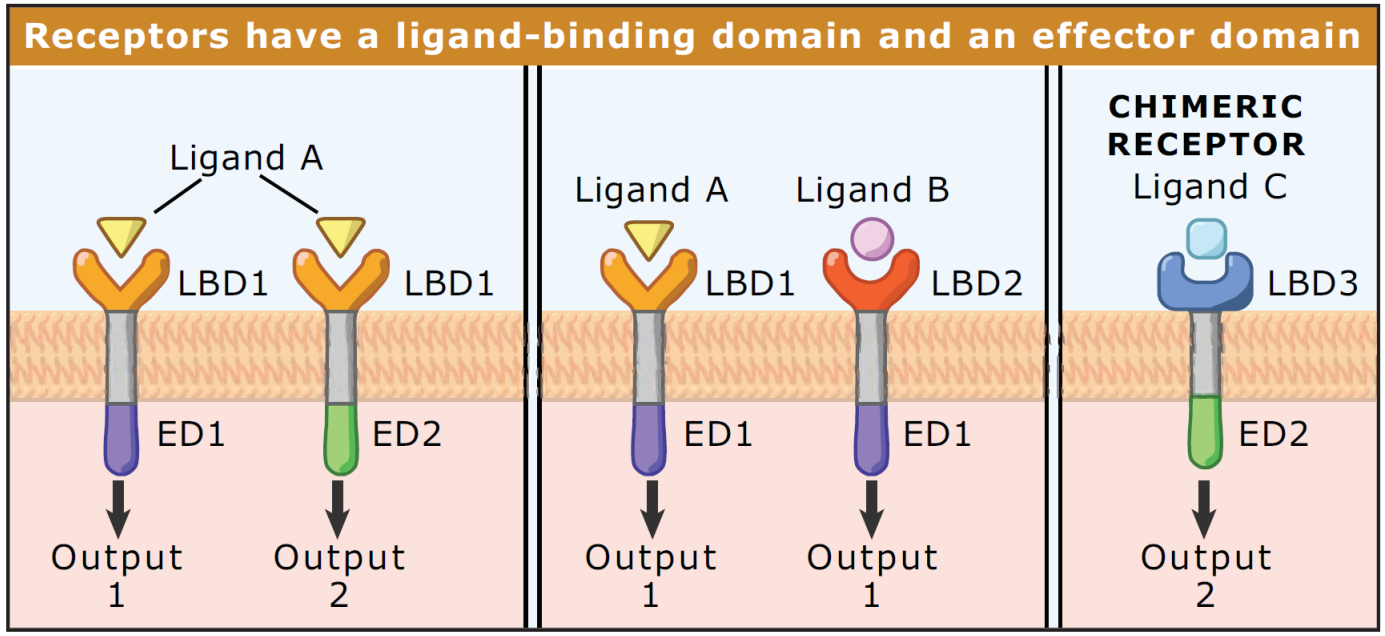
- Types of ligands & receptors
- Principles of ligand-receptor interactions
- Pathways of cellular signaling



The receptor's **two-domain** nature allows the cell to **regulate** the **binding of ligand** and the **effect of ligand** independently.

Receptor modularity allows a wide variety of signals to use a limited number of cell regulatory mechanisms (e.g. outputs)

Expression of a receptor that is not normally expressed in a cell is often sufficient to confer responsiveness to that receptor's ligand.
This responsiveness often occurs because the cell already expresses the other components necessary for propagating the intracellular signal from the receptor.



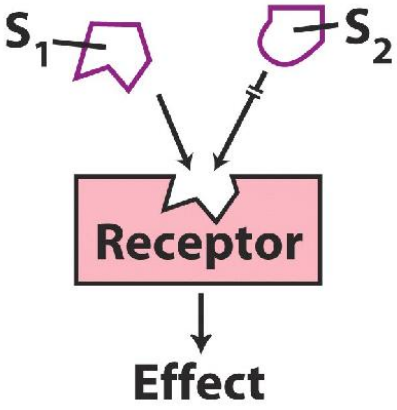

create an artificial chimeric receptor with novel properties

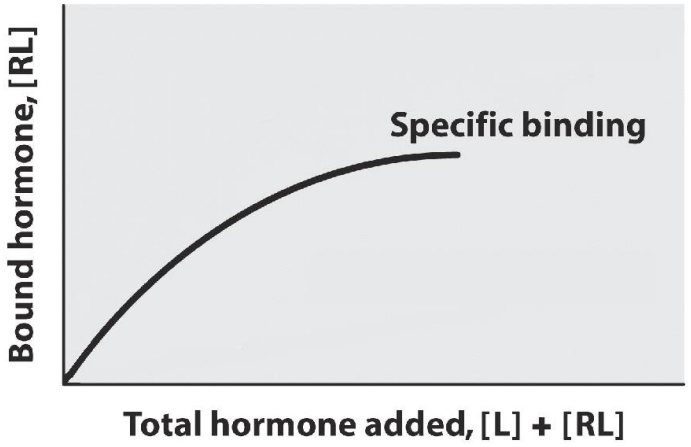
Two receptor isoforms that respond to the **same ligand** with **distinct effects** mediated by **different effector domains** (e.g. Acetylcholine)

Two receptors that respond to **different ligands** could initiate the **same function** by activating **similar effector domains** (e.g. production of the intracellular signaling molecule cAMP)

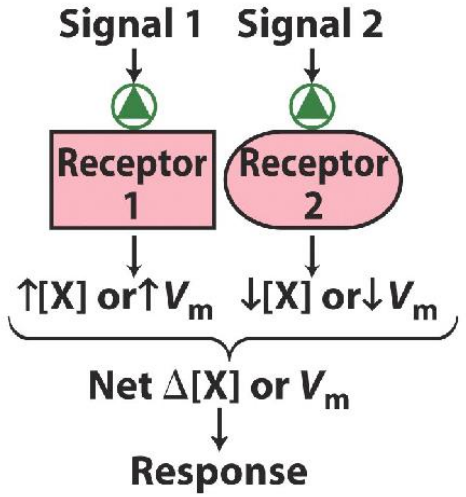
Receptors act to **accelerate intracellular functions** and thus are functionally analogous to enzymes or other catalysts.

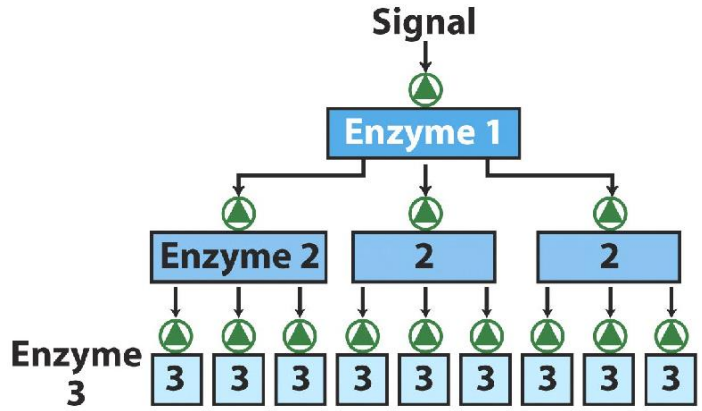
Some receptors are themselves enzymes (e.g. protein kinases) and thus classical biochemical catalysts.

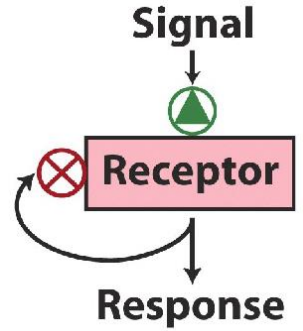


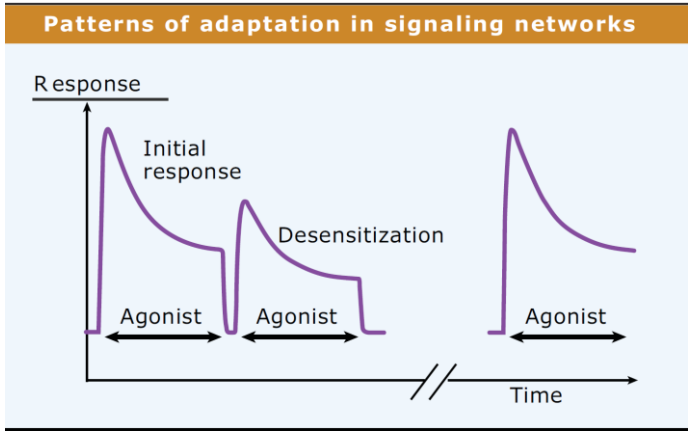




- Specificity
- Affinity
- Saturation
- Cooperativity
- Amplification
- Integration
- Desensitization/Adaptation



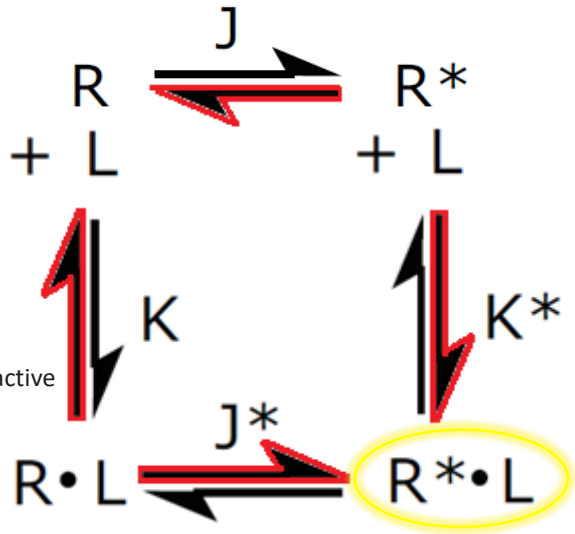



Receptors can exist in **inactive (R)** or **active (R*)** molecular conformations. Ligand binding changes the receptor conformation and, as a simple consequence of its relative affinities for the receptor's R* and R conformations, the ligand can drive the receptor toward the active conformation in which the effector domain is functional (→ coupling of ligand binding and effector domains isomerization)

R and R* are in equilibrium, which is described by the equilibrium constant J<<1 (because unliganded receptors are usually minimally active)

L can bind to the receptor in either of its conformations (described by association constants K for the RL state and K* for the R*L state)




the RL pair remains inactive for a short while, then becomes active (R*L)

PATH INDEPENDENCE IN A SYSTEM OF COUPLED EQUILIBRIA:

$J \bullet K^* = K \bullet J^*$

Therefore, $J^*/J = K^*/K$

Ligands that bind with higher affinity for the R* conformation than for R will be activators (agonists, K* > K)

Thus, if binding to the R*L configuration is preferred → K*/K>>1, then ligand binding to any R will shift the conformation equilibrium of RL to the R*L state to an equivalent extent → J*/J>>1

## PROPERTIES OF RECEPTORS

J must be greater than zero. Thus, even unliganded receptors have some activity (R*).

Because physiological receptors are nearly inactive in the absence of ligand, J must be much less than 1 and is probably
less than 0.01; most receptors are less than 1% active (R*) without agonist.

Overexpressed receptors frequently display their intrinsic low activity.

Chemical manipulation of a ligand's structure varies its selectivity between R and R* and can often alter its activity as an agonist.

A ligand that binds equally well to both the R and R* states will not cause activation, but may still occupy the binding site and thereby competitively inhibit binding of an activating ligand.

Such competitive inhibitors (**antagonists**) are frequently used as drugs to block unwanted activation of a receptor in various
disease states.

Receptors can exist in **inactive (R)** or **active (R*)** molecular conformations. Ligand binding changes the receptor conformation and, as a simple consequence of its relative affinities for the receptor's R* and R conformations, the ligand can drive the receptor toward the active conformation in which the effector domain is functional (→ coupling of ligand binding and effector domains isomerizations)

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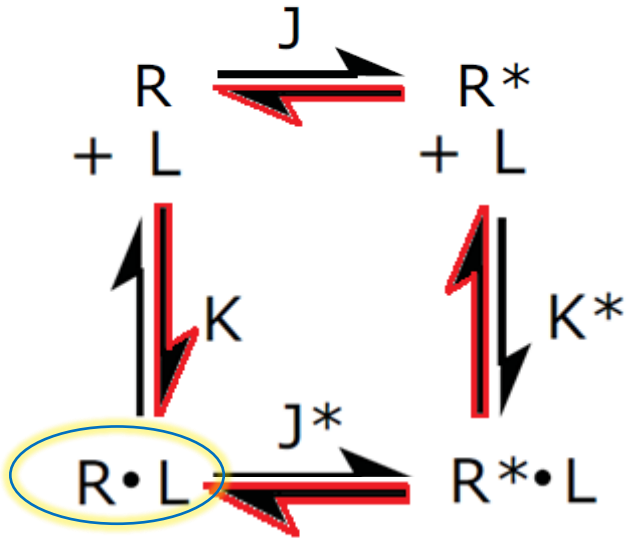


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On the contrary,…

**PROPERTIES OF RECEPTORS**

A ligand that binds preferentially to R relative to R* will further shift the conformational equilibrium to the inactive state and cause net inhibition (**inverse agonist**)

In this case, K/K*>>1 → J/J*>>1
BUT given that J<<1 (as axiomatically defined)
THEN must be J*<<J<<1