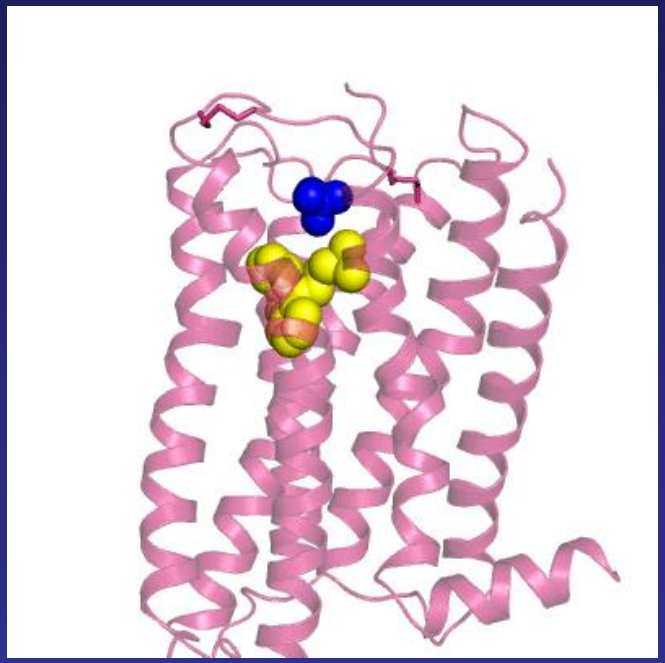
Introduction to Receptor Pharmacology

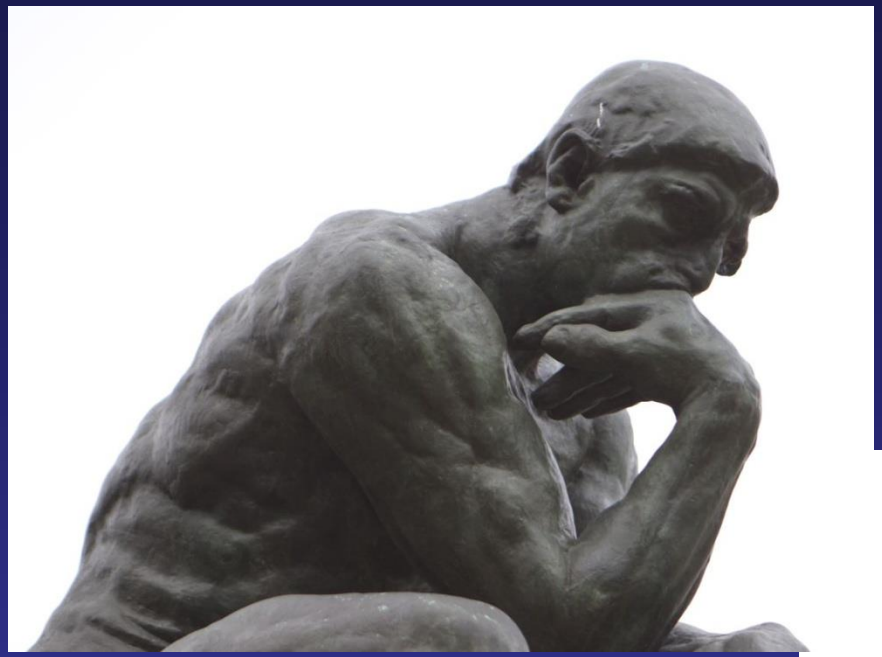


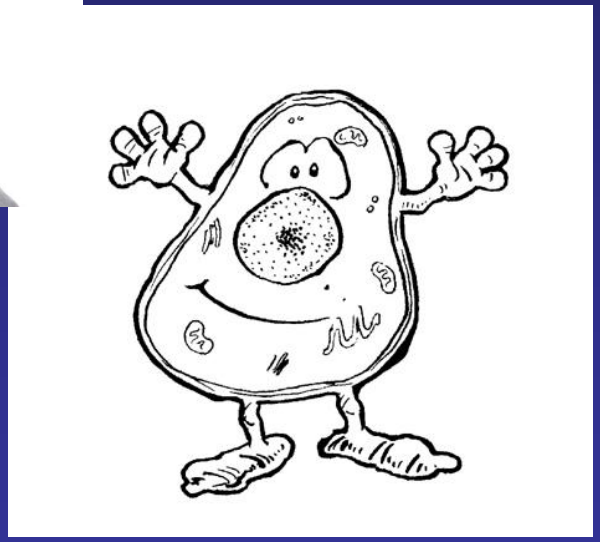
Dr Taufiq Rahman

2nd August 2016

Part I:
A general overview of receptors

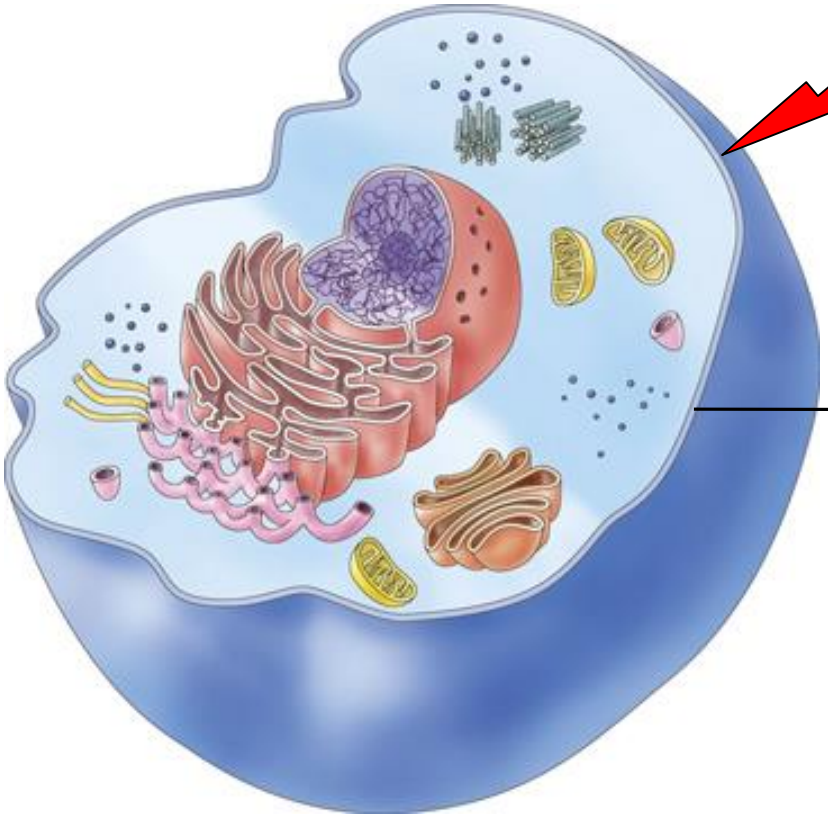
what is sustaining life?





how a cell biologist will look at this?

sustaining life means that cells are ‘alive & kicking’ properly



external world
(continually changing, full of pleasant & unpleasant surprises

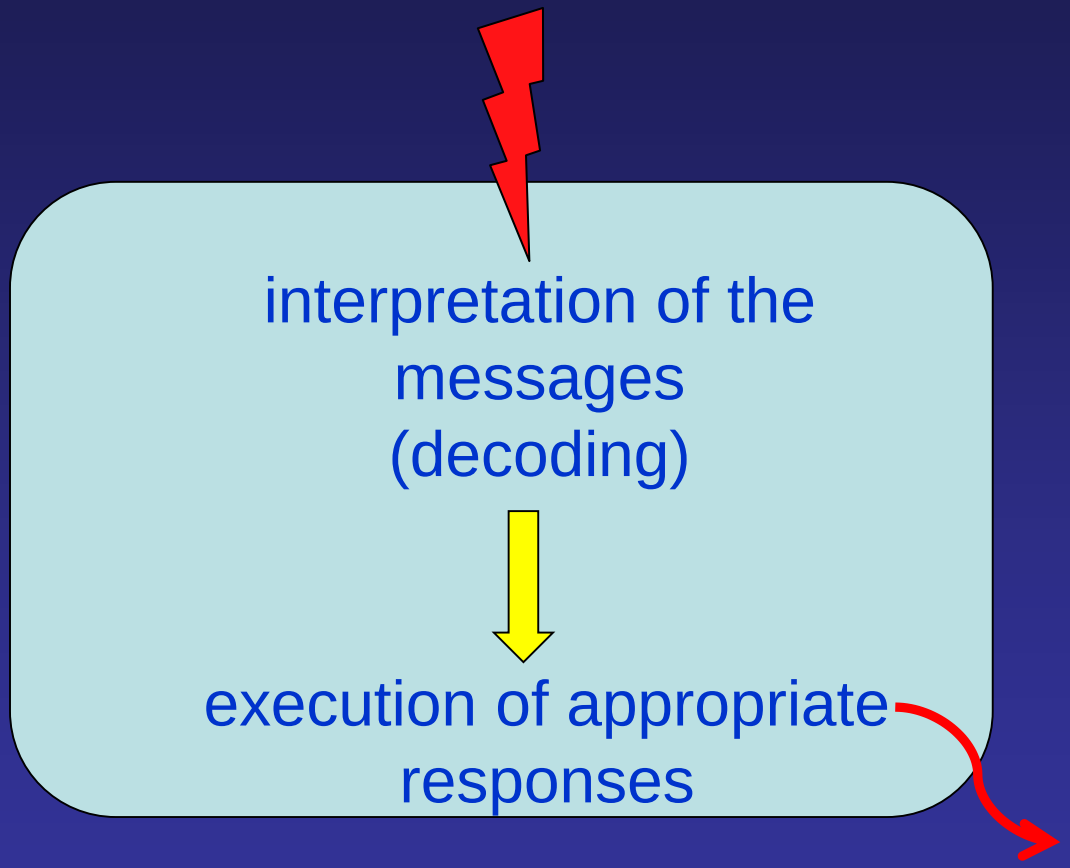
cells, though insulated by a membrane, need to adapt to these changes

it is absolutely critical that these external changes are

recognized properly and on time

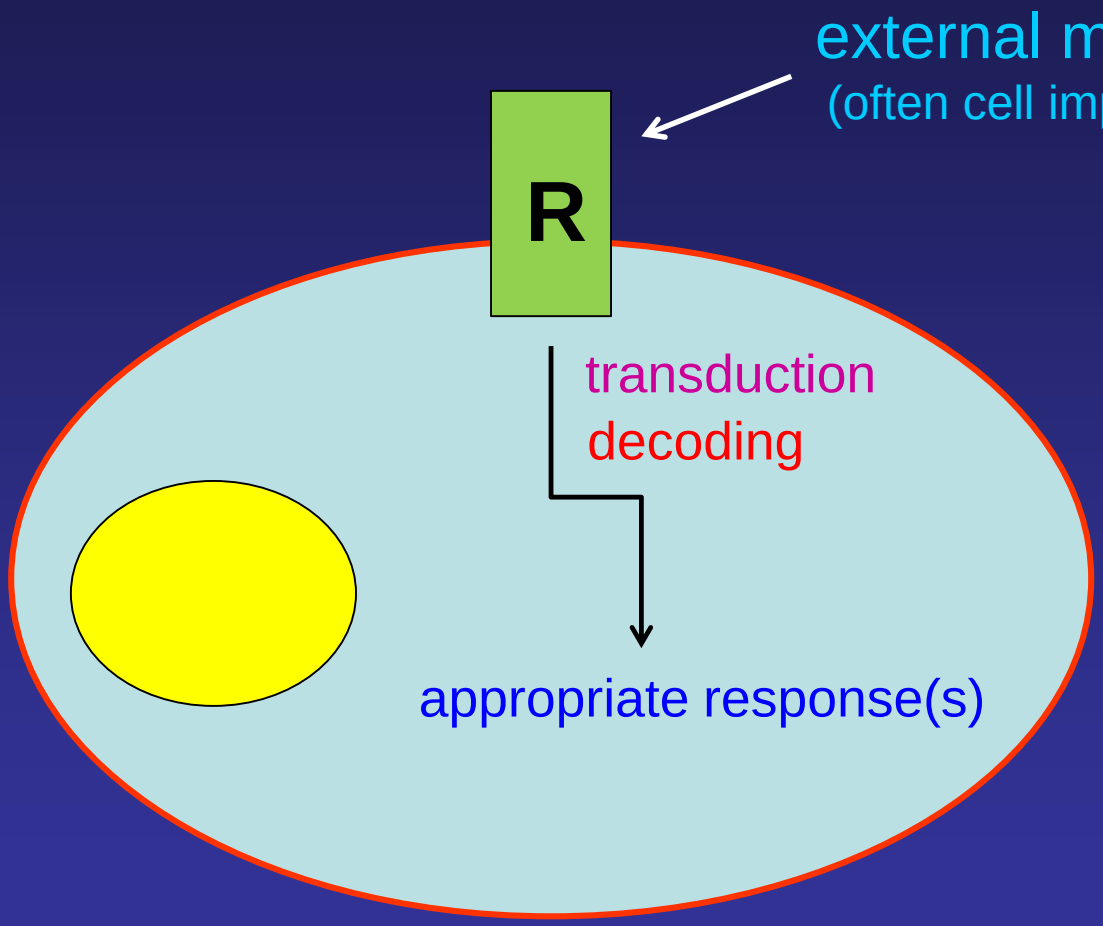
sustaining life then becomes.....

receiving the external changes (recognition)



this is crucial for maintaining the normalcy within (homeostasis)

cells have receptors to ‘receive’ and ‘process’ the extracellular information



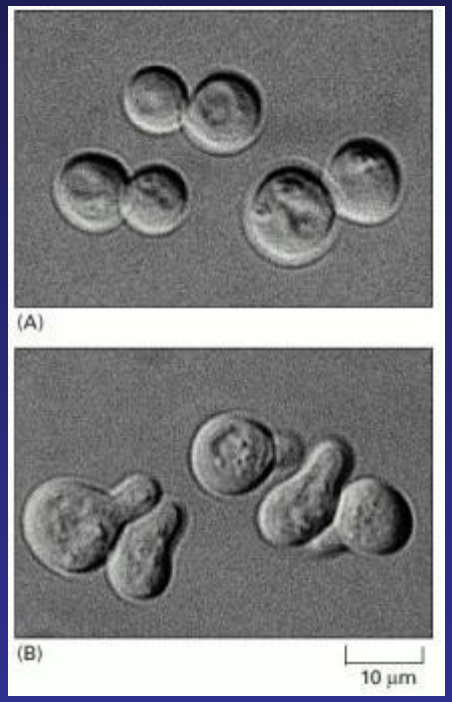
receptors ensure that cells always know what they are, where they are, and what they should be doing

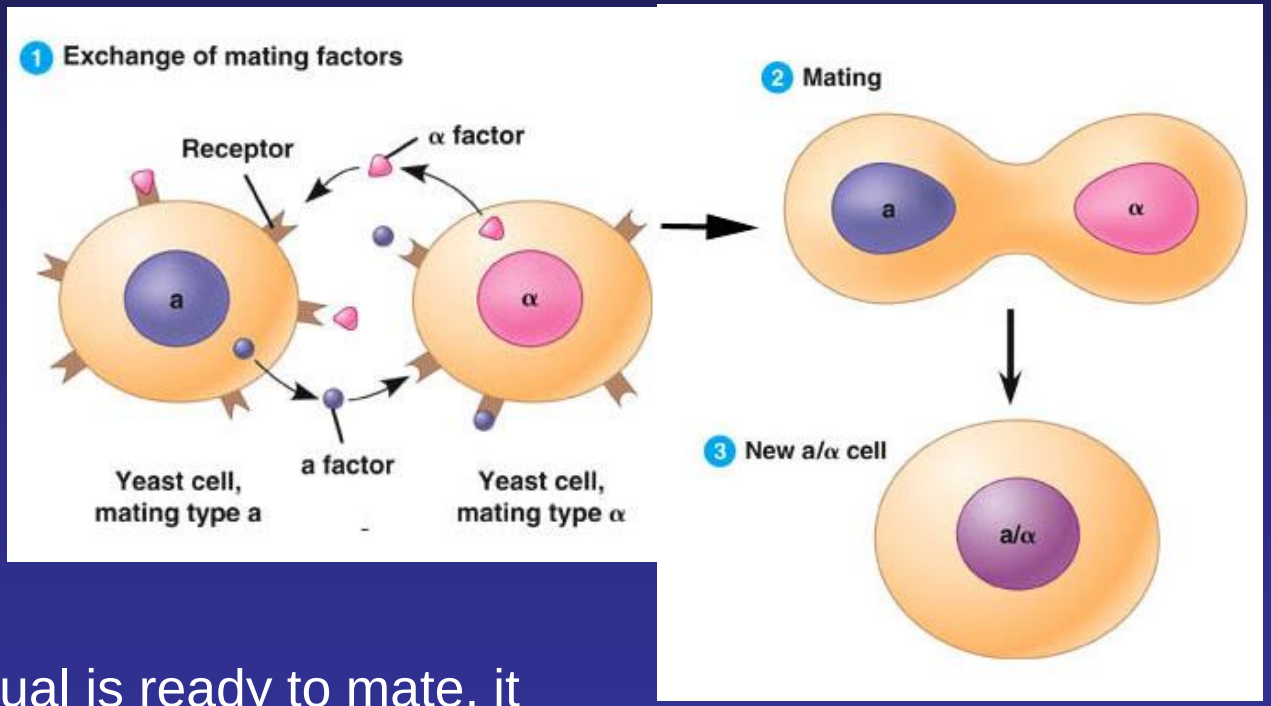
what are receptors

- these are specialized, membrane-bound proteins
- they receive (bind to) external stimuli
- upon receiving external signal, they undergo structural changes
- this ultimate trigger various cellular activities
- thus they effectively serve as signal transducer

receptors are primitive means for cell survival

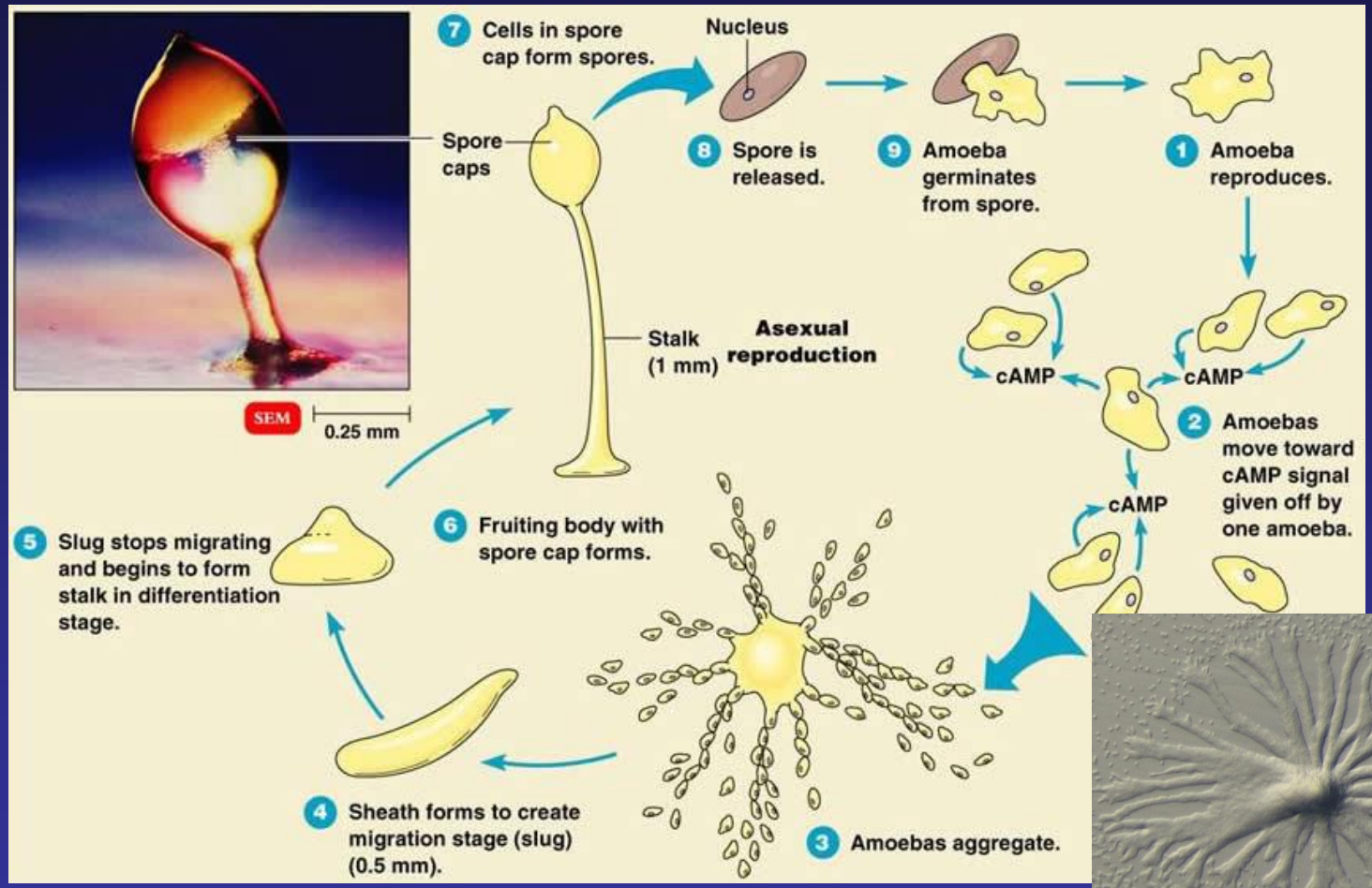
pheromone signalling of haploid Yeast (*Saccharomyces cerevisiae*)





when a haploid individual is ready to mate, it secretes a peptide *mating factor* that signals cells of the opposite mating type to stop proliferating and prepare to mate

receptors are primitive means for survival



slime mold *(Dictyostelium discoideum)*

once the supply of food is exhausted, individual amoebae begin to move together (~1mm/hr) – triggered by cAMP released from starving ones!

receptors' role as readers are critical

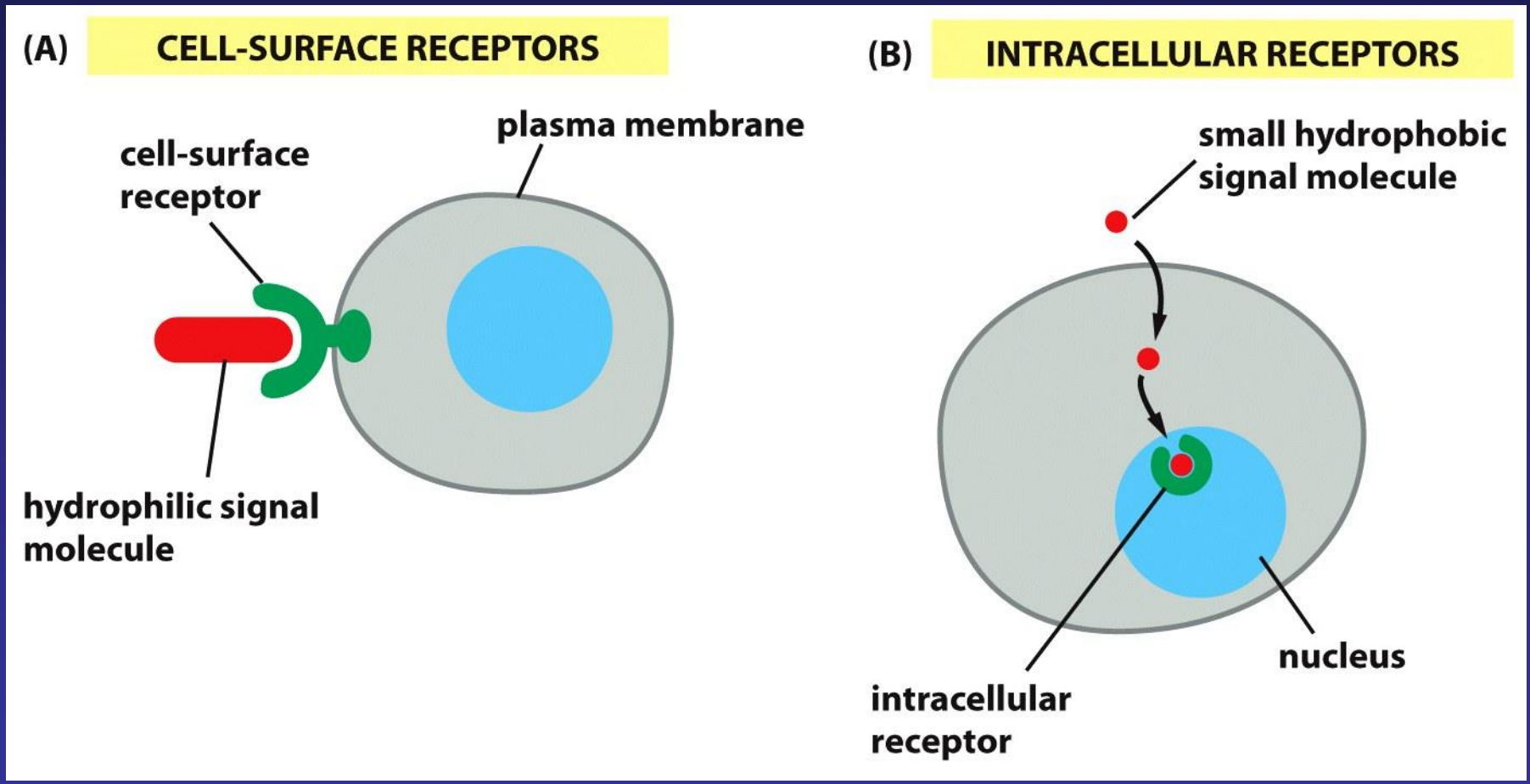
problem occurs.....

failure in reading

reading too much

reading the wrong message

what do receptors read – the first messenger



common first messengers for receptors

- Amino acids and their derivatives – glutamate, GABA, glycine
- Proteins & peptides (various hormones, growth factors)
- Nucleotides – ATP, ADP, AMP
- Small inorganic ion (eg. Ca^{2+})

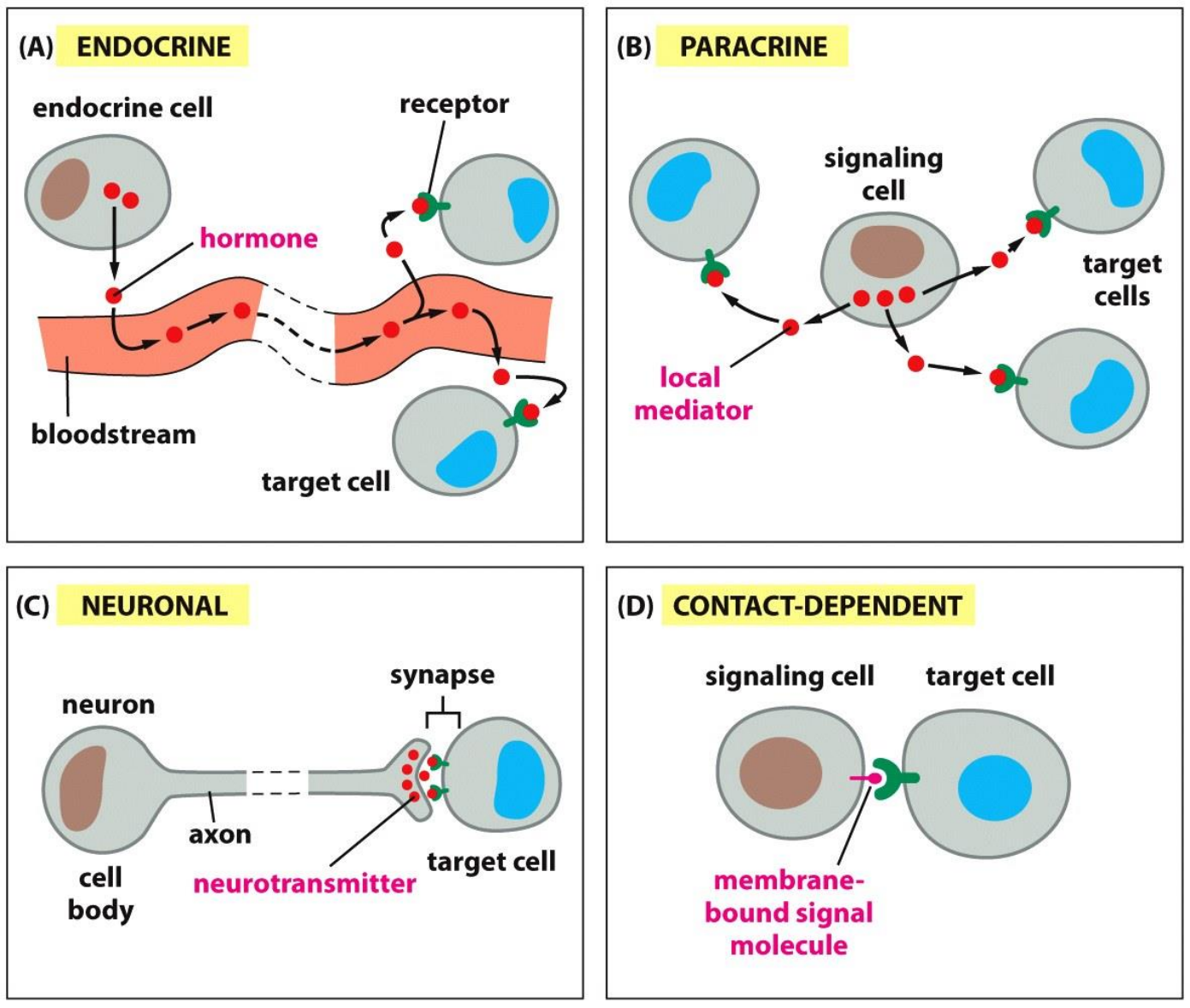
- derivatives of fatty acids
- steroids
- retinoids

- gases (NO, H_2S)
- physical stimuli (heat, cold, touch, smell, light etc.)
- and most of the drug molecules

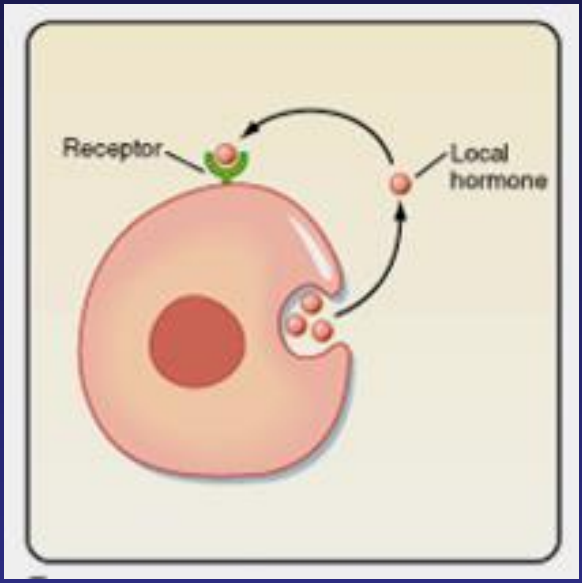
if any of the above (most actually do) physically binds to a receptor, it is called a '**ligand**'

delivering the signal to its receptor

first messengers operate over various distances



delivering the signal to its receptor

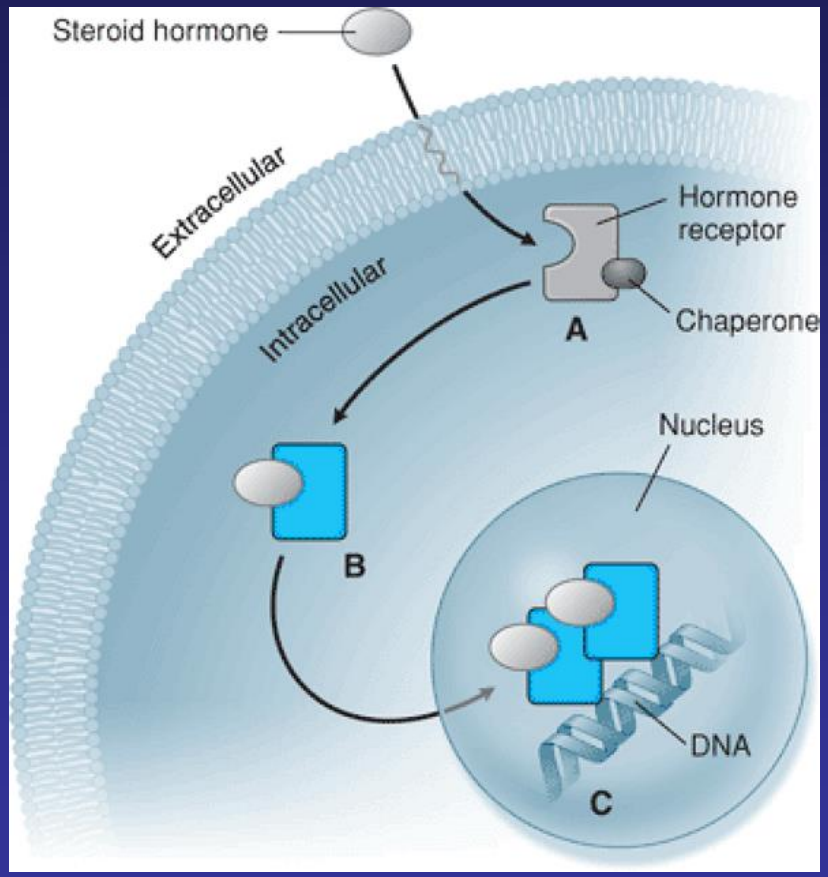


autocrine

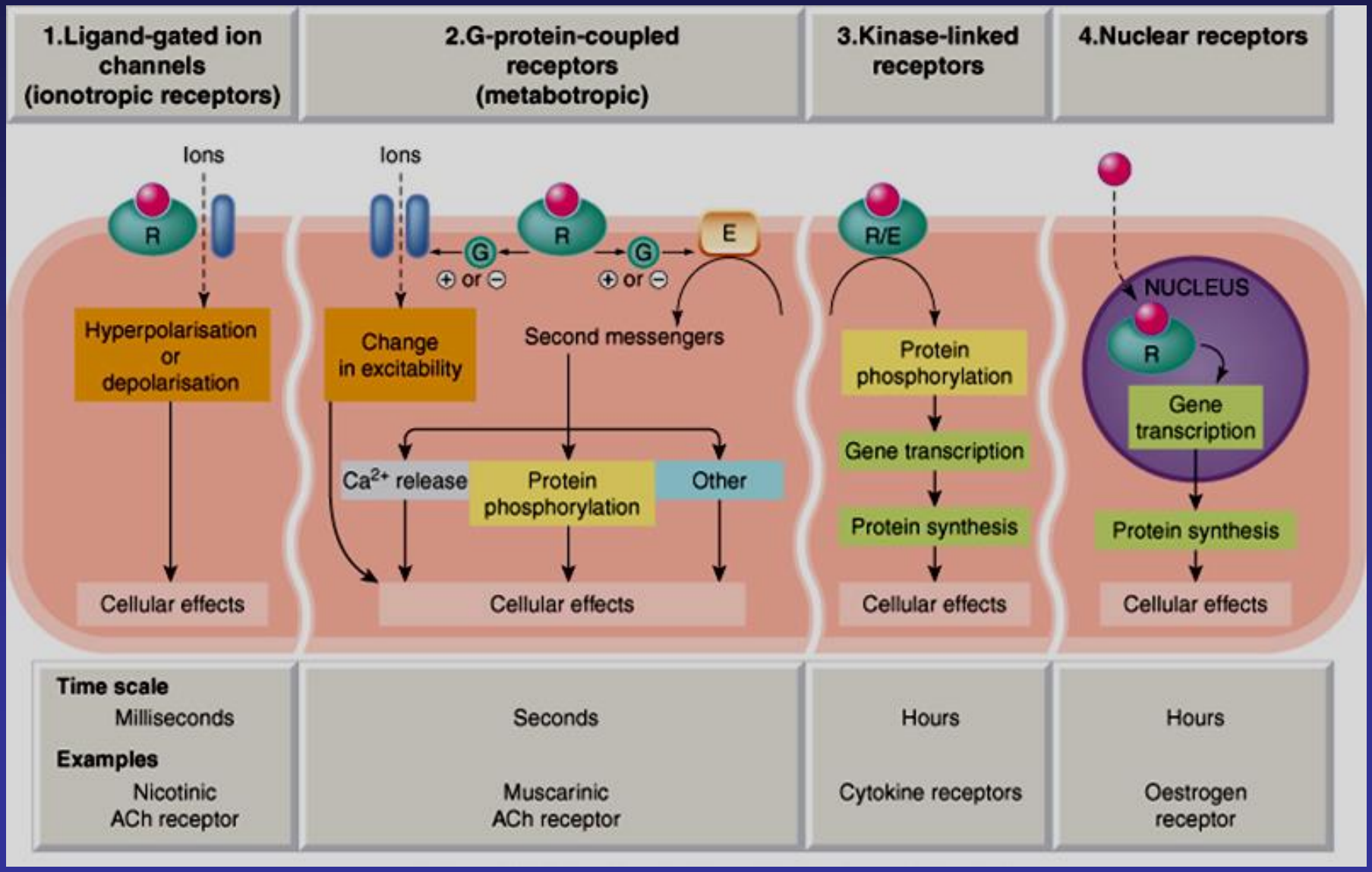
self-stimulating process

can be problematic (cancer)

intracrine



major types of receptors



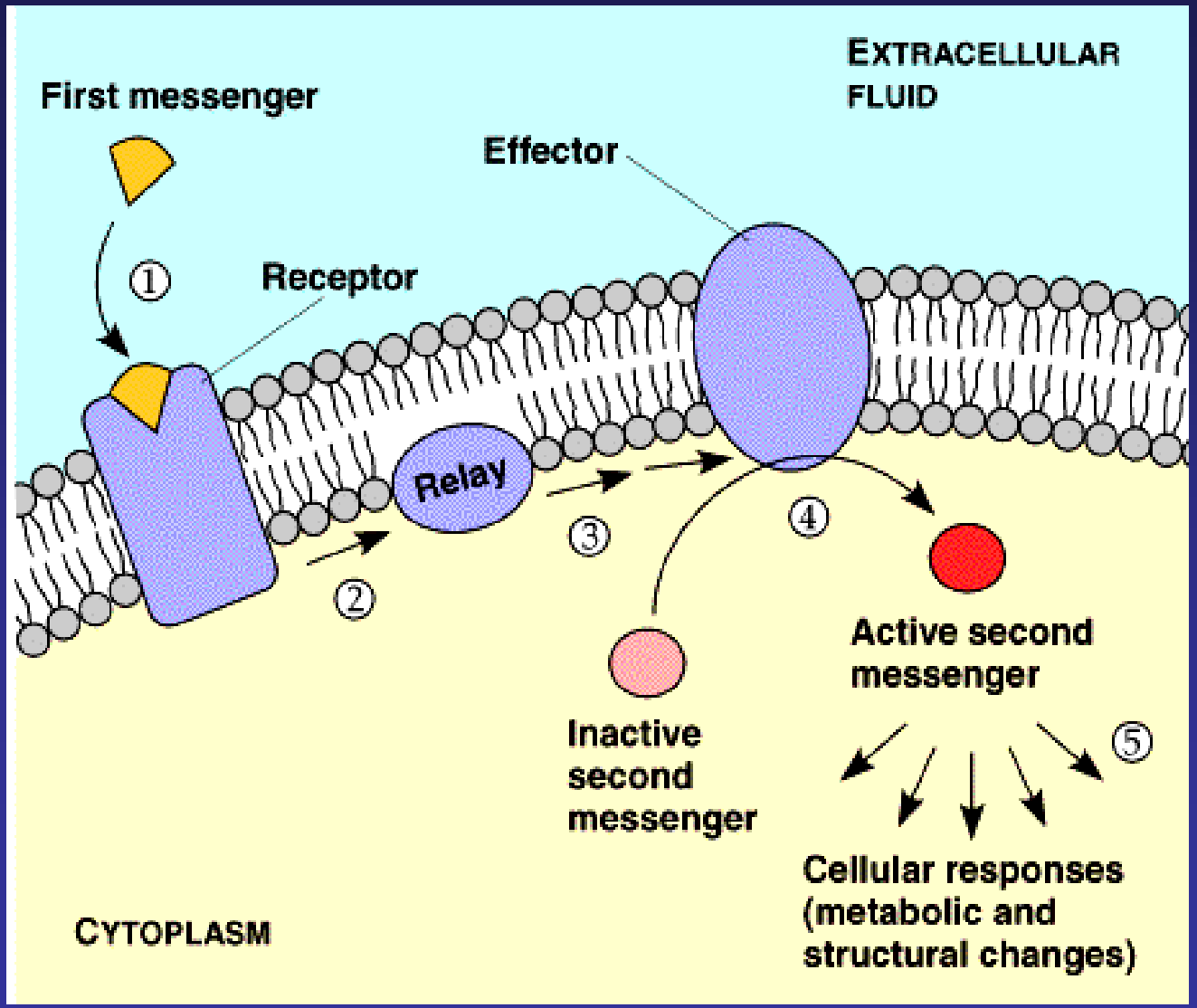
how prompt our receptor need to be?

- VERY FAST (milliseconds)
  nerve conduction, vision
  - ion channels

- FAST (seconds)
  vision, metabolism, cardiovascular activities
  - G protein-coupled receptors

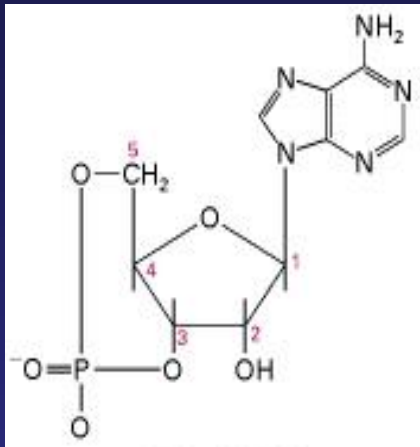
- SLOW (minutes to hours)
  cell division, proliferation, developmental processes
  - growth factor receptors
  -steroid hormone receptors

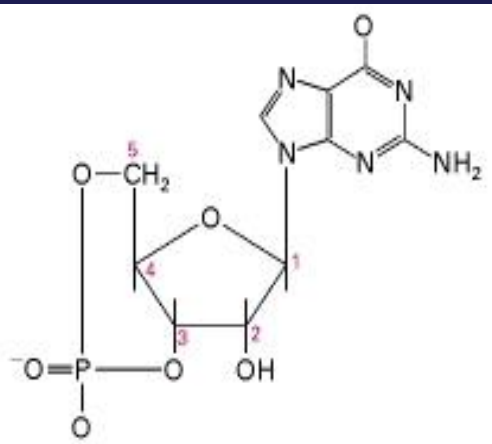
receptor activation often produces 2nd messengers

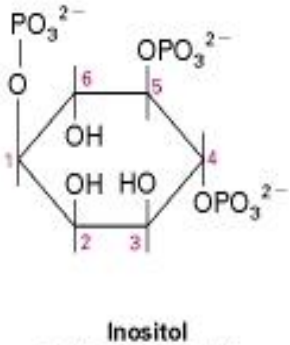


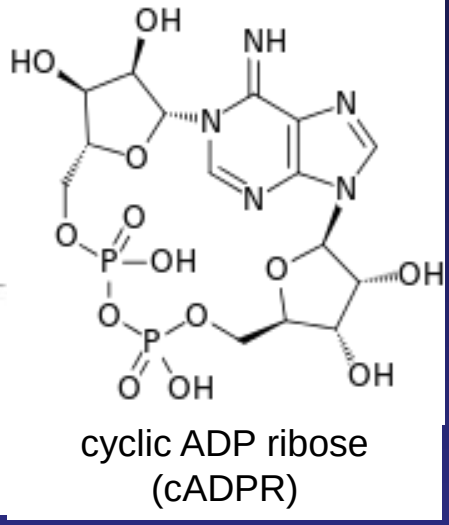
some common 2nd messengers

- soluble second messengers

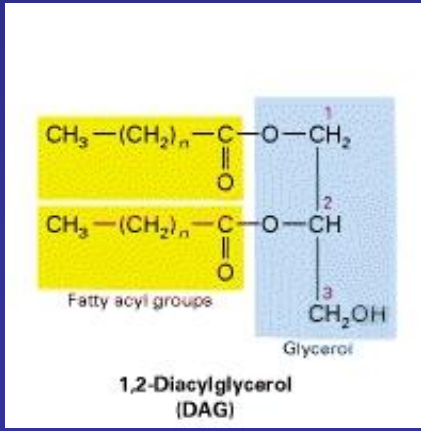


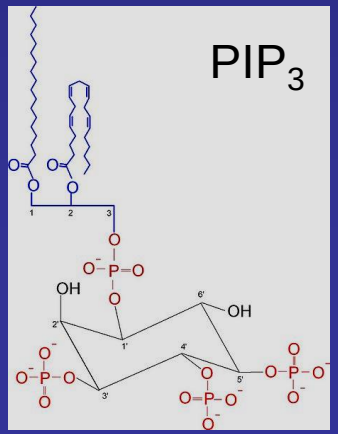


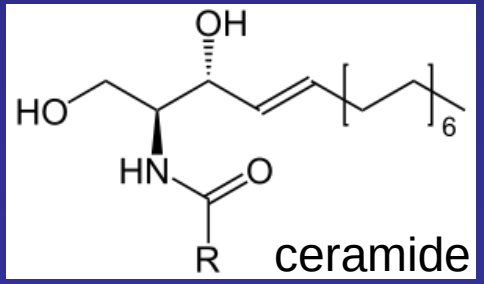


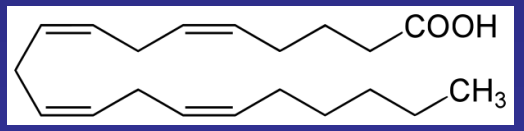


- membrane bound second messengers



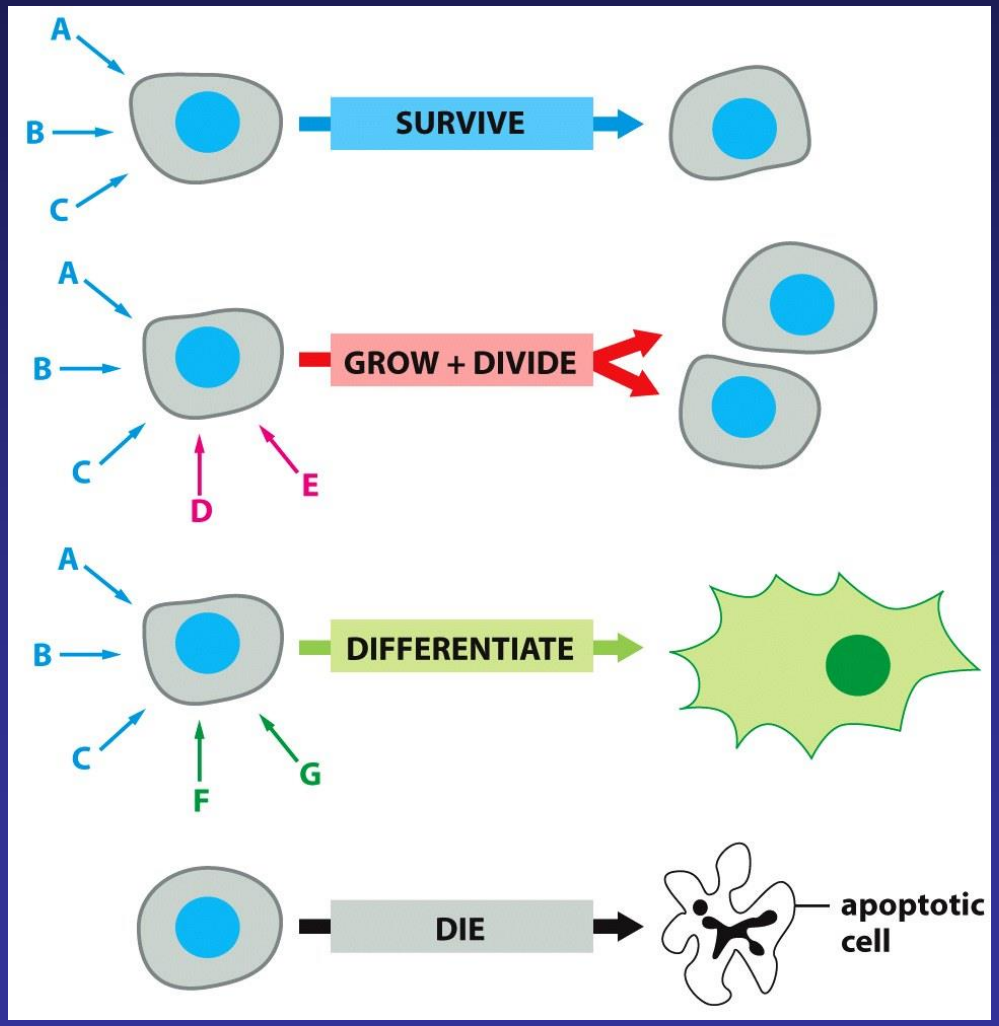






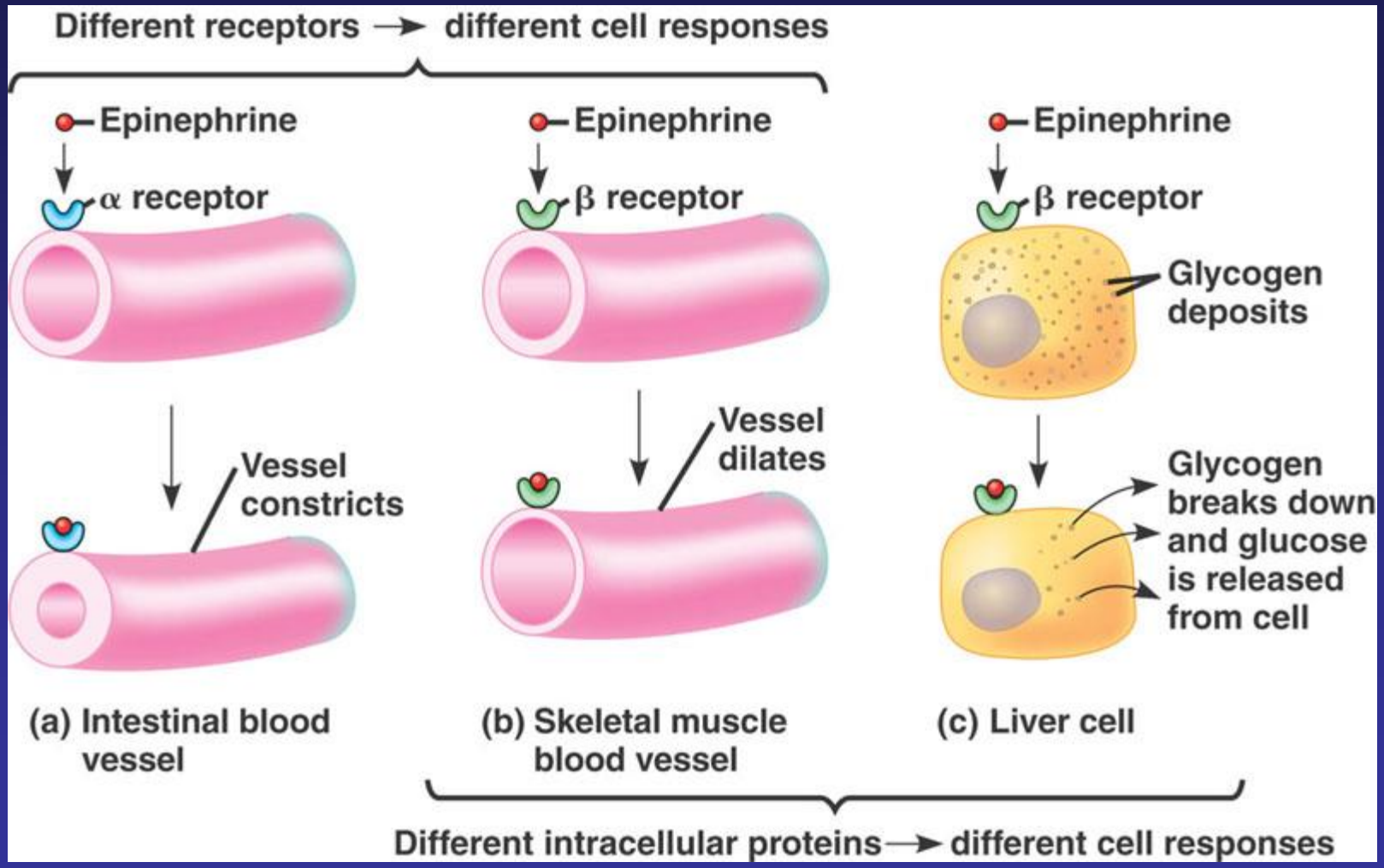
what dictates the cellular activity

(specially when it never receives single stimulus)

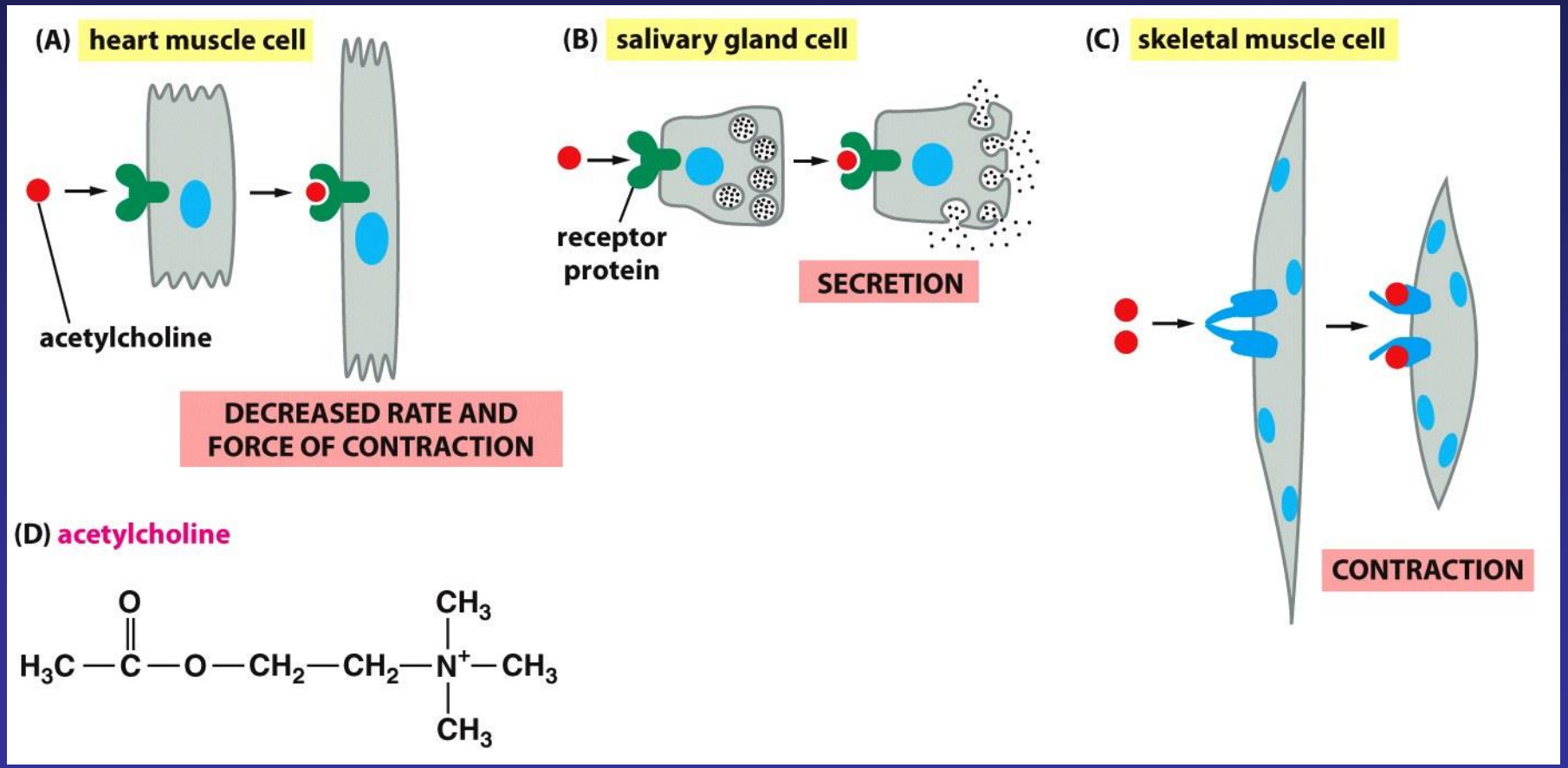


each cell expresses a cohort of receptors & other signalling proteins that eventually govern its responses to different stimuli without confusing

nature of response depends on types of receptors

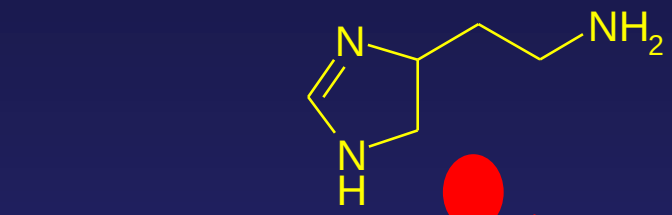


nature of response depends on types of receptors

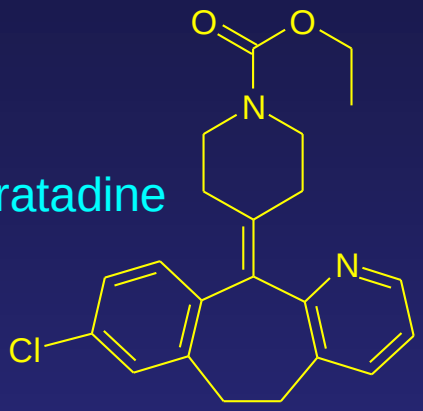


quiz: histamine receptors

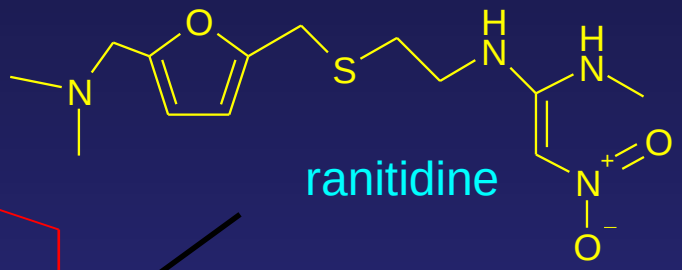
histamine

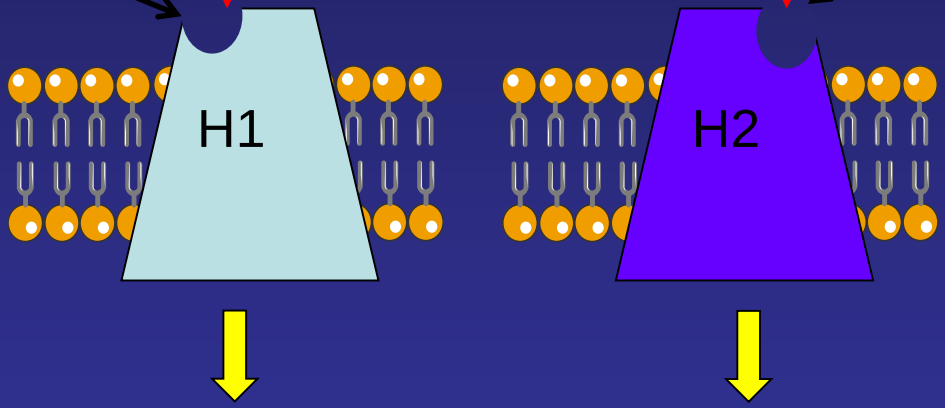


loratadine



ranitidine



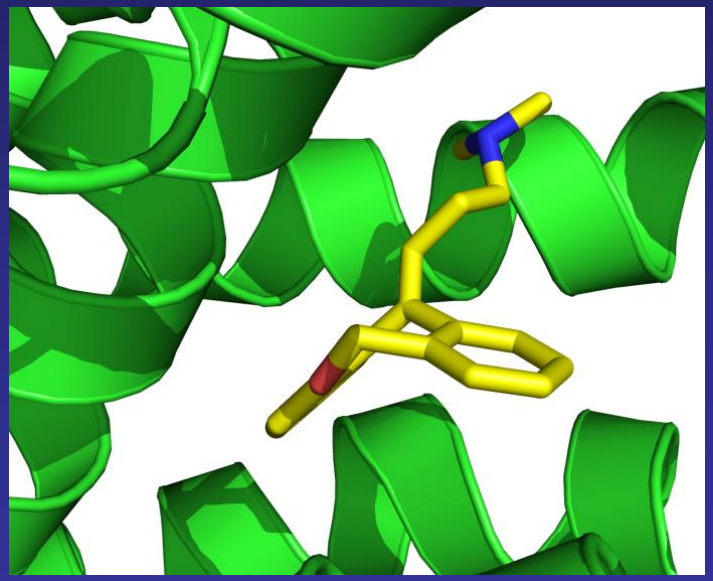


allergic reaction

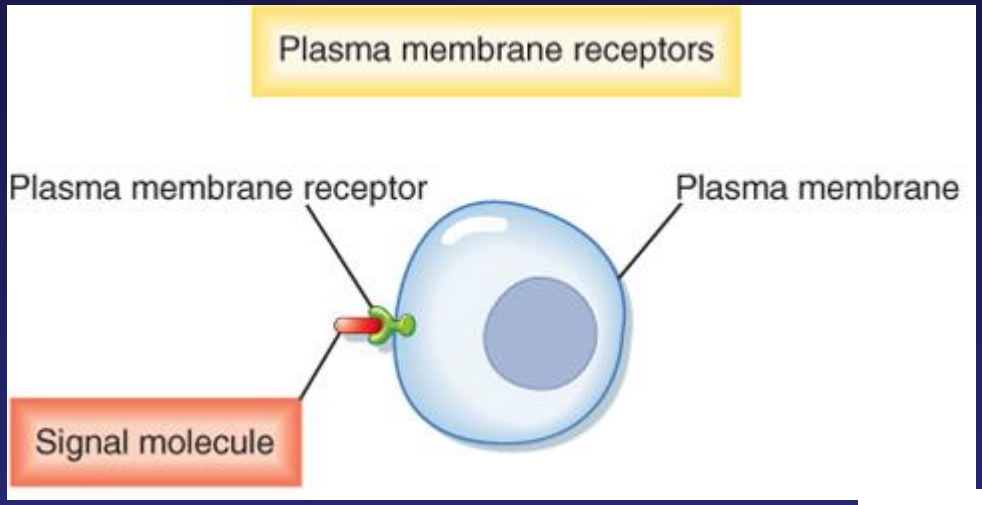
gastric acid secretion

end of part I

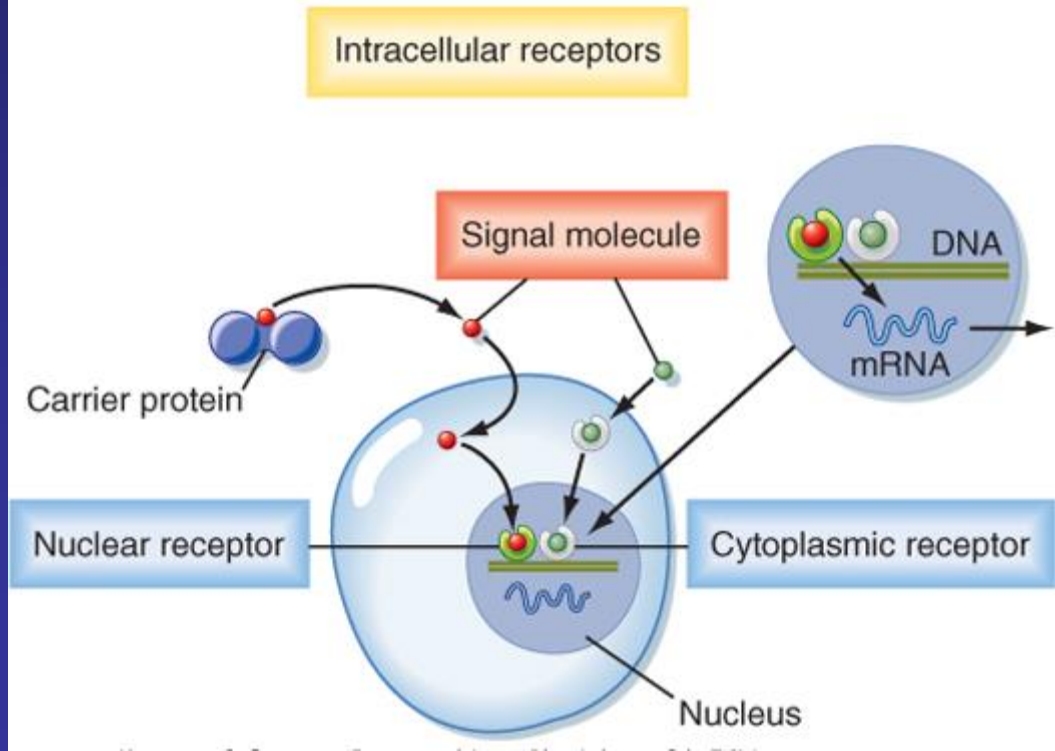
part II:
receptor-ligand interaction



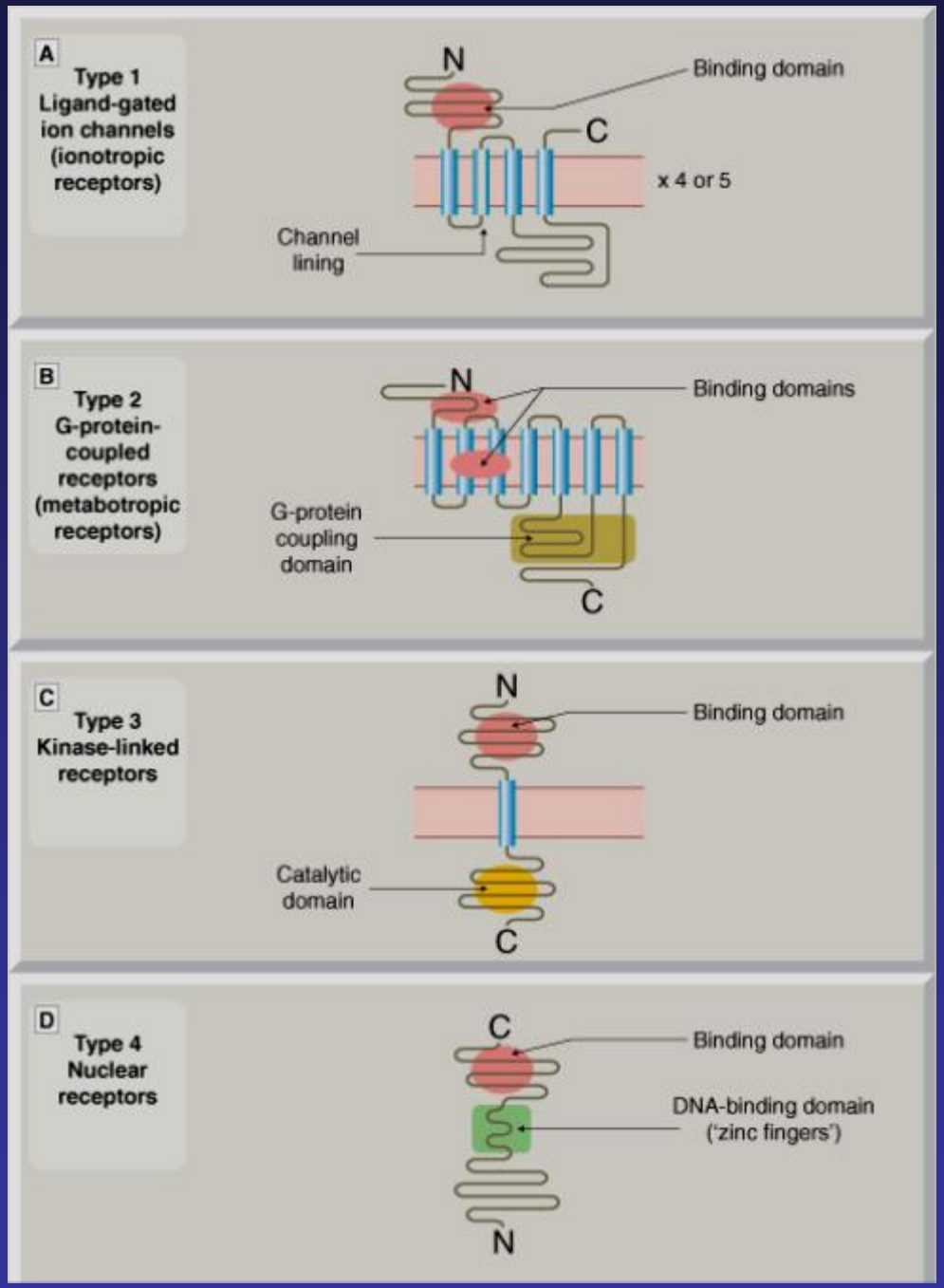
receptor-ligand interaction



receptors are present
in the plasma membrane
as well as inside the cells.



receptor-ligand interaction



- A ligand interacts with a binding site on the receptor
- ligand binding triggers a local conformational change
- conformational change is propagated via the membrane spanning helices
- conformational changes occur on the intracellular face of the receptor that initiates cellular response

introduction of the 'receptor' concept

John N. Langley (1852-1925) Professor of Physiology, University of Cambridge

1878 - a drug (pilocarpin, atropine) forms 'compounds' with a physiological substance

"There is some substance.....in the nerve endings or gland cells with which atropine and pilocarpin are capable of forming compounds.....according to some law of which their relative mass and chemical affinity for the substances are factors."

1905 - 'receptive substance'

"...that nicotine and curare act on the 'receptive substance' of muscle cells."

Paul Ehrlich (left; Nobel Prize 1908) with Emil von Behring (right; Nobel Prize 1901)

1878 - ...specific chemical characteristics of a cell responsible for specific binding...

In 1897, Ehrlich developed the 'side-chain theory' for the binding of toxins to cells: certain side-chains of the cell could bind certain toxins (specificity and stereo-selectivity).

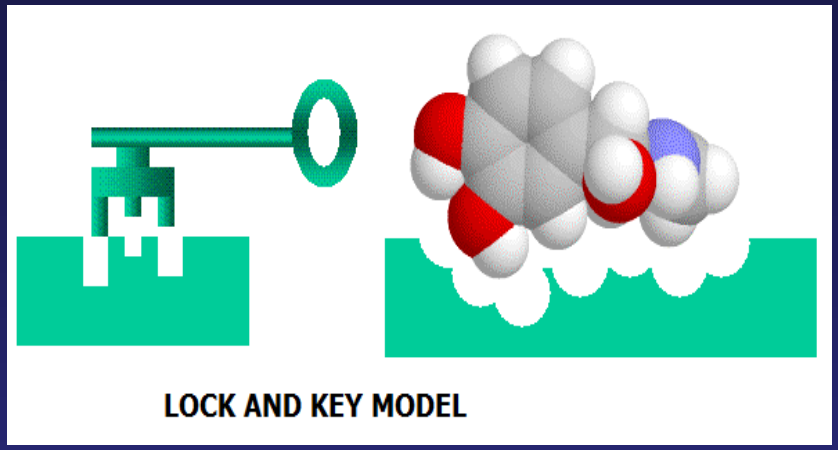
1907 - 'chemoreceptors' for drugs

CORPORA NON AGUNT NISI FIXATA

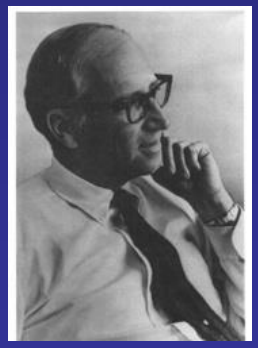
An early 'model' of a receptor-ligand complex by Paul Ehrlich

recognition of the ligand at its receptor site

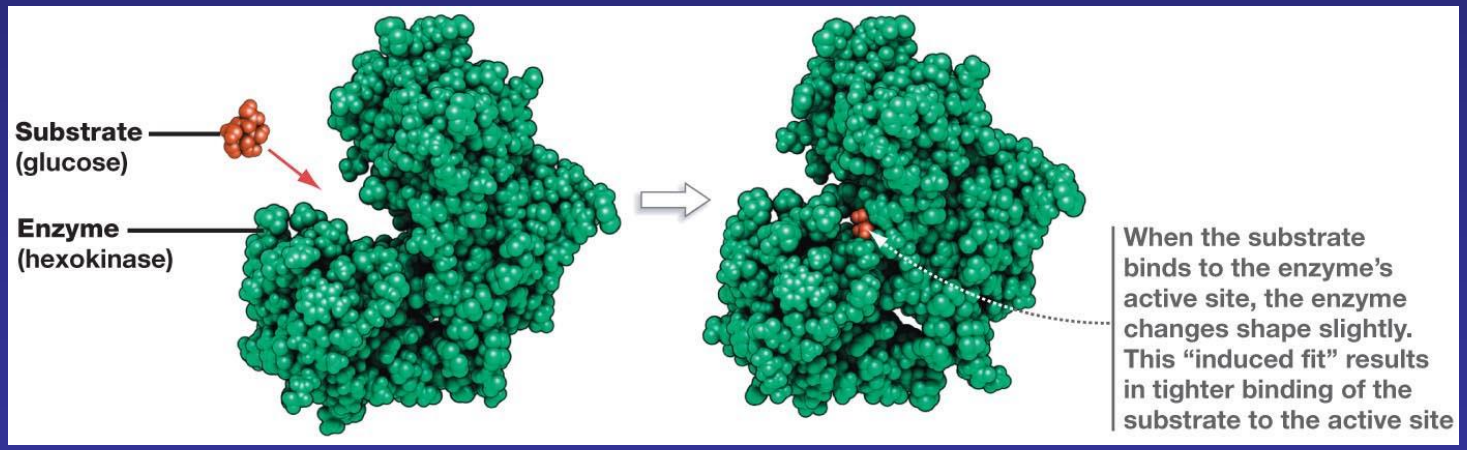
Lock and key theory
(Fischer, 1890)



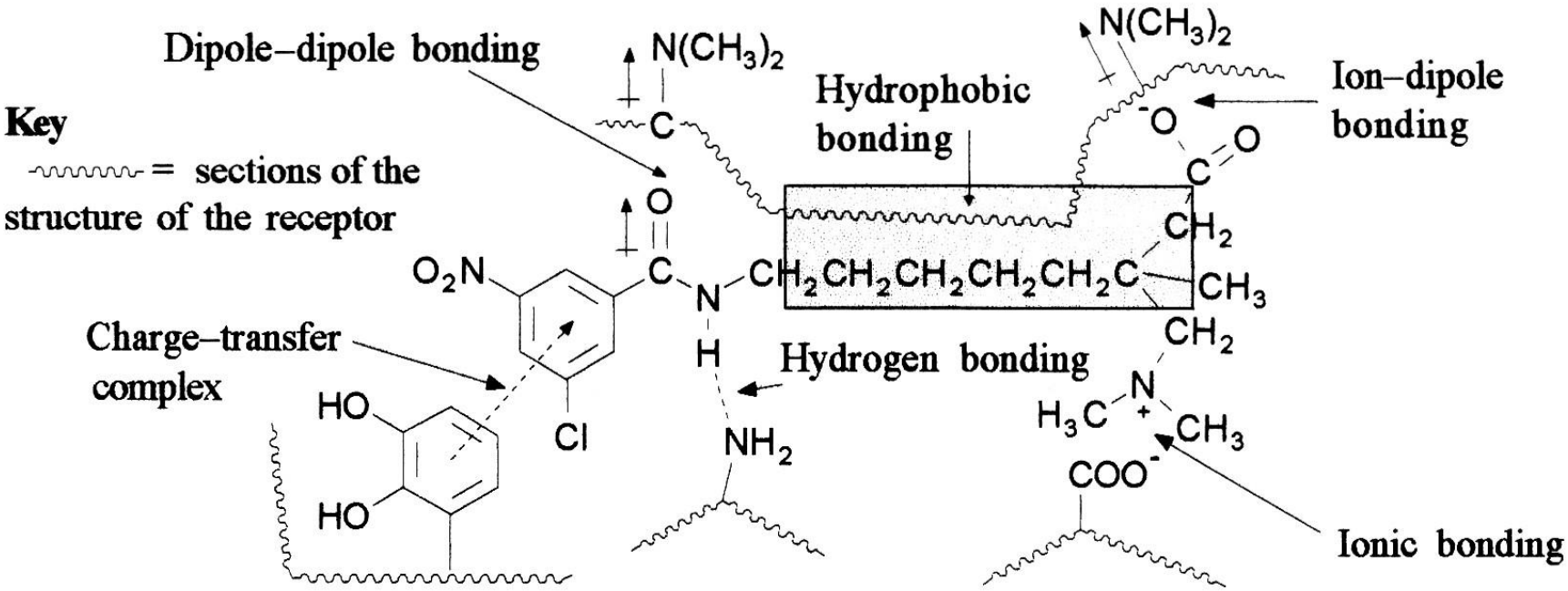
‘’*To use a picture, I would like to say that enzyme and glucoside have to fit to each other like a lock and key in order to exert a chemical effect on each other*.”



induced fit theory
(Koshland 1958)



recognition of the ligand at its receptor site



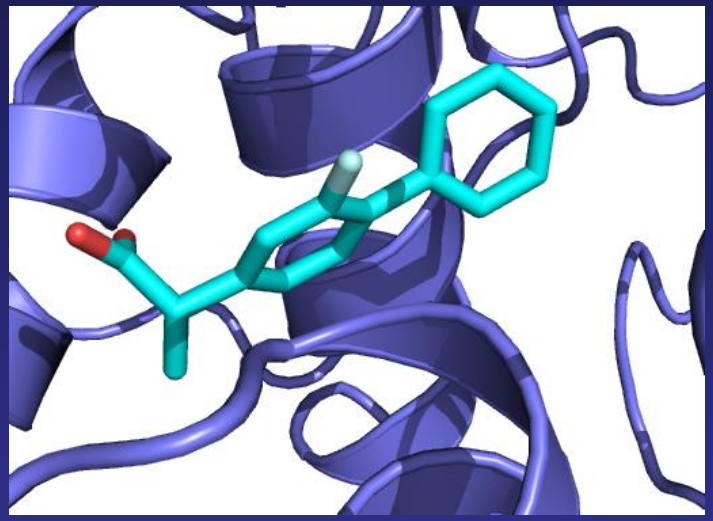
various types of forces are typically involved

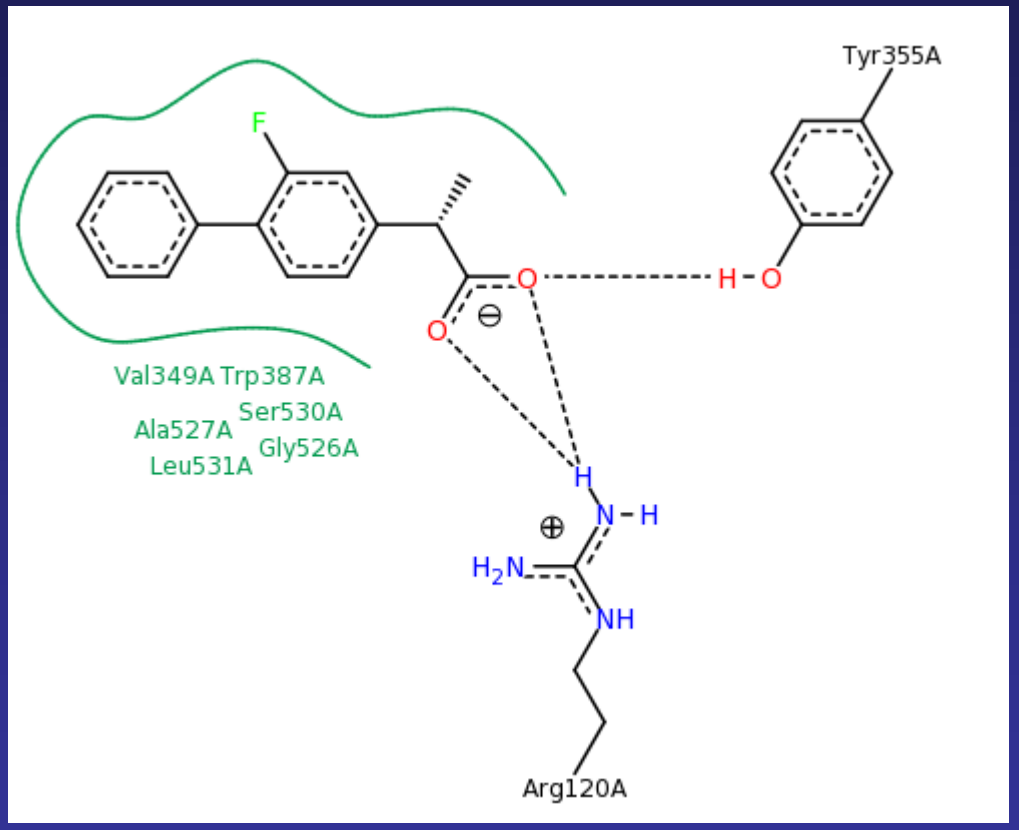
molecular recognition of the ligand

‘together we bind’

multiple but individually weak forces make sure
that a functionally viable but reversible
ligand-receptor complex is formed.

recognition of the ligand at its receptor site





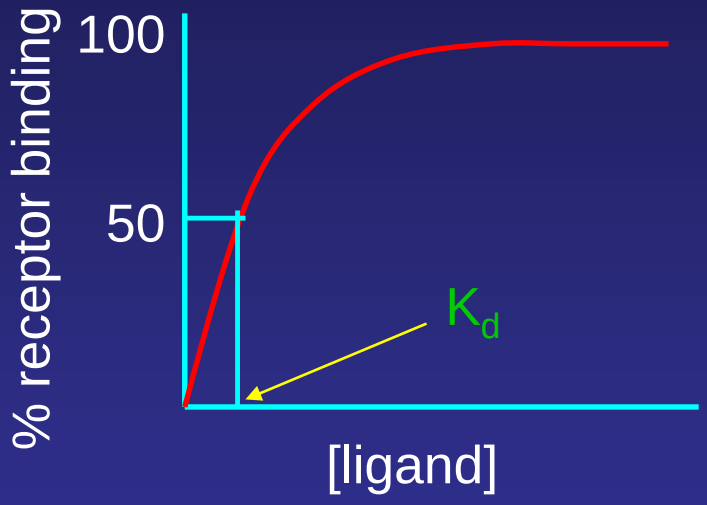
An enzyme (COX-2) bound to a painkiller (Flurbiprofen)

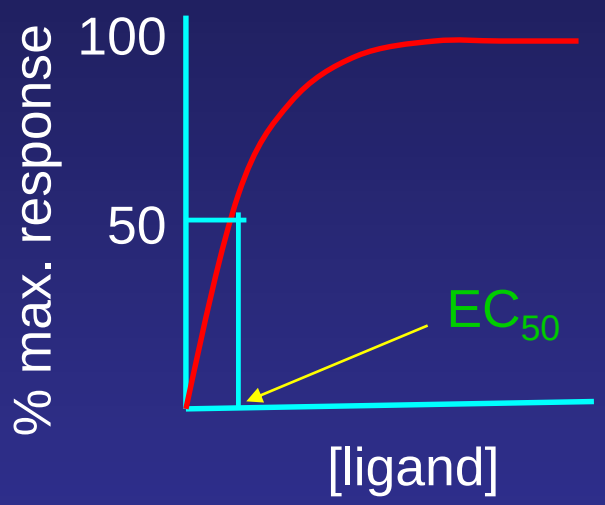
techniques to measure ligand-receptor interaction

Ligand binding assays address the first step of ligand-receptor interaction – the physicochemical properties and kinetics of ligand-receptor complex formation

Functional assays measure the actual biological response (electrical or biochemical or physical) evoked by the ligand via its receptor

quantification of ligand-receptor interaction





K_d ⟶ affinity

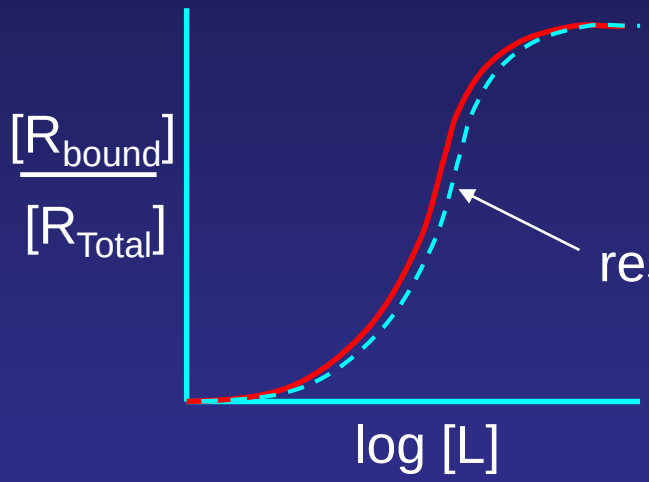
EC_{50} ⟶ potency

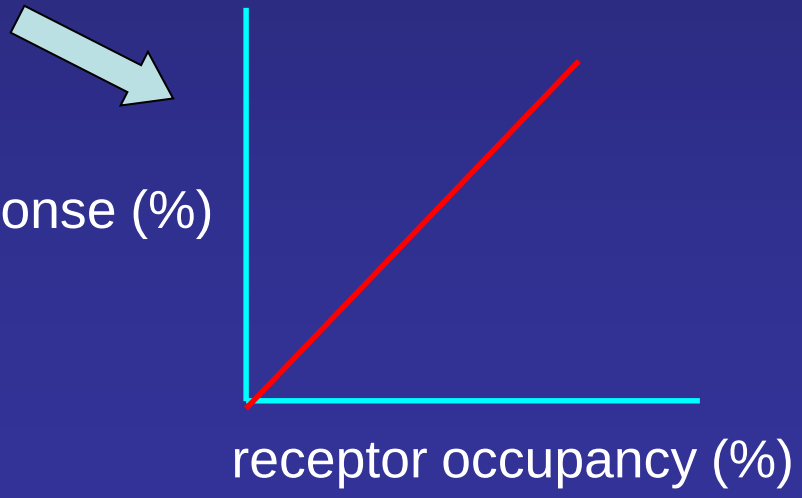
quiz: why do the curves plateau?

quantification of ligand-receptor interaction

A. J. Clark
(1937)

biological response ∝ receptor occupancy

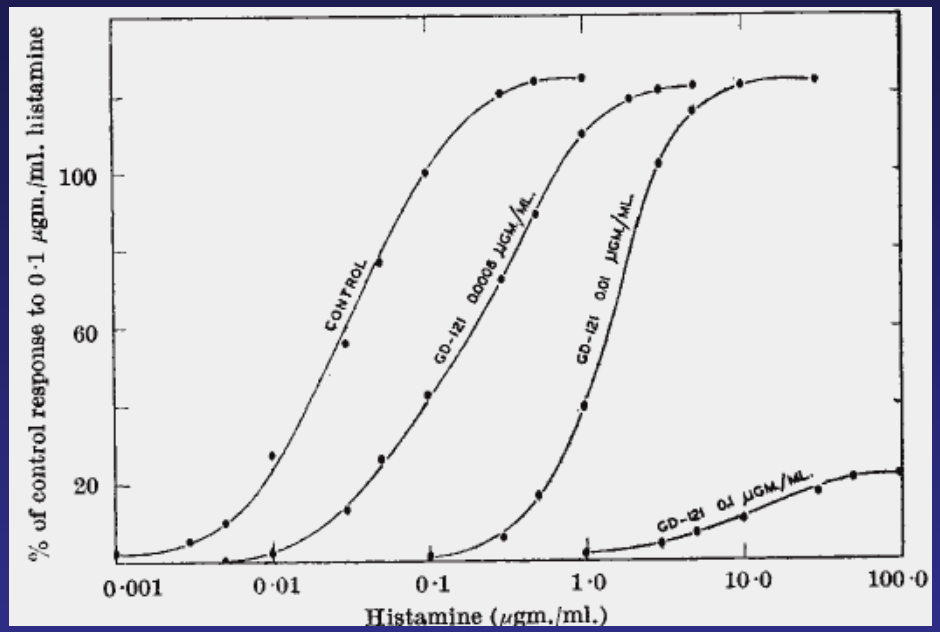




Occupancy theory: $EC_{50} = K_D$

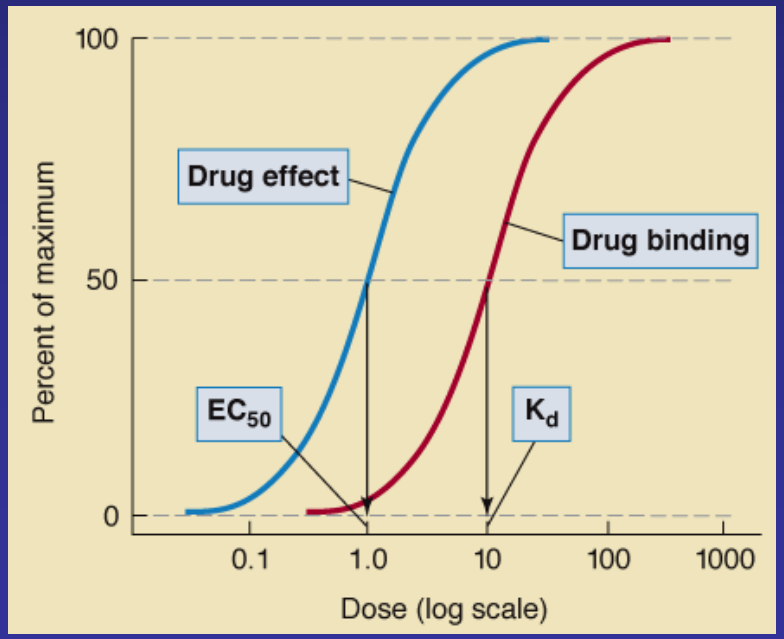
quantification of ligand-receptor interaction

modification of the occupancy theory



Nickerson (1956); *Nature*

occupancy 1% of histamine receptors was adequate to produce maximum effect

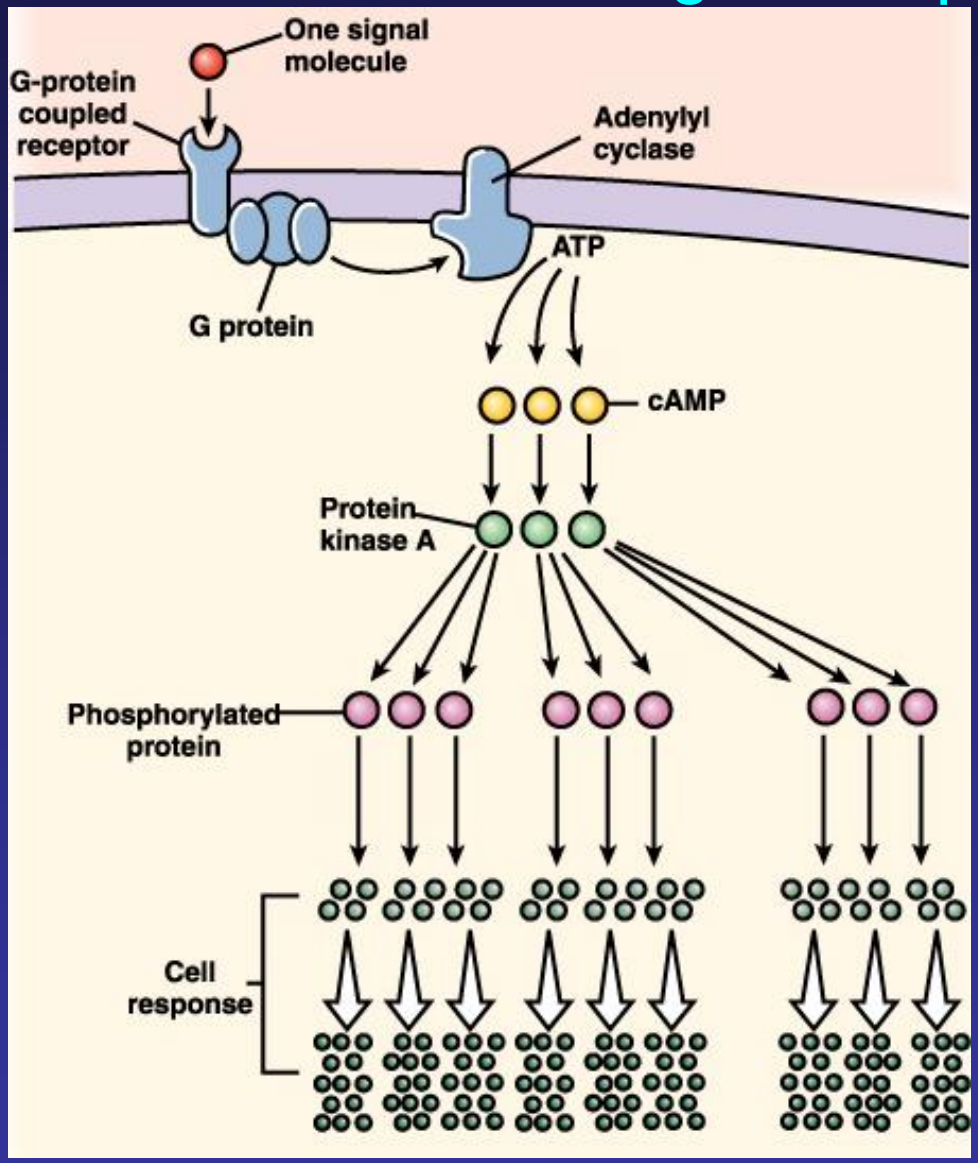


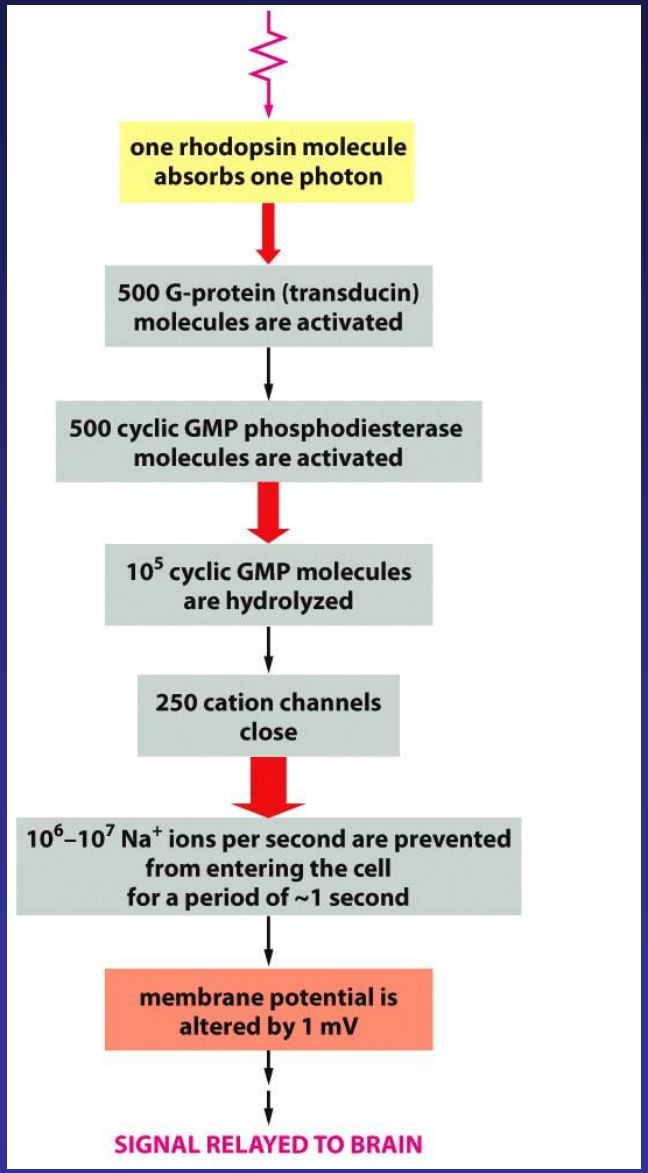
tissues tend to have 'spare receptors'

EC_{50} values are typically $<<K_d$

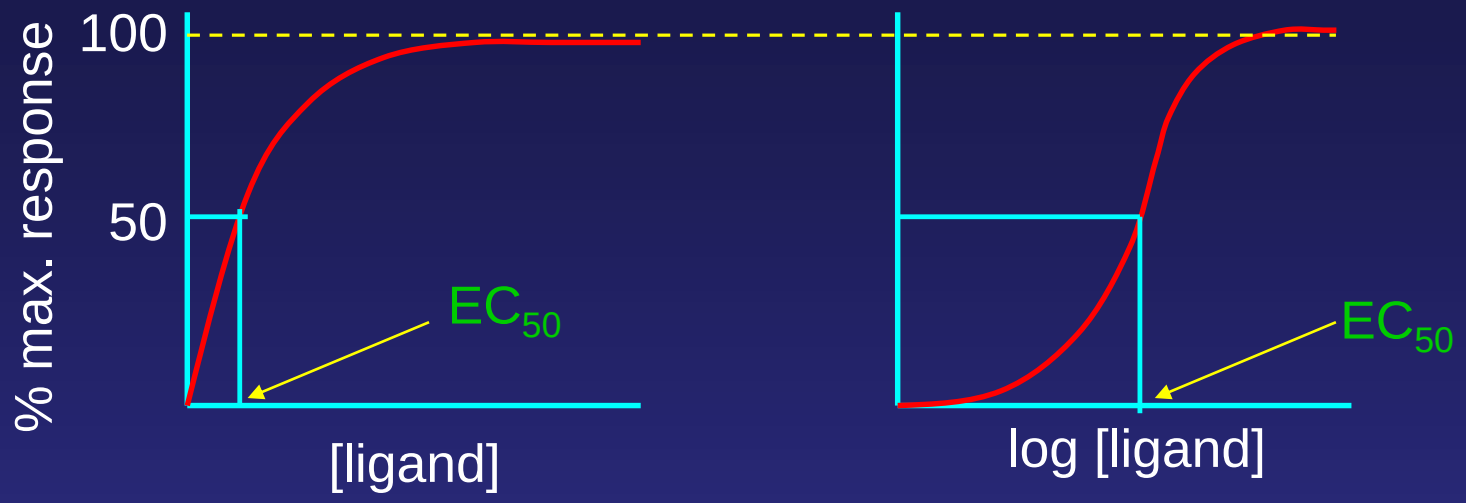
what allows EC_{50}<<Kd:

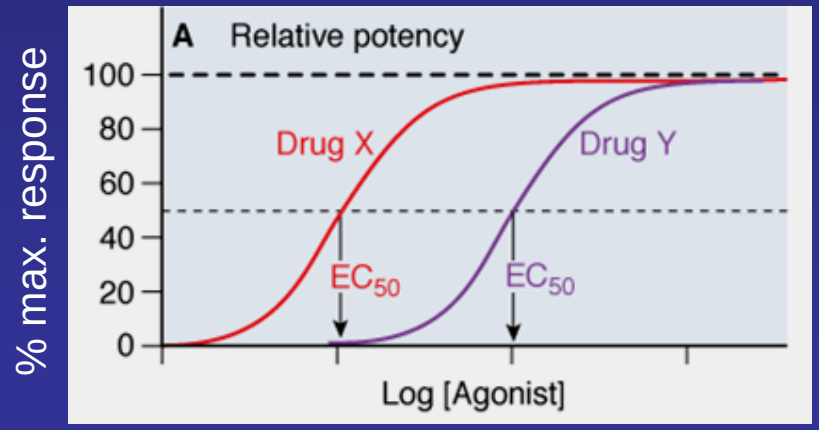
signal amplification

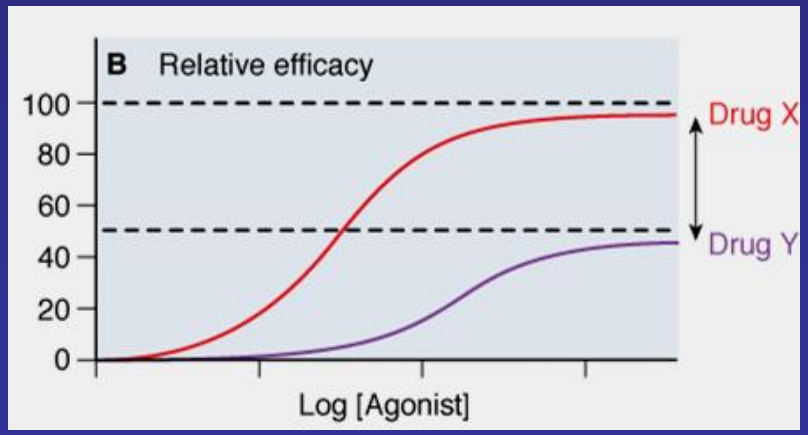




ligand conc. – biologic response relationship







quantification of ligand-receptor interaction

modification of the occupancy theory

occupancy theory: $EC_{50} = K_D$

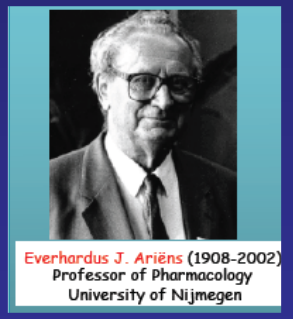
$$\text{occupancy} = \frac{[\text{bound receptors}]}{[\text{total receptors}]} = \text{magnitude of response}$$

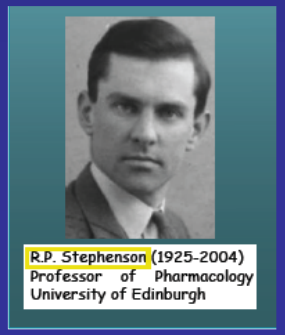
But some ligands fail to produce maximum response even at very high concentrations

Ariens (1954) & Stephenson (1956)

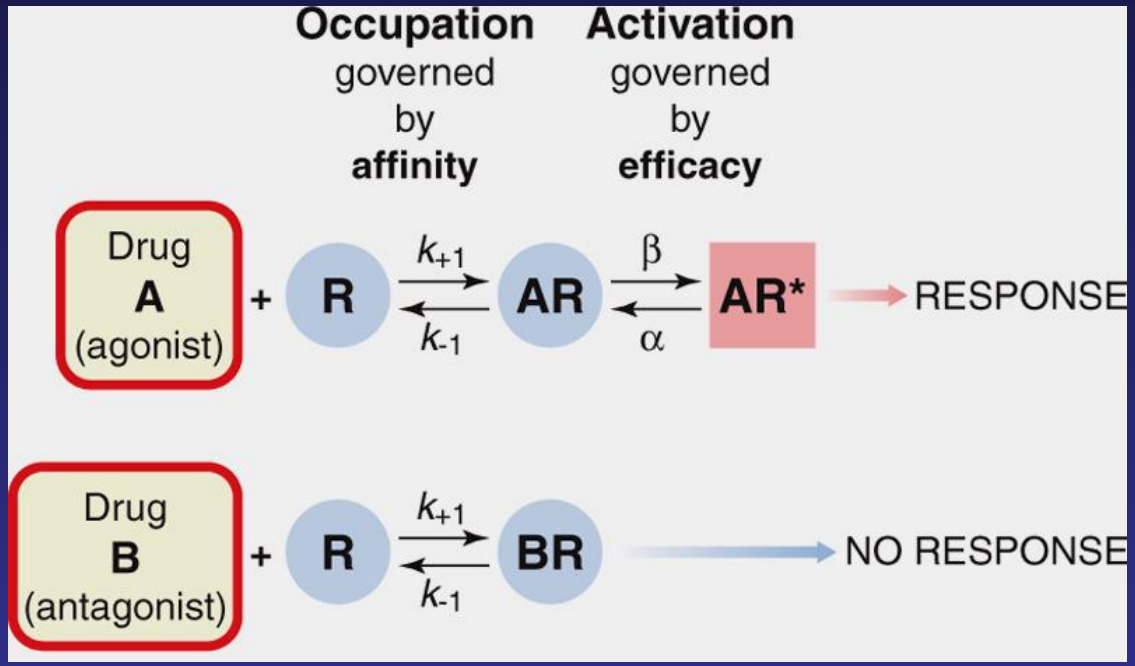
magnitude of response = ε_A . fractional occupancy

efficacy or *intrinsic activity*

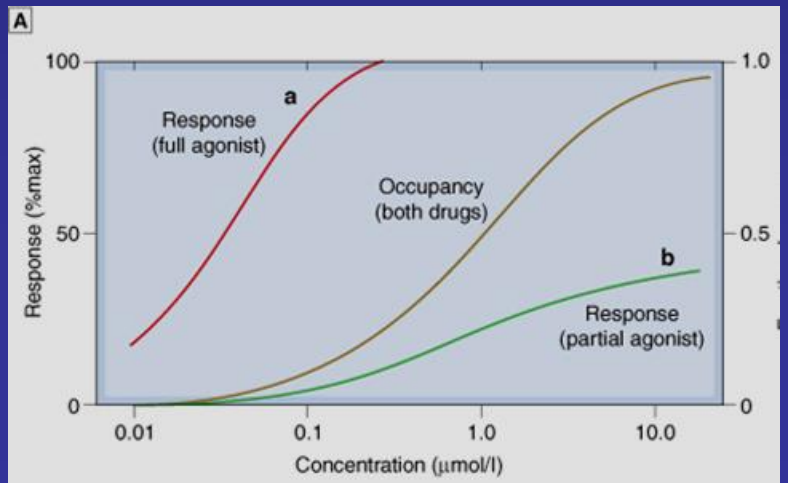




ligand-receptor interaction: affinity vs efficacy



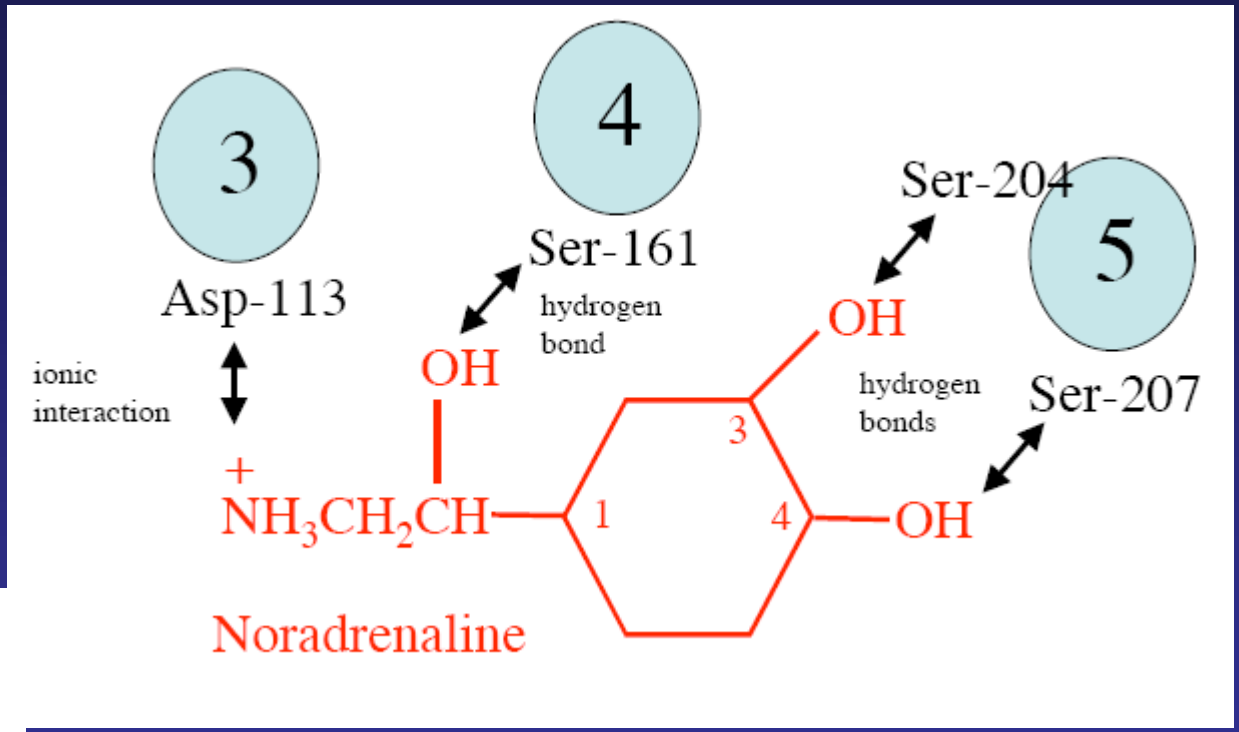
- affinity: ability to bind
- efficacy: ability to activate

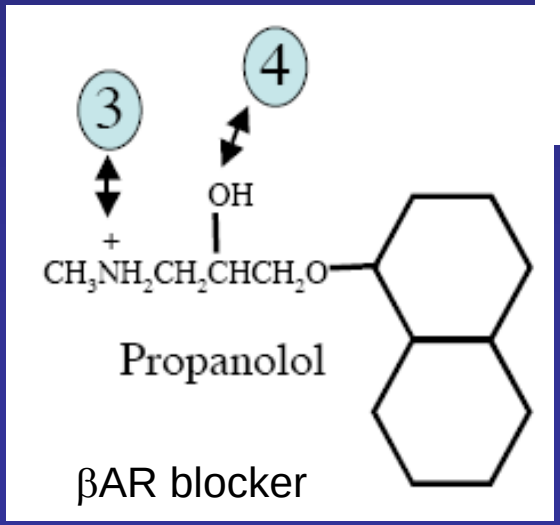


- antagonists have same (or higher) affinity but no efficacy
- partial agonists have lower efficacy

what underlie the differences between affinity and efficacy

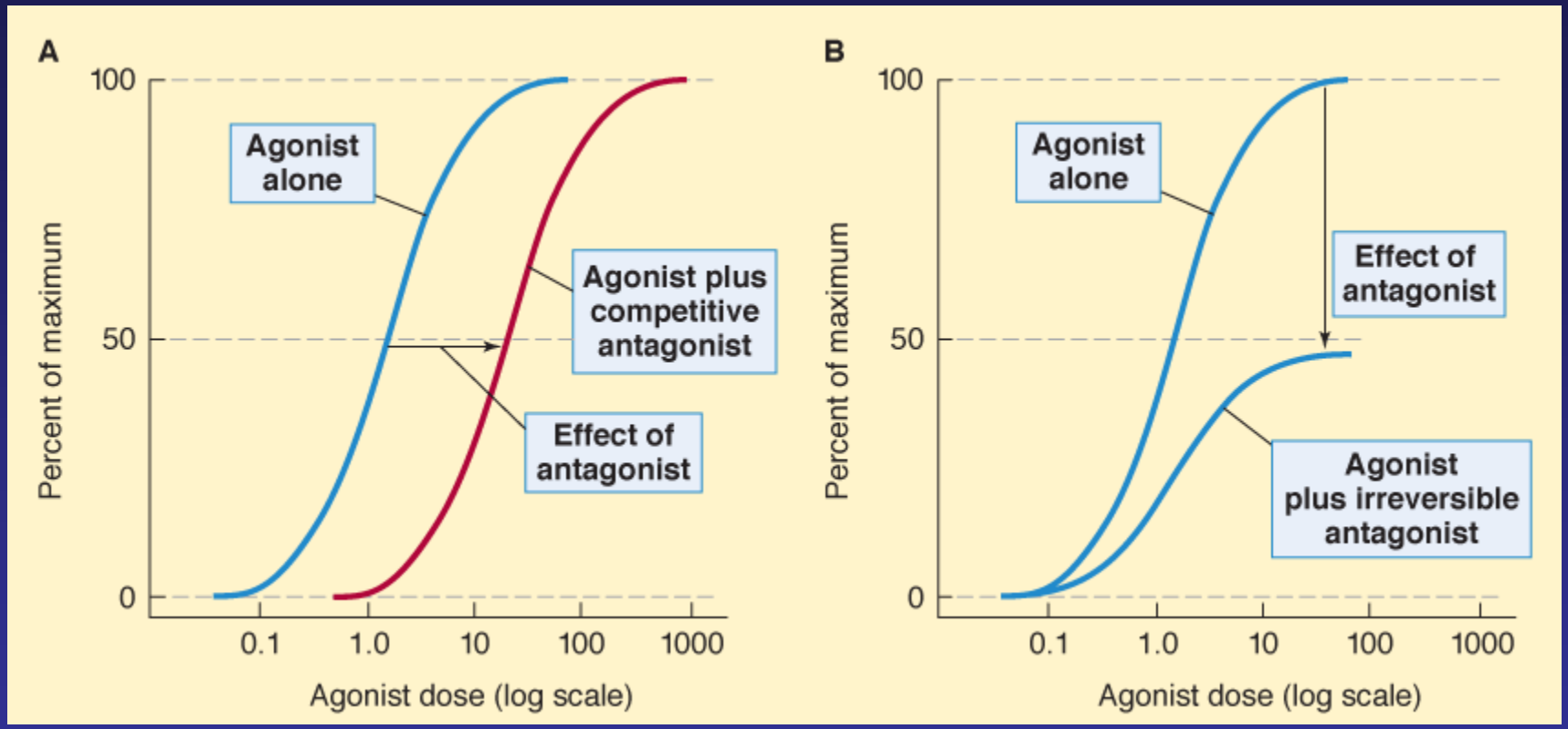
β-adrenergic receptor (β–AR)





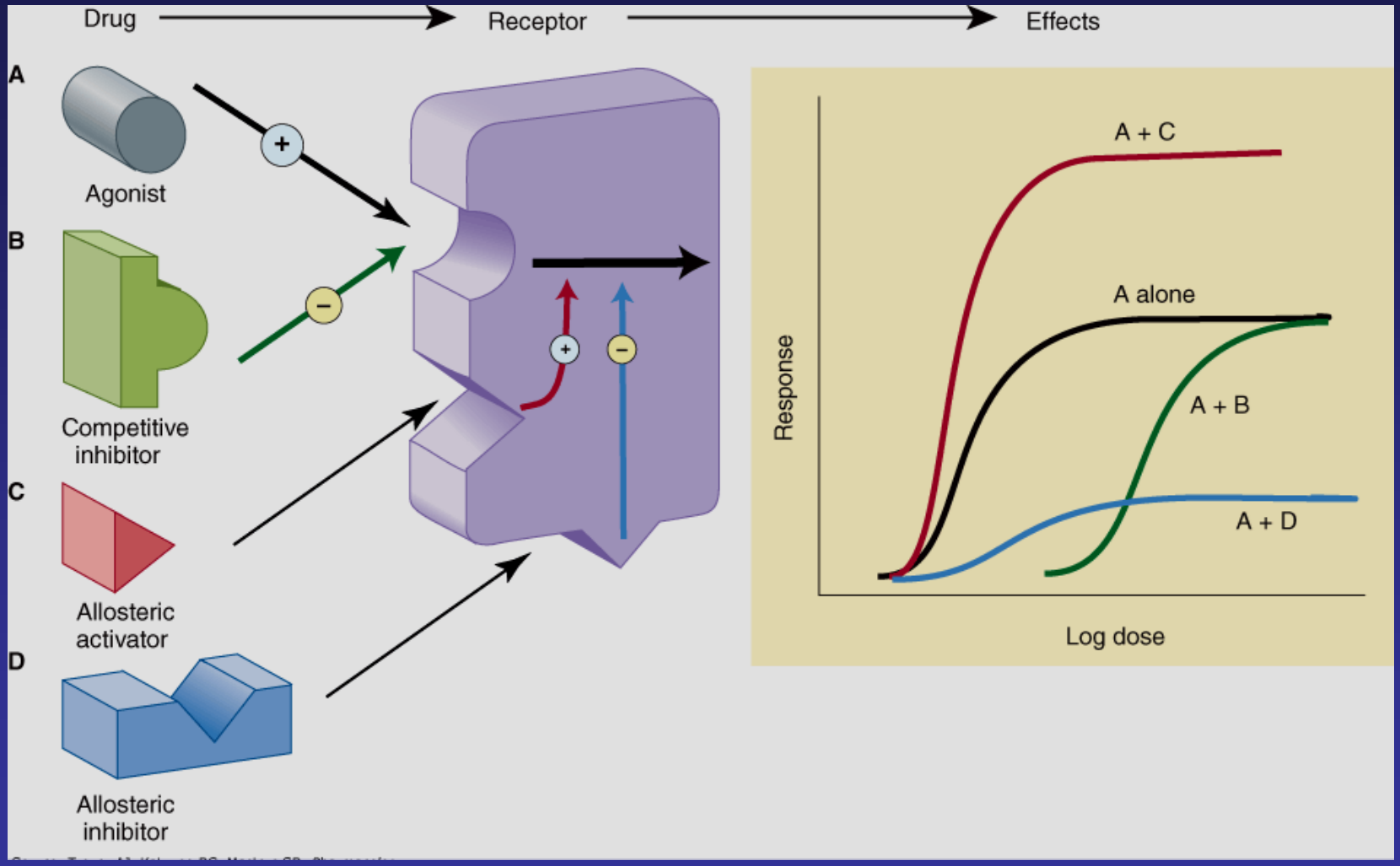
certain contacts can be crucial for activity

various forms of receptor antagonism



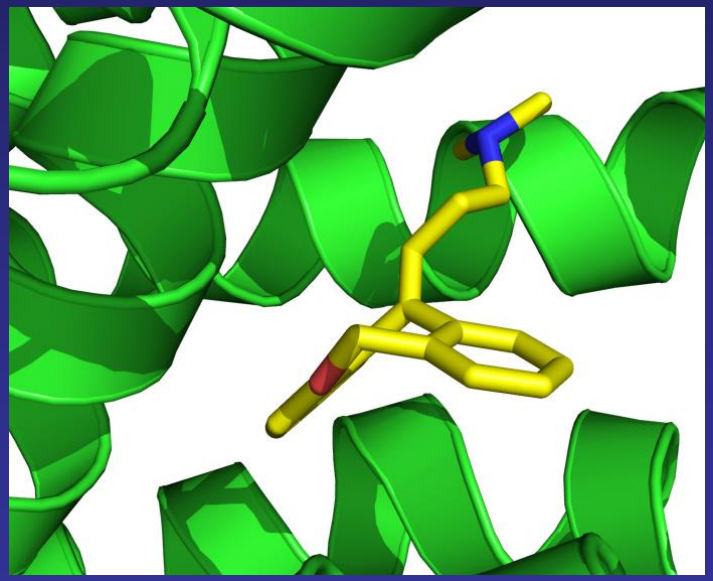
receptor can be reversibly or irreversibly inhibited

various forms of receptor modulation

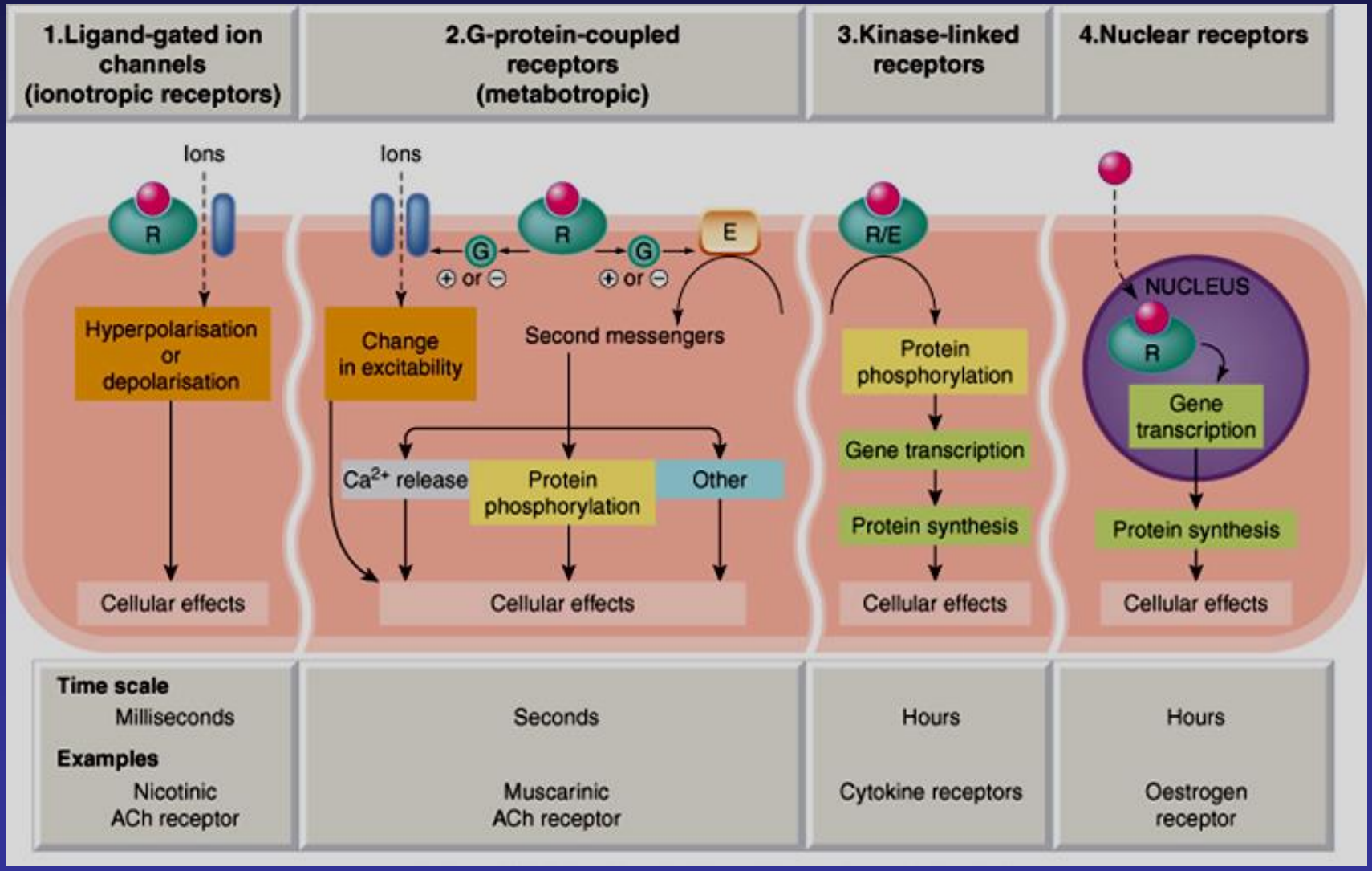


end of part II

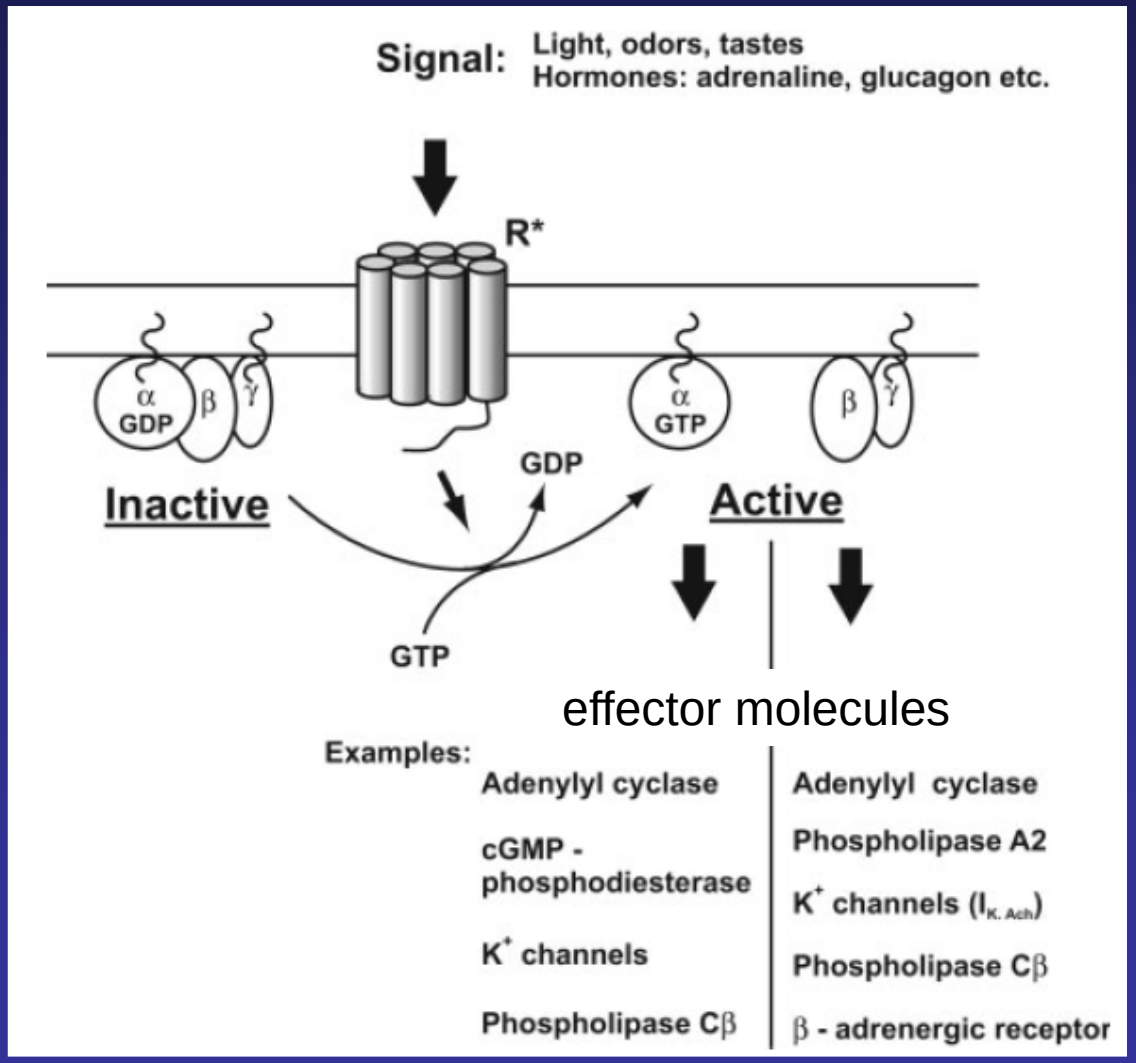
Part III:
common receptor classes
terminating active receptors

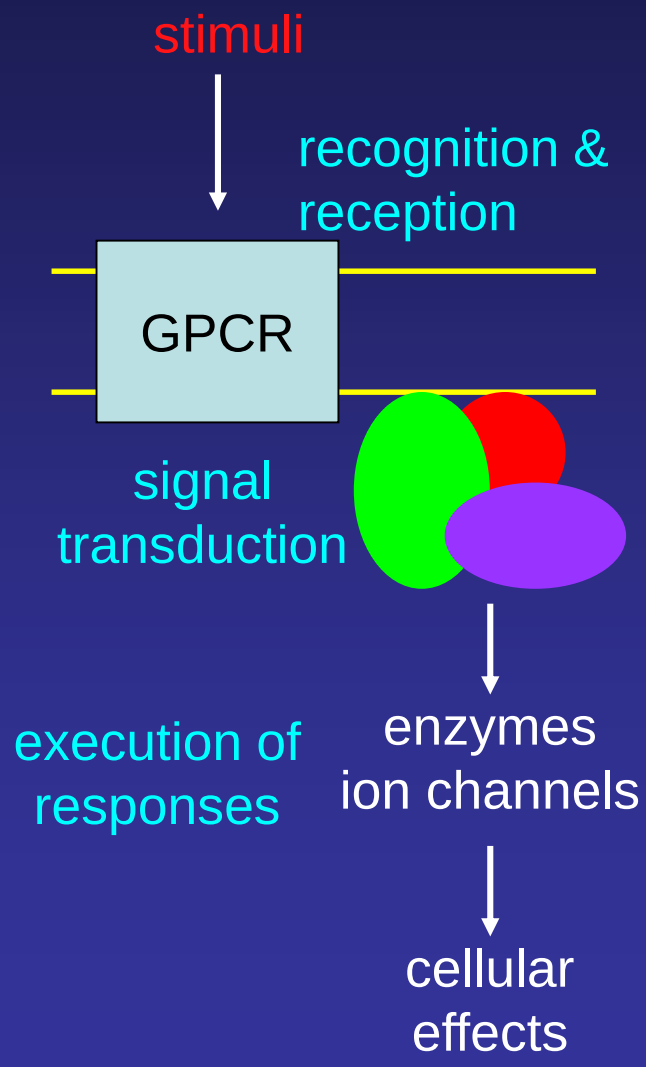


major types of receptors

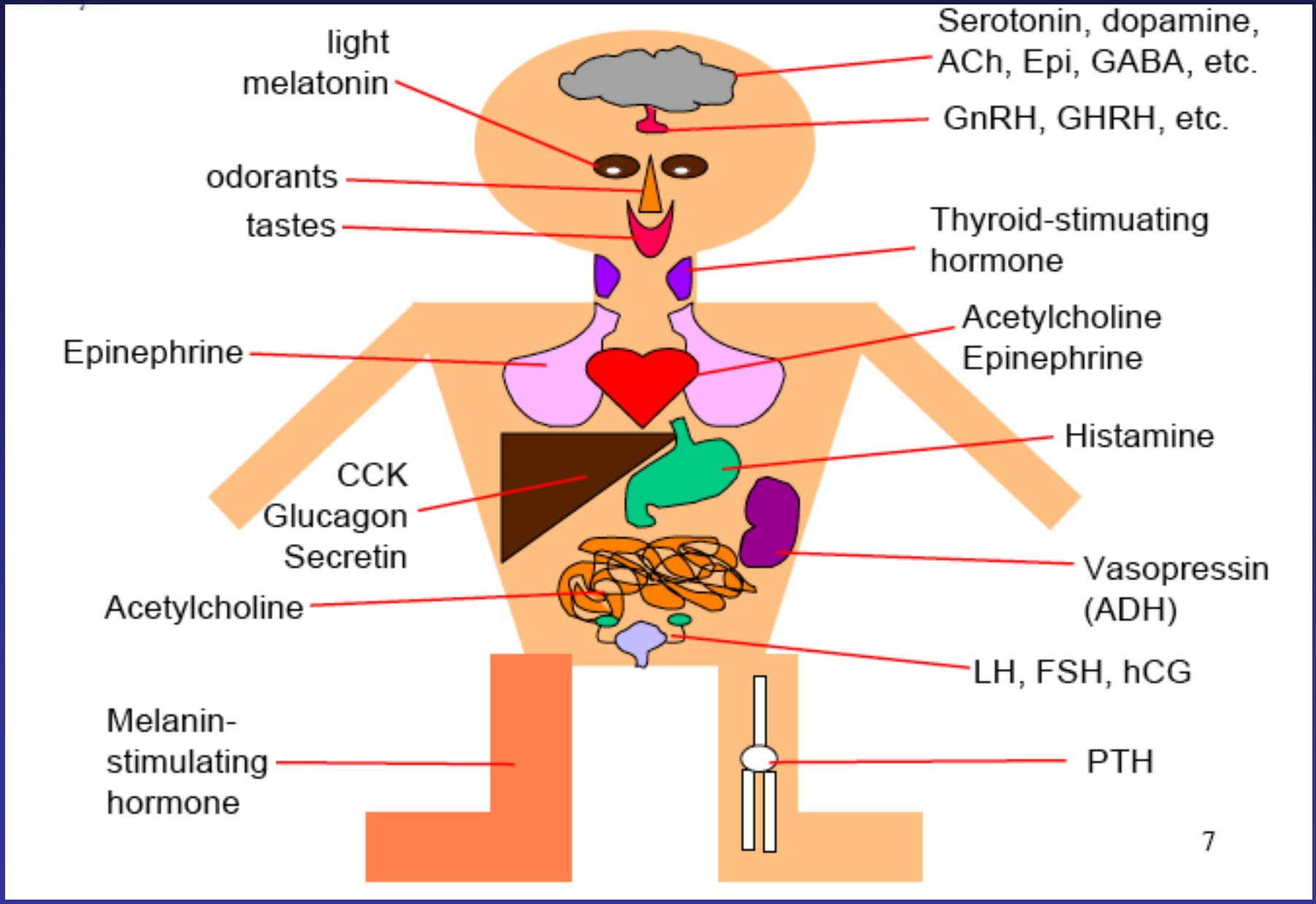


heterotrimeric G proteins act as transducers for GPCRs





diversity of GPCRs



GPCR signalling shapes organism response

‘fight or flight’ response

sympathetic nervous system

Adrenalin/noradrenalin mediated via α-AR and β-AR

‘rest & digest’ response’

parasympathetic nervous system

acetylcholine mediated via muscarinic and nicotinic AChR

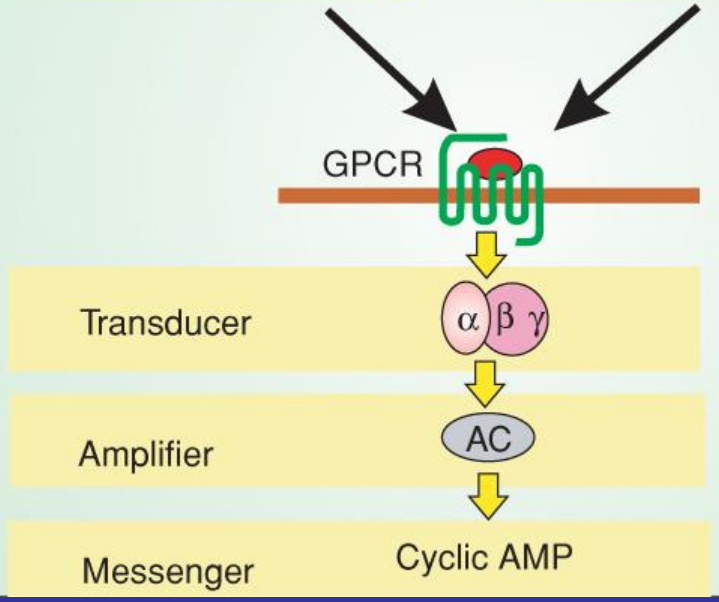
some GPCRs signal by regulating the production of cyclic AMP

NEUROTRANSMITTERS

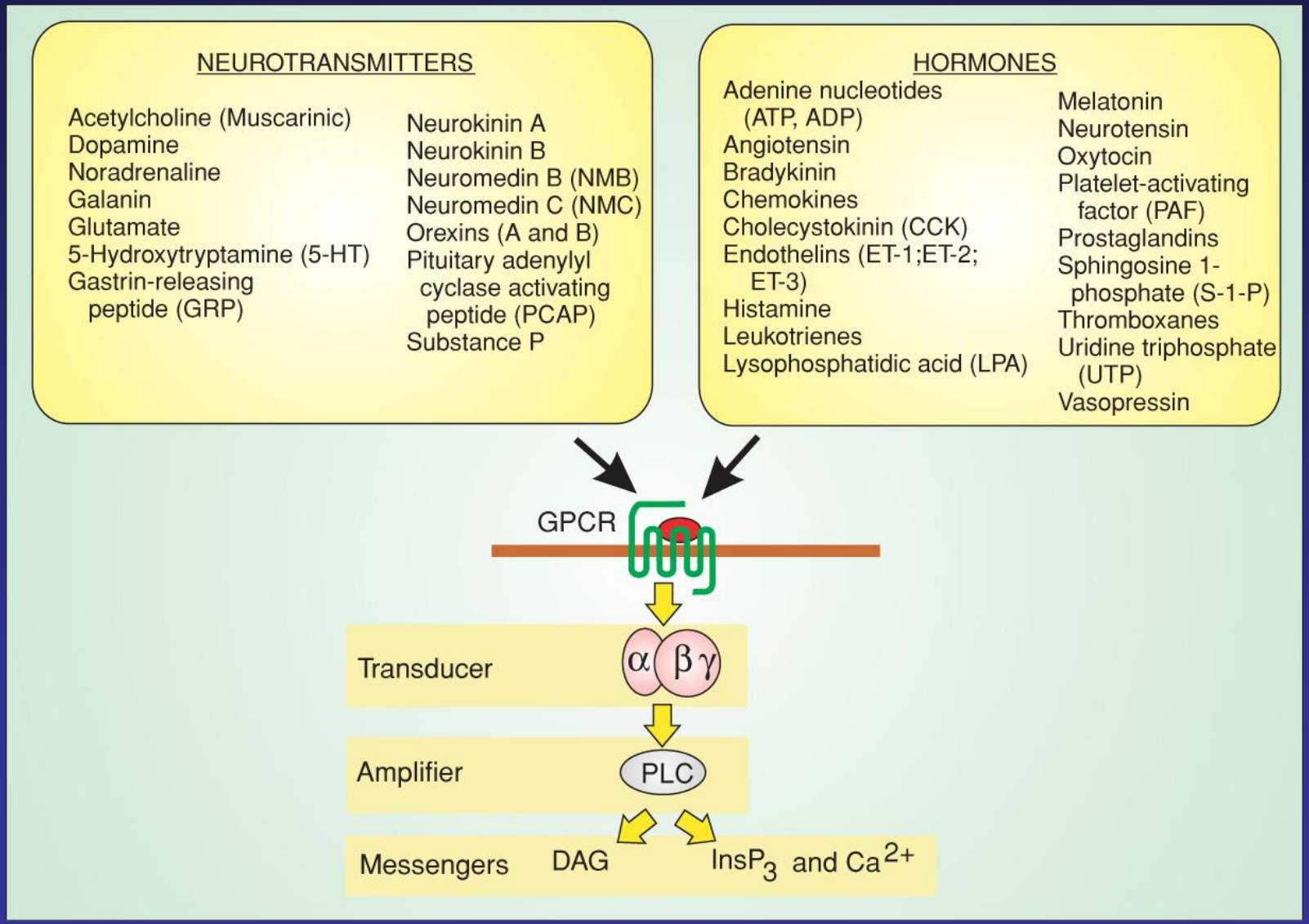
- Acetylcholine (Muscarinic)
- Amylin
- Adrenomedullin (ADM)
- Calcitonin gene-related peptide (CGRP)
- Corticotropin-releasing factor (CRF)
- Dopamine
- Noradrenaline
- Δ–Tetrahydrocannabinol
- γ-Aminobutyric acid (GABA)
- Galanin
- Glutamate
- 5-Hydroxytryptamine (5-HT)
- Melanocyte stimulating hormone (α-MSH; γ-MSH)
- Neuropeptide Y
- Opioids (Met-enk; Leu-enk; dynorphins; β-endorphin)
- Somatostatin
- Pituitary adenylyl cyclase activating peptide (PCAP)
- Vasoactive intestinal peptide (VIP)

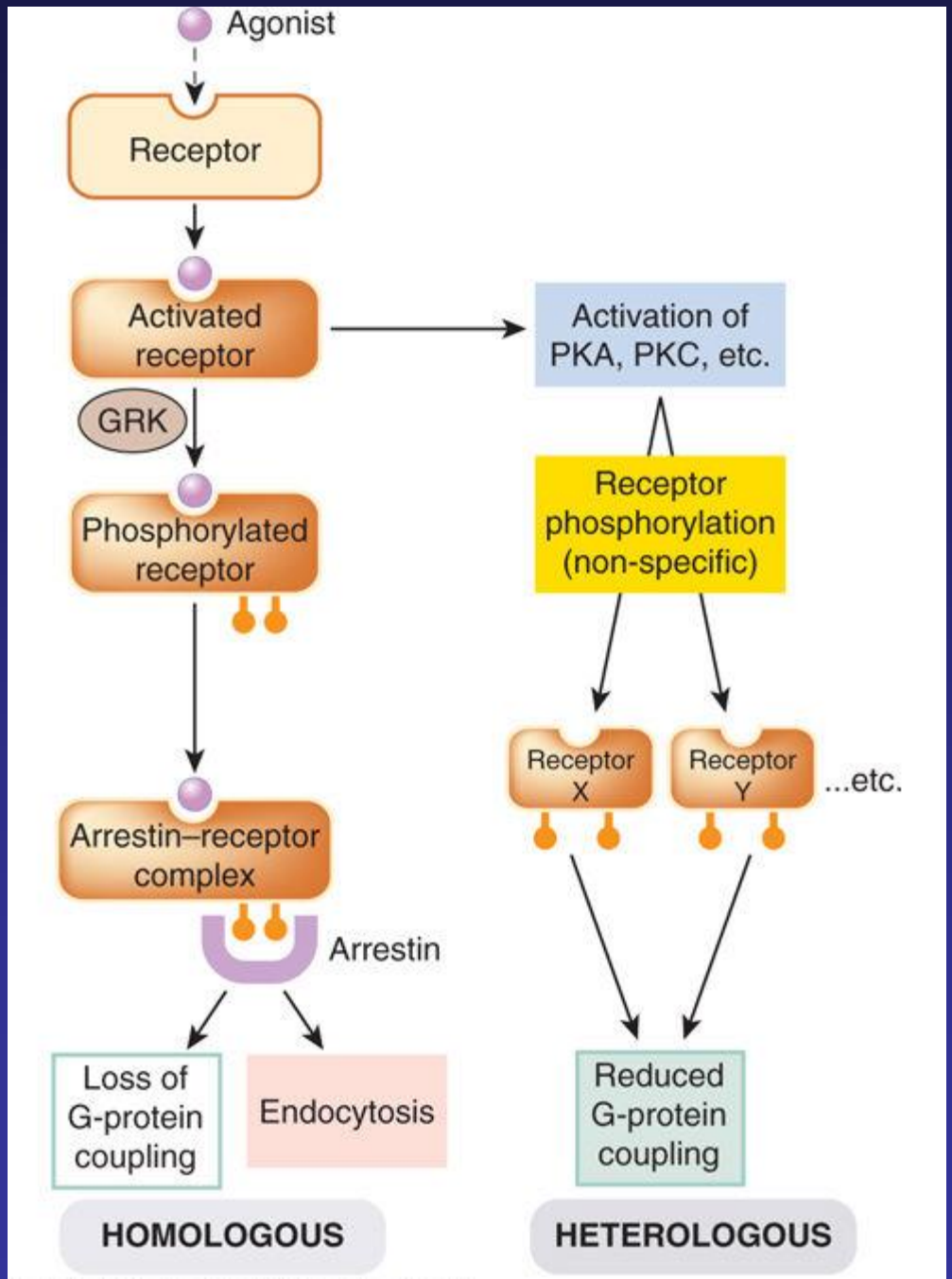
HORMONES

- Adenine nucleotides (ATP, ADP)
- Adenosine
- Adrenaline
- Adrenocorticotropic hormone (ACTH)
- Angiotensin
- Chemokines
- Glucagon
- Glucagon-like peptide 1 (GLP-1
- Histamine
- Lysophosphatidic acid (LPA)
- Sphingosine 1-phosphate (S-1-P)
- Melatonin
- Prostaglandins
- Uridine triphosphate (UTP)
- Vasopressin

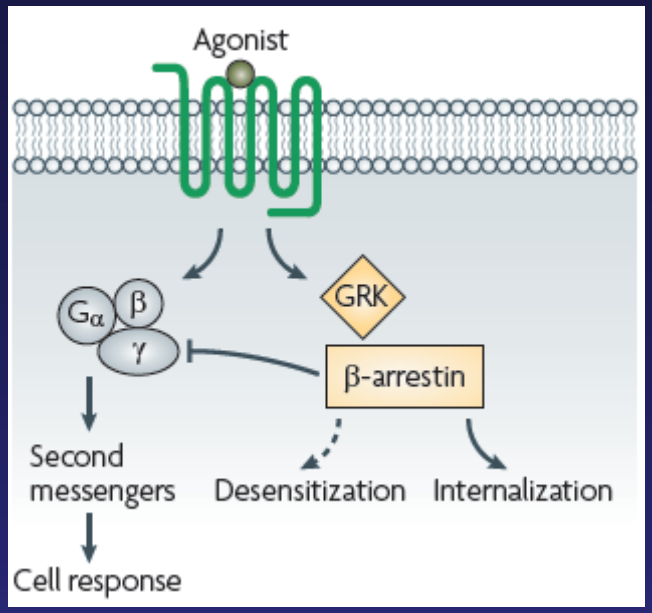


some GPCRs activate the inositol phospholipid signalling pathway



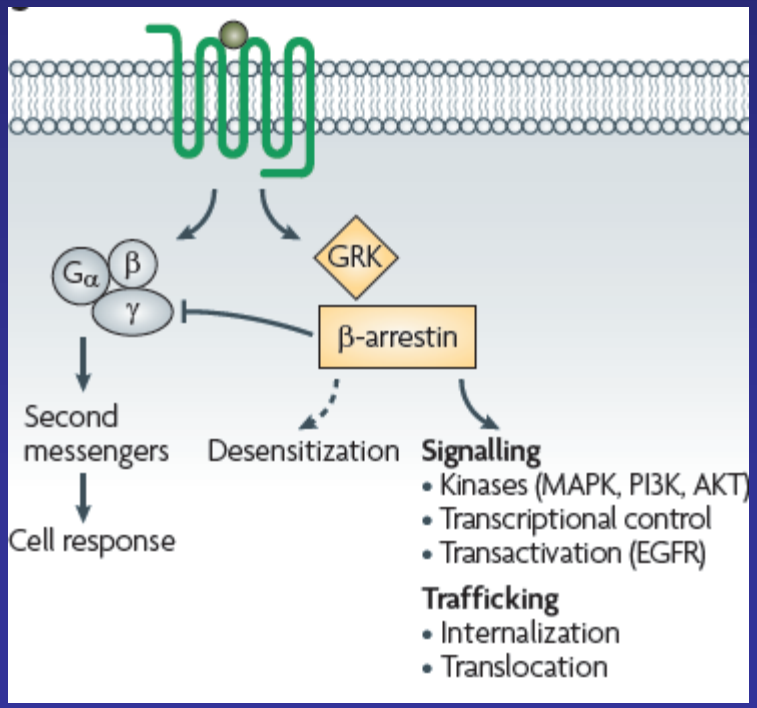


termination of GPCR signaling (routes for desensitization)



classical model of GPCR signalling

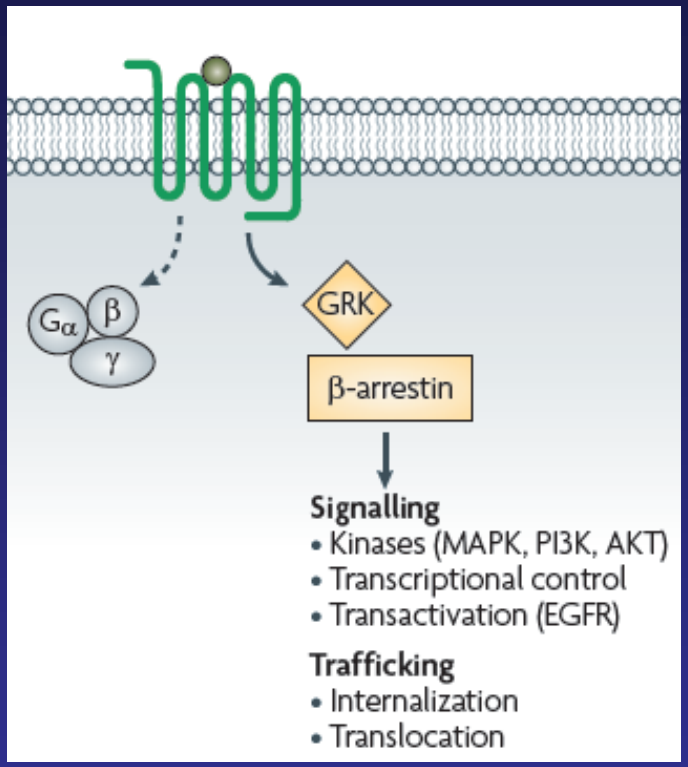
- signalling is mediated by Gα and βγ only
- β-Arrestin is only involved for receptor desensitization and internalisation



current view of GPCR signalling

- signalling is mediated by Gα and βγ as well as by β-Arrestin
- β-Arrestin also mediates receptor desensitization and internalisation

biased agonism or stimulus trafficking



original notion

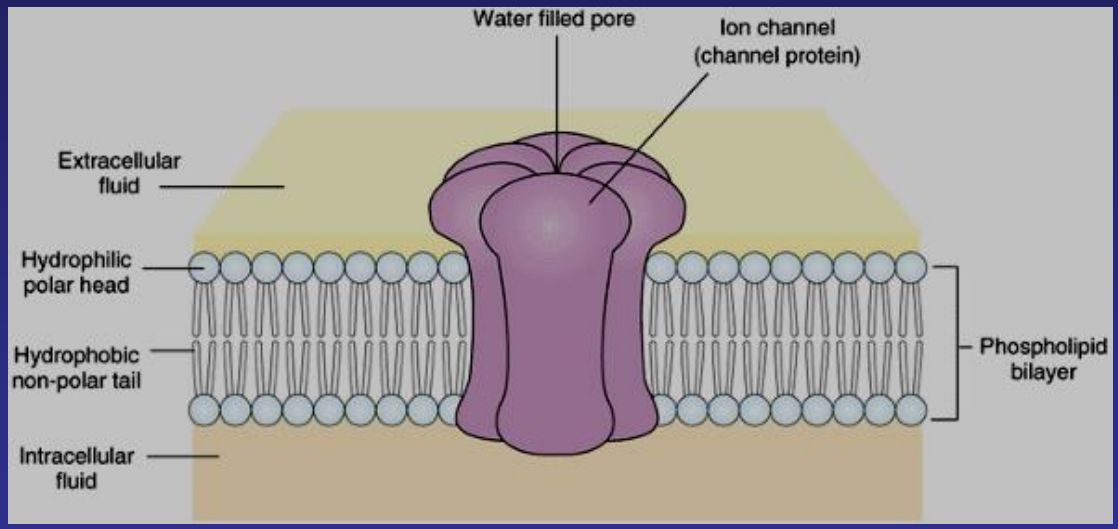
Ligands that bind GPCR have unbiased preference towards G protein and β-arrestin mediated downstream signalling pathways i.e. they signal equally through both

current view

Ligands that bind GPCR may selectively promote either G protein or β-arrestin mediated downstream signalling pathways

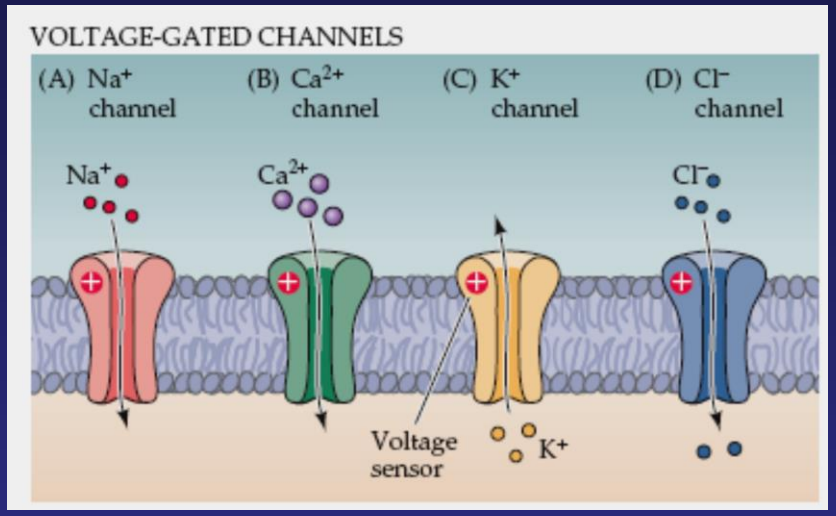
ion channels – receptors with holes

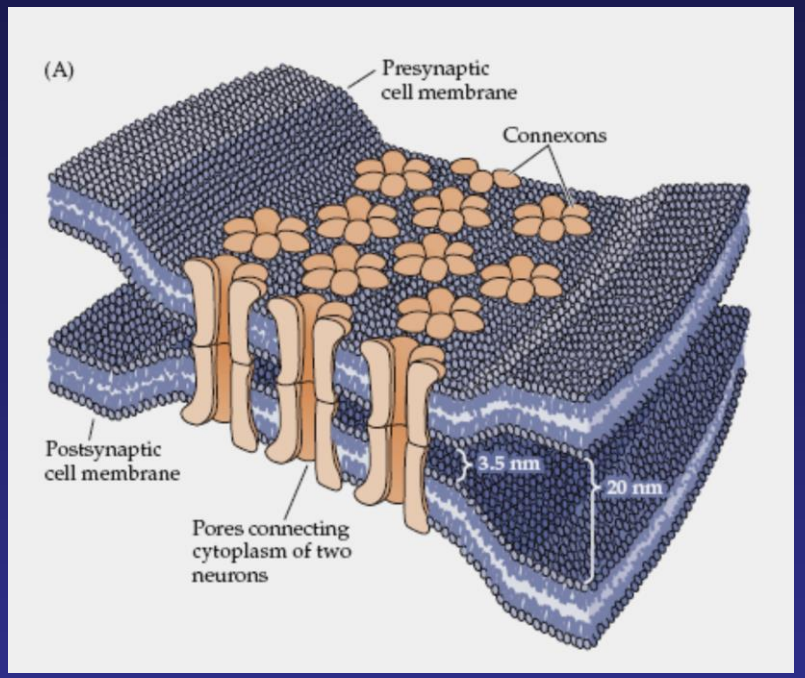
- integral membrane proteins
- contain ion conductive pores
- allow influx or efflux of ions across biological membranes

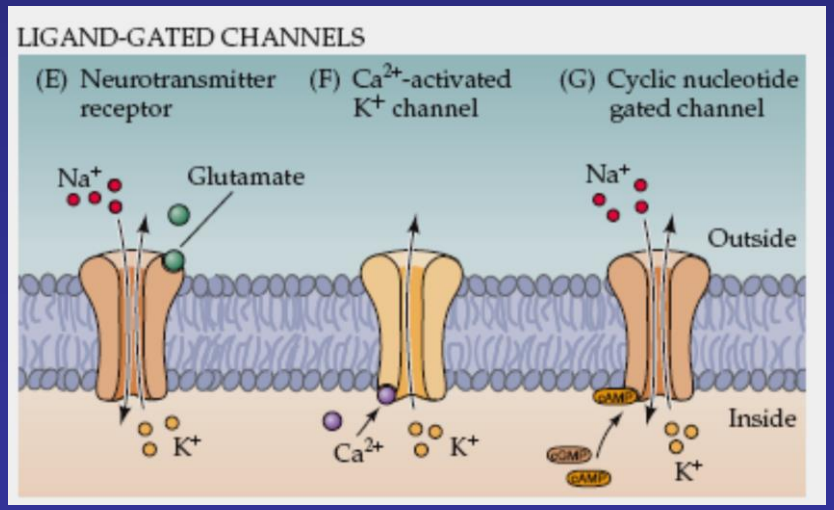


- can be activated
  - by changes in membrane potential
  - binding of particular ligands
  - changes in pH, temperature, cell volume
  - changes in intracellular Ca^{2+} concentration
  - mechanical deformation or stress

major types of ion channels







- voltage-gated
- ligand-gated
- gap junctions
- others e.g. mechanosensitive

receptors with enzyme activity

growth factor receptors

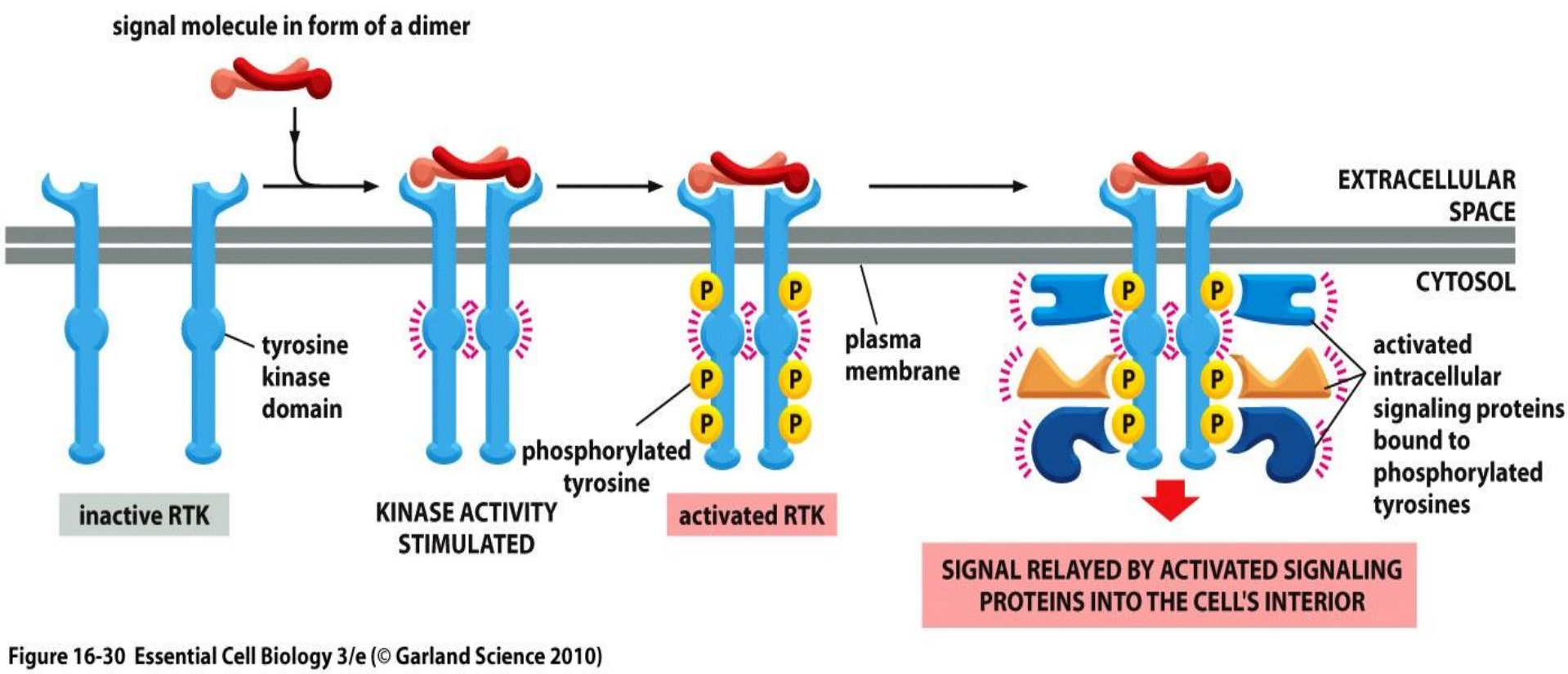
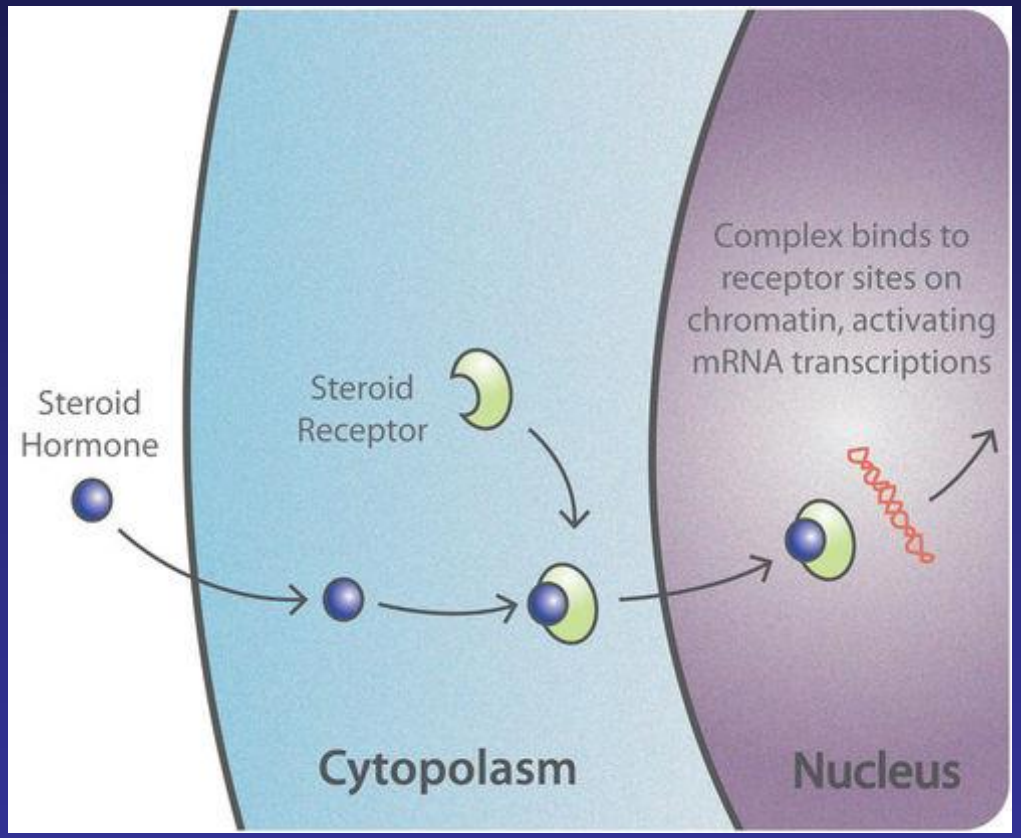


Figure 16-30 Essential Cell Biology 3/e (© Garland Science 2010)

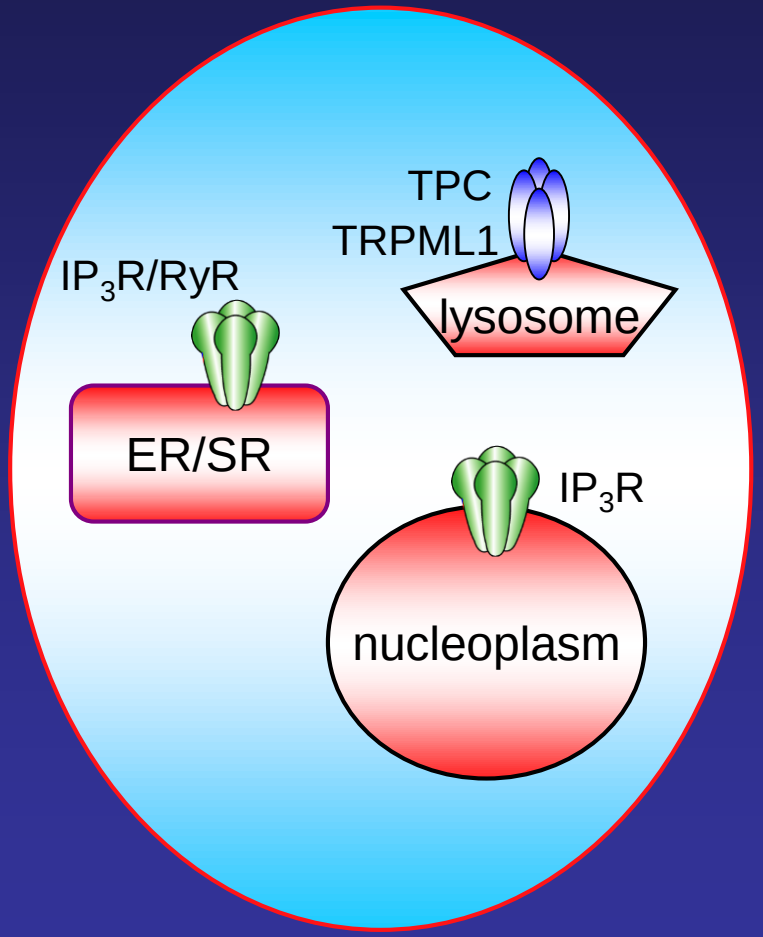
the substrate protein can be an enzyme or an adaptor protein

intracellular receptors

nuclear hormone receptors



intracellular ionotropic receptors (ion channels)



A very good and up to date resource on receptors & cell signalling

cell signallingbiology

Written by
Professor Sir Michael Berridge
University of Cambridge

http://www.cellsignallingbiology.org/csb/

If interested, may also consider visiting :
http://www.guidetopharmacology.org/

THANKS