

HOW DRUGS ACT

Corpora non agunt nisi fixata

(drugs do not act unless they are bound)



Paul Ehrlich (1854-1915)

CLASSIFICATION OF PROTEIN TARGETS FOR DRUG BINDING

1. RECEPTORS

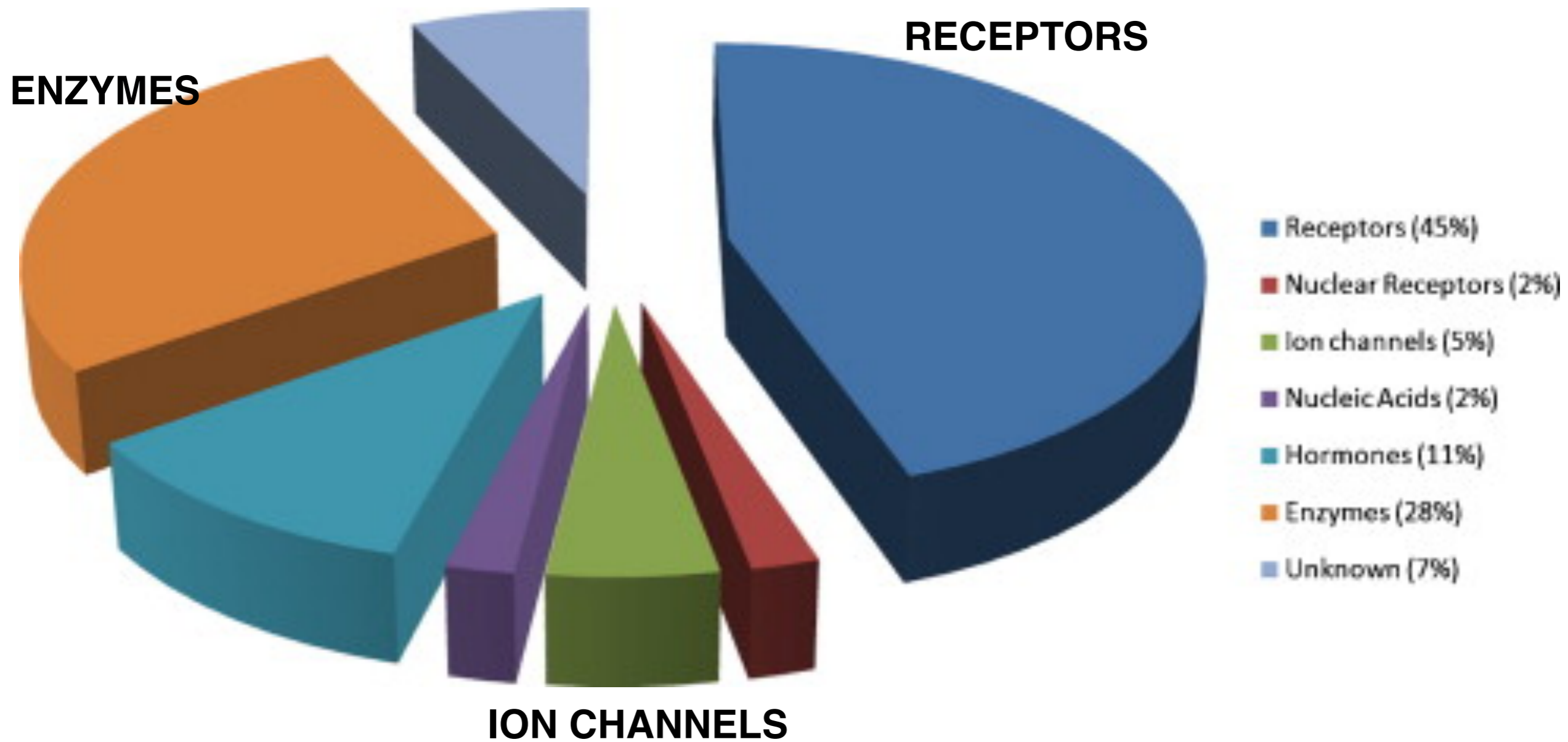
2. VOLTAGE DEPENDENT ION CHANNELS

3. ENZYMES

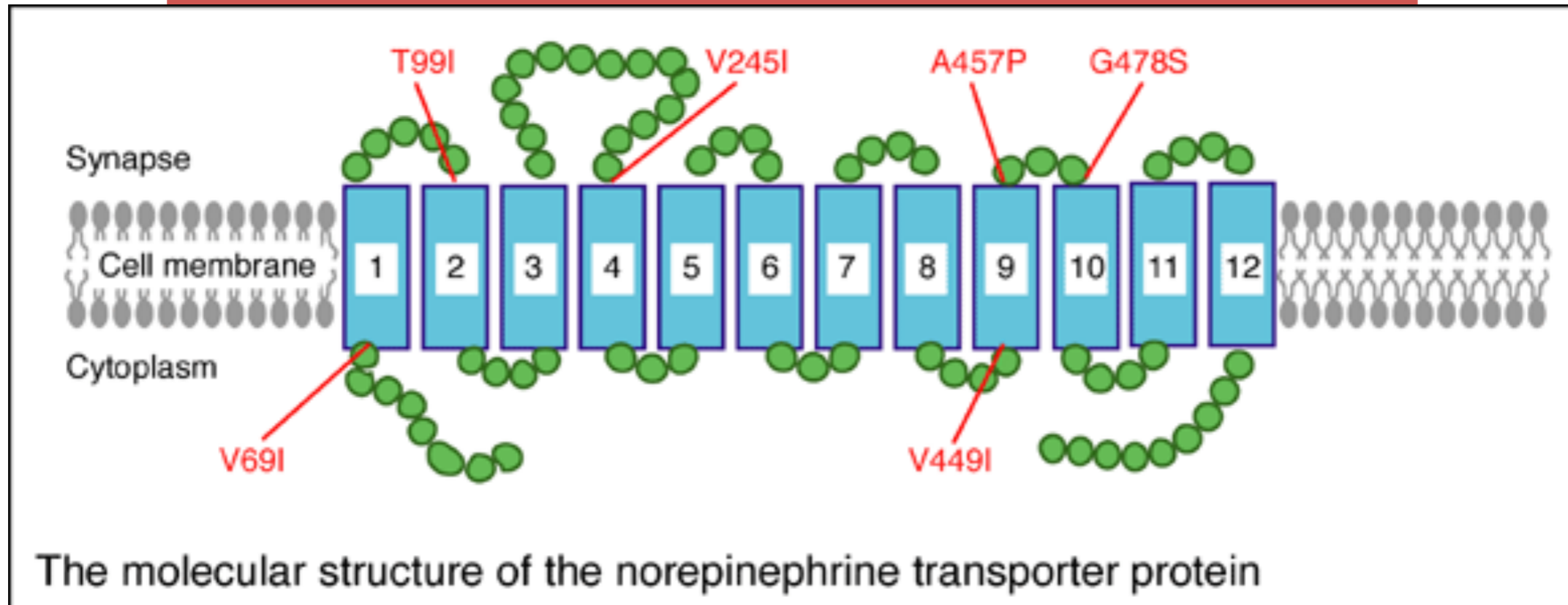
4. TRANSPORTERS

**In pharmacology, the term "receptor" describes protein molecules whose function is to recognise and respond to endogenous chemical signals
Other macromolecules with which drugs interact to produce their effects are "drug target"**

PROTEIN TARGETS FOR DRUG BINDING



4. TRANSPORTERS or CARRIERS



TYPE	INHIBITORS	FALSE SUBSTRATE	CLINICAL USE
Noradrenaline transporter (NAT)	Tricyclic antidepressant Cocaine	Amphetamine	Depression
MDR transporter	Probenecid		
Na ⁺ /K ⁺ /Cl ⁻ Co-transporter	Loop Diuretics		Hypertension Diuresis
Na ⁺ /K ⁺ ATPase	Digitoxin		Heart failure

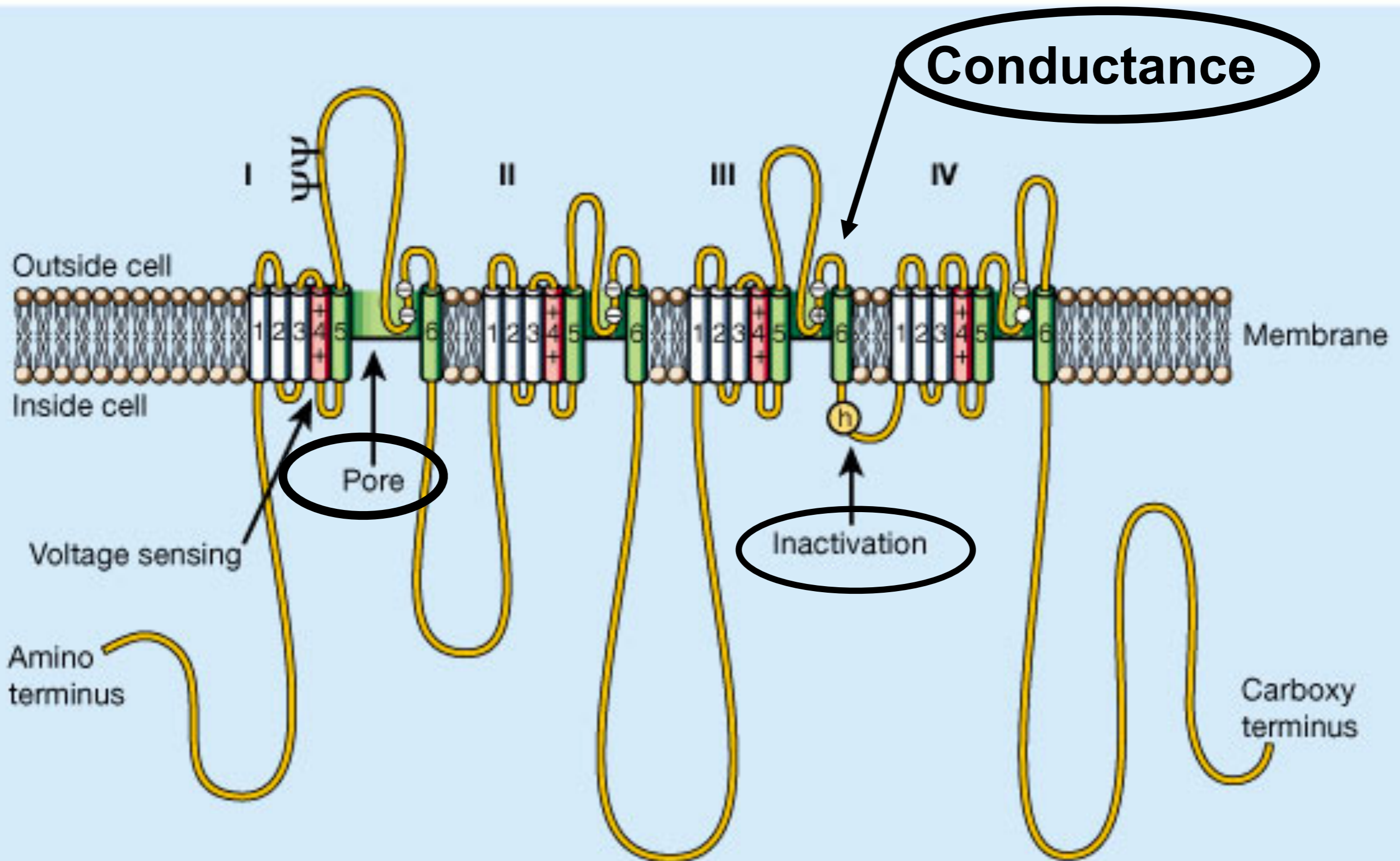
3. ENZYMES

TYPE	INHIBITORS	FALSE SUBSTRATE	CLINICAL USE
Acetylcholinesterase	Donezepil Organophosphates		Alzheimer Insecticide
Cyclo-oxygenase	Aspirin		Anti-inflammatory Anti-aggregation (platelets)
Nitric Oxide Syntase	L-NMMA L-NAME		
Monoamine Oxidase (MAO)	Meclobemide		Depression Parkinson's
DOPA- decarboxylase		L-DOPA	Parkinson's




2. VOLTAGE DEPENDENT ION CHANNELS

TYPE	BLOCKERS	MODULATORS	CLINICAL USE
Na ⁺ channels	Lidocaine Tetrodotoxin	Veratridine	Local anesthesia Anti-arithmetic
Ca ⁺ channels	Divalent cations e.g.: cadmium	Dihydropiridines	Hypertension
ATP-sensitive K ⁺ channels	ATP	Sulfonylurea derivatives	Diabetes type 2

2. VOLTAGE-DEPENDENT ION CHANNELS General Features



VOLTAGE DEPENDENT Na⁺ CHANNELS

Neurotoxin Receptor site	Toxin	Origin
1	Tetrodotoxin Saxitoxin (PSP) μ-conotoxin	Fugu rubripes (blowfish) Dinoflagellates Conus geografus
2	veratridin batracotoxin aconitin grayanotoxin	Veratrum (rhizome, Liliacee) Phyllobates terribilis (frog)
3	α-scorpion toxin Sea anemone toxin	
4	β-scorpion toxin	
5	brevitoxins ciguatoxins	Dinoflagellate 
6	δ-conotoxin	Conus

Bufo alvarius (Colorado River toad or Sonoran Desert toad)

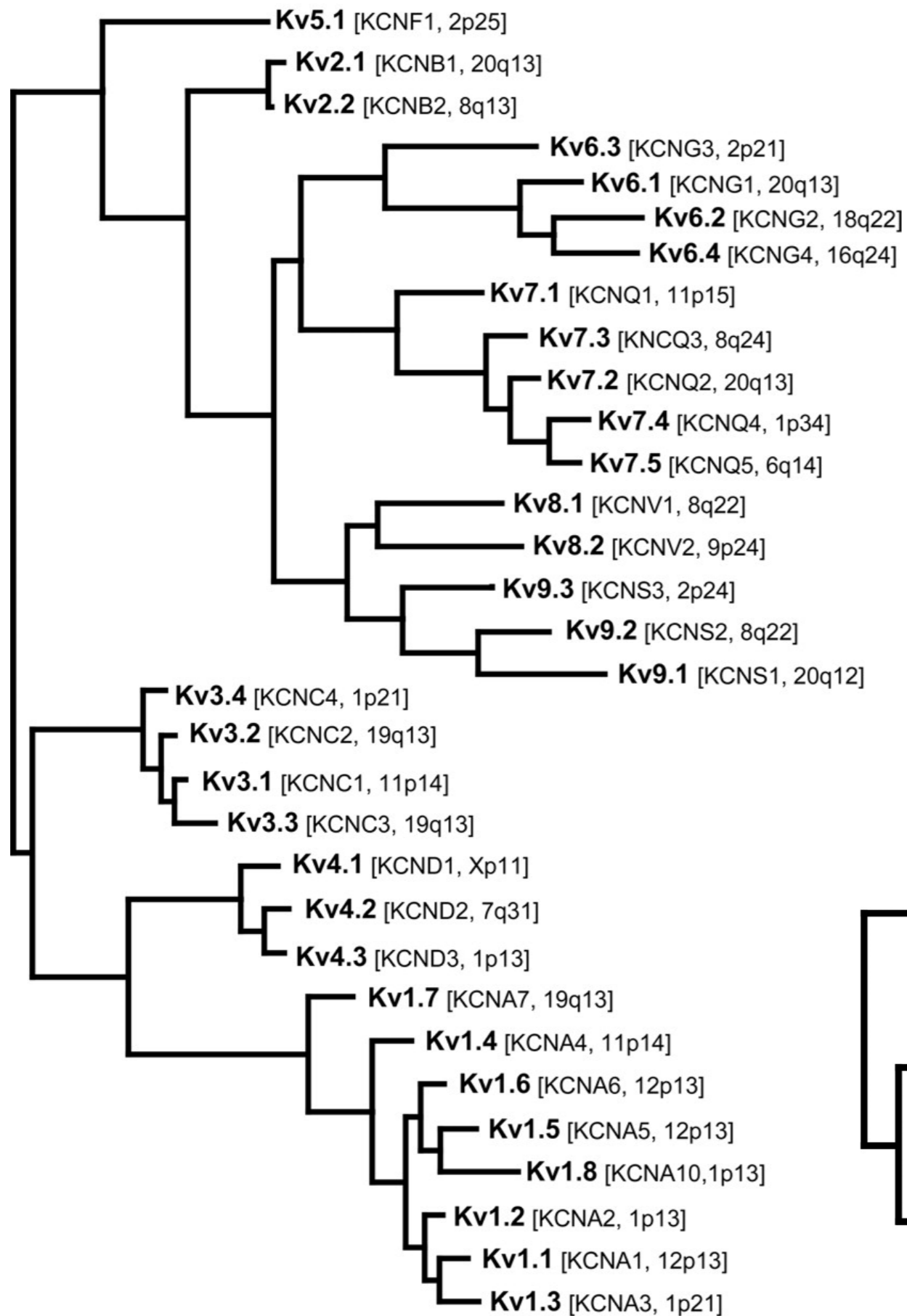


Bufotoxin: cardioactive steroid
5MeO-DMT and bufotenin: family of hallucinogenic
tryptamines (LSD)

VOLTAGE-DEPENDENT Ca²⁺ CHANNELS

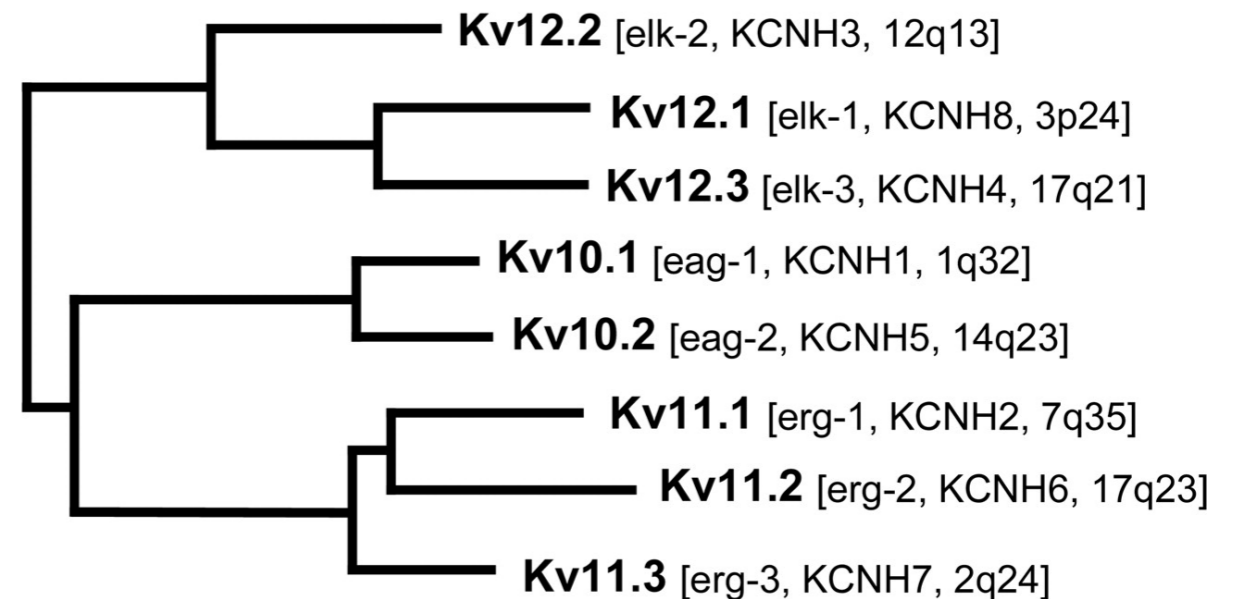
α_1 subunit	Subunit (type of current)	Localization	Main function	Drugs	Toxins
Ca _v 1 (HVA current, long-lasting kinetics of inactivation)	Ca _v 1.1 (L-type)	Skeletal muscle	Initiation of contraction and secretion	calcium channel blockers-sensitive	
	Ca _v 1.2 (L-type)	Cardiac muscle Endocrine cells Neurons Smooth muscle			
	Ca _v 1.3 (L-type)	Endocrine cells Neurons			
	Ca _v 1.4 (L-type)	Retina			
Ca _v 2 (HVA current, long-lasting kinetics of inactivation)	Ca _v 2.1 (P/Q-type)	Nerve terminals Dendrites	Initiation of neurotransmission at most fast synapses	calcium channel blockers-insensitive	ω -agatoxin-IVA, ω -conotoxin MVIIC
	Ca _v 2.2 (N-type)	Nerve terminals Dendrites			ω -conotoxin GVIA ω -conotoxin MVIIC
	Ca _v 2.3 (R-type)	Cell bodies Dendrites Nerve terminals			SNX-482
Ca _v 3 (LVA current, transient kinetics of inactivation)	Ca _v 3.1 (T-type)	Cardiac muscle Skeletal muscle Neurons	Involvement in shaping the action potential and controlling patterns of repetitive firing	calcium channel blockers-insensitive	
	Ca _v 3.2 (T-type)	Cardiac muscle Neurons			
	Ca _v 3.3 (T-type)	Neurons			

Phylogenetic Tree, Kv1-9 Families

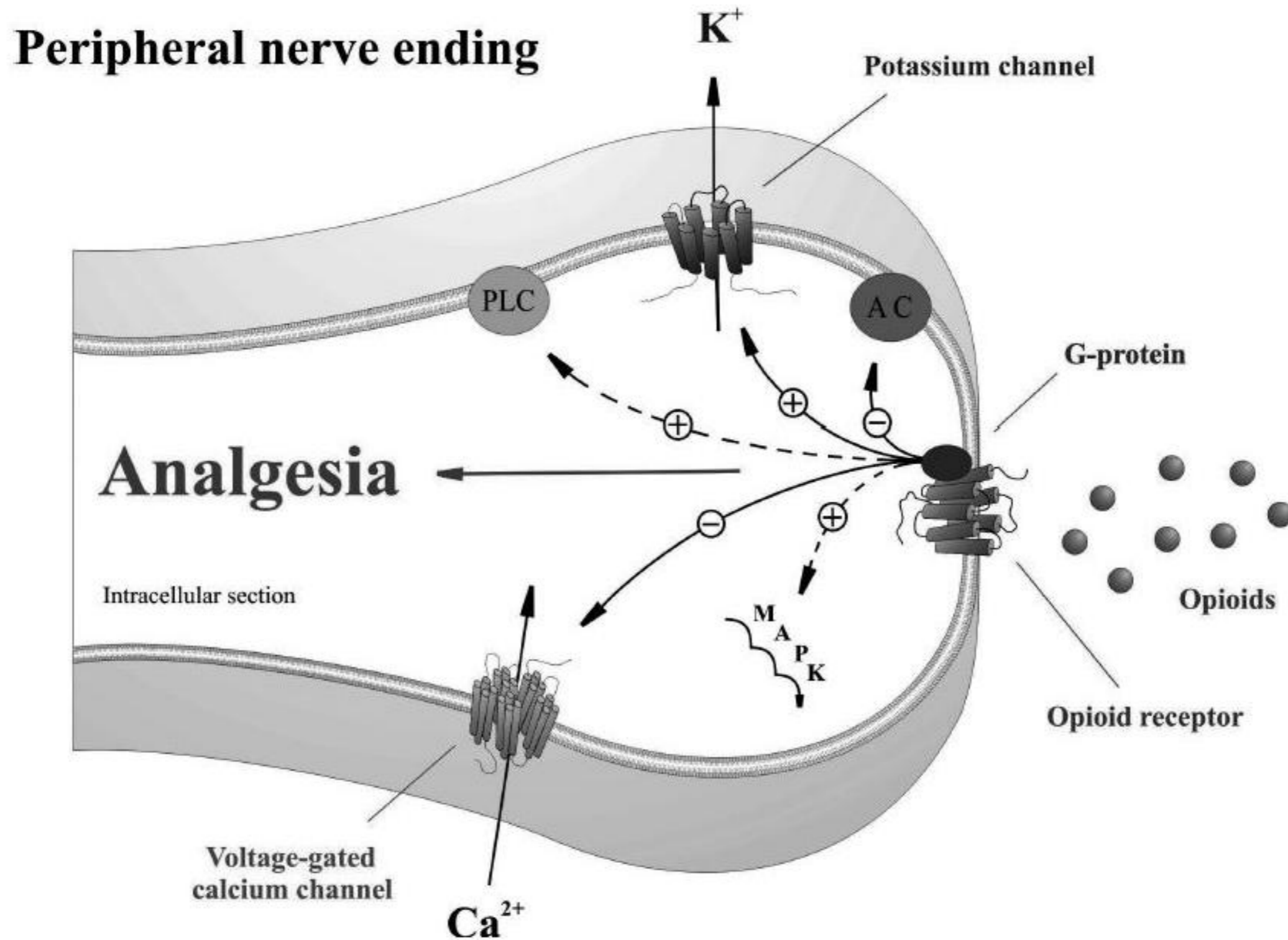


VOLTAGE-GATED K⁺ CHANNELS

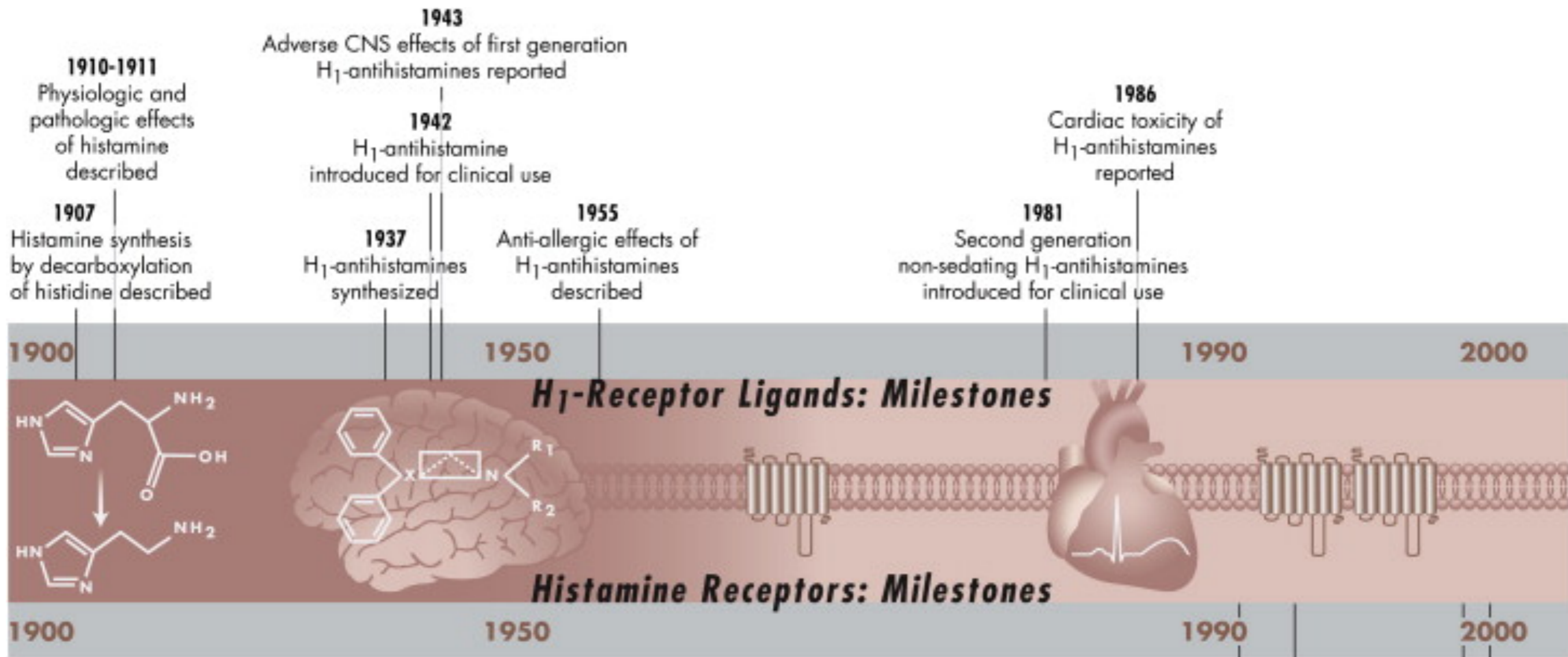
Phylogenetic Tree, Kv10-12 Families



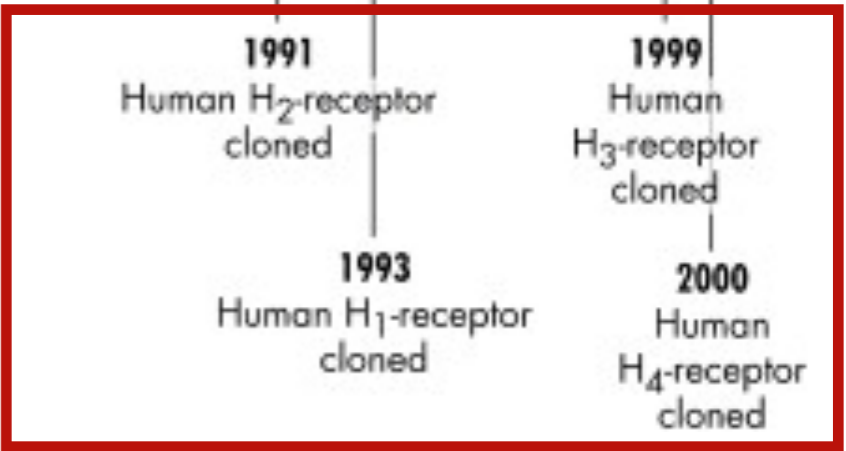
Proposed model for opioid receptor-mediated analgesia at peripheral terminals of primary sensory neurones



1. RECEPTORS



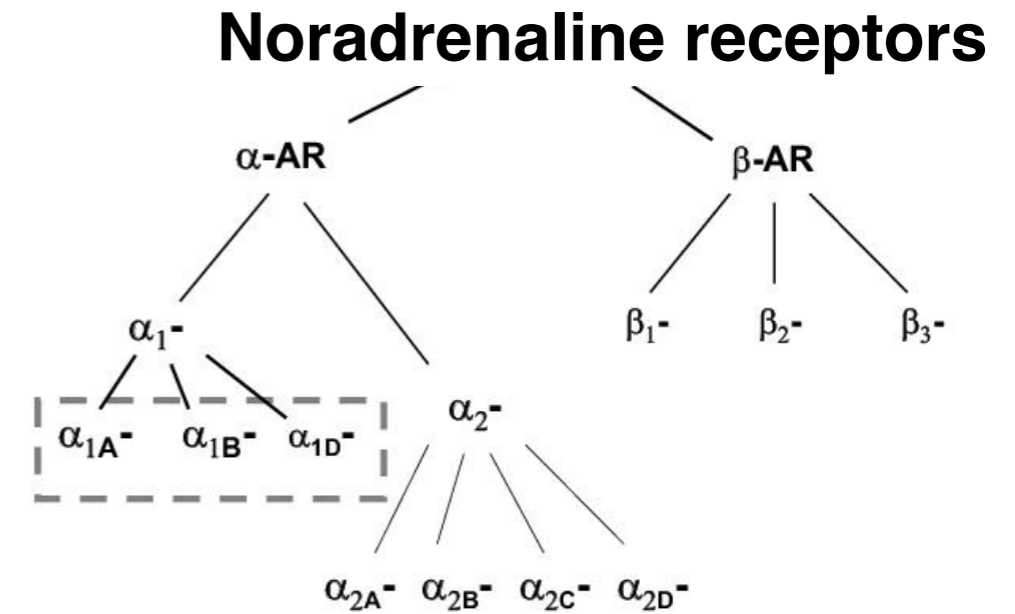
Serotonin receptor subtypes



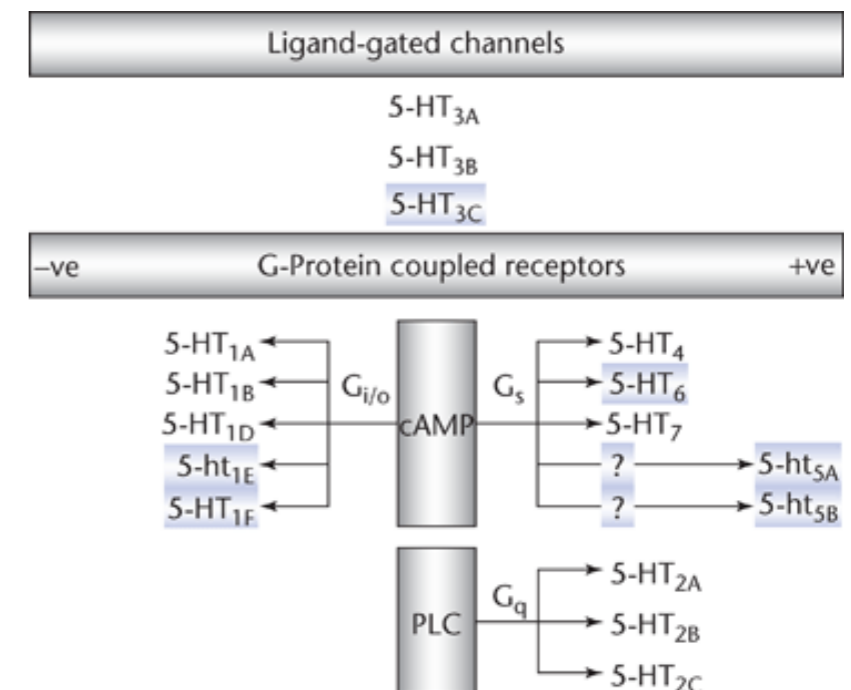
RECEPTOR HETEROGENEITY AND SUBTYPES

Receptors within a family generally occur in several subtypes with similar structure but significant differences in their

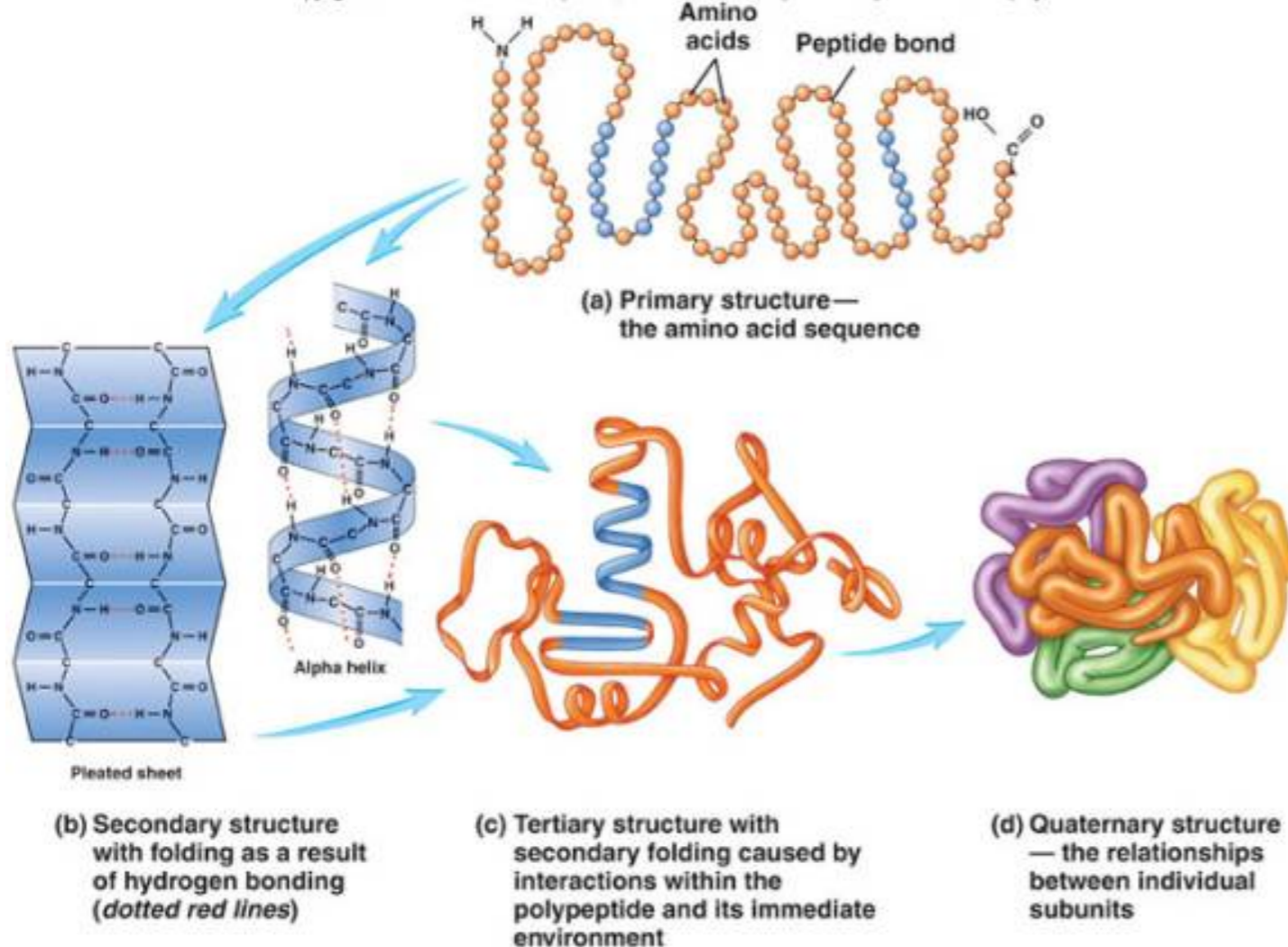
- 1) aminoacidic sequences
- 2) pharmacological properties
- 3) tissue distribution
- 4) regulatory mechanisms



Serotonin receptors

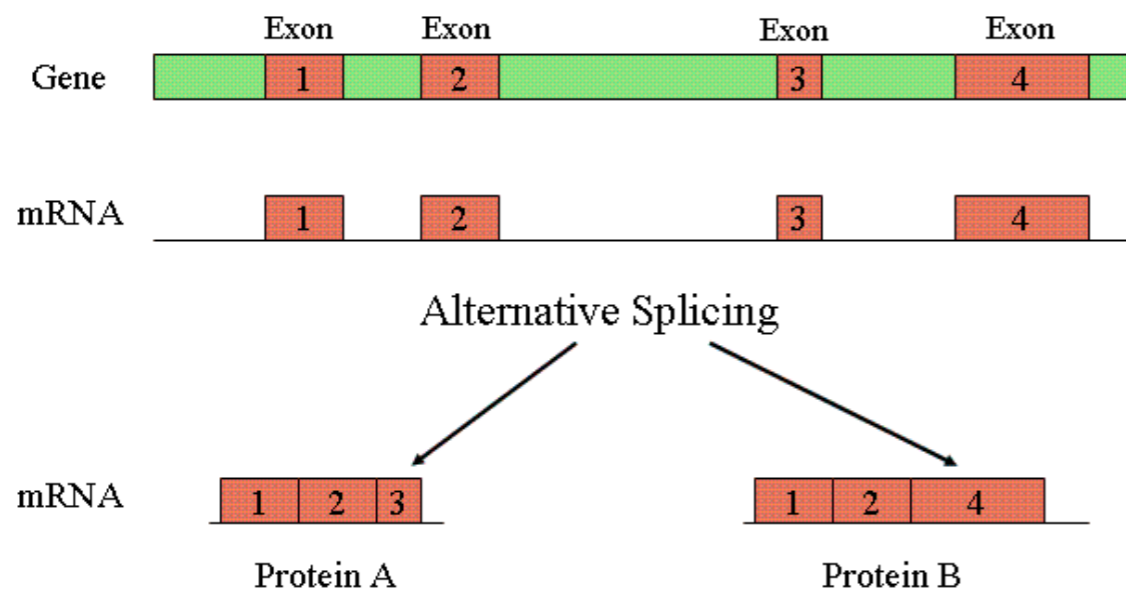
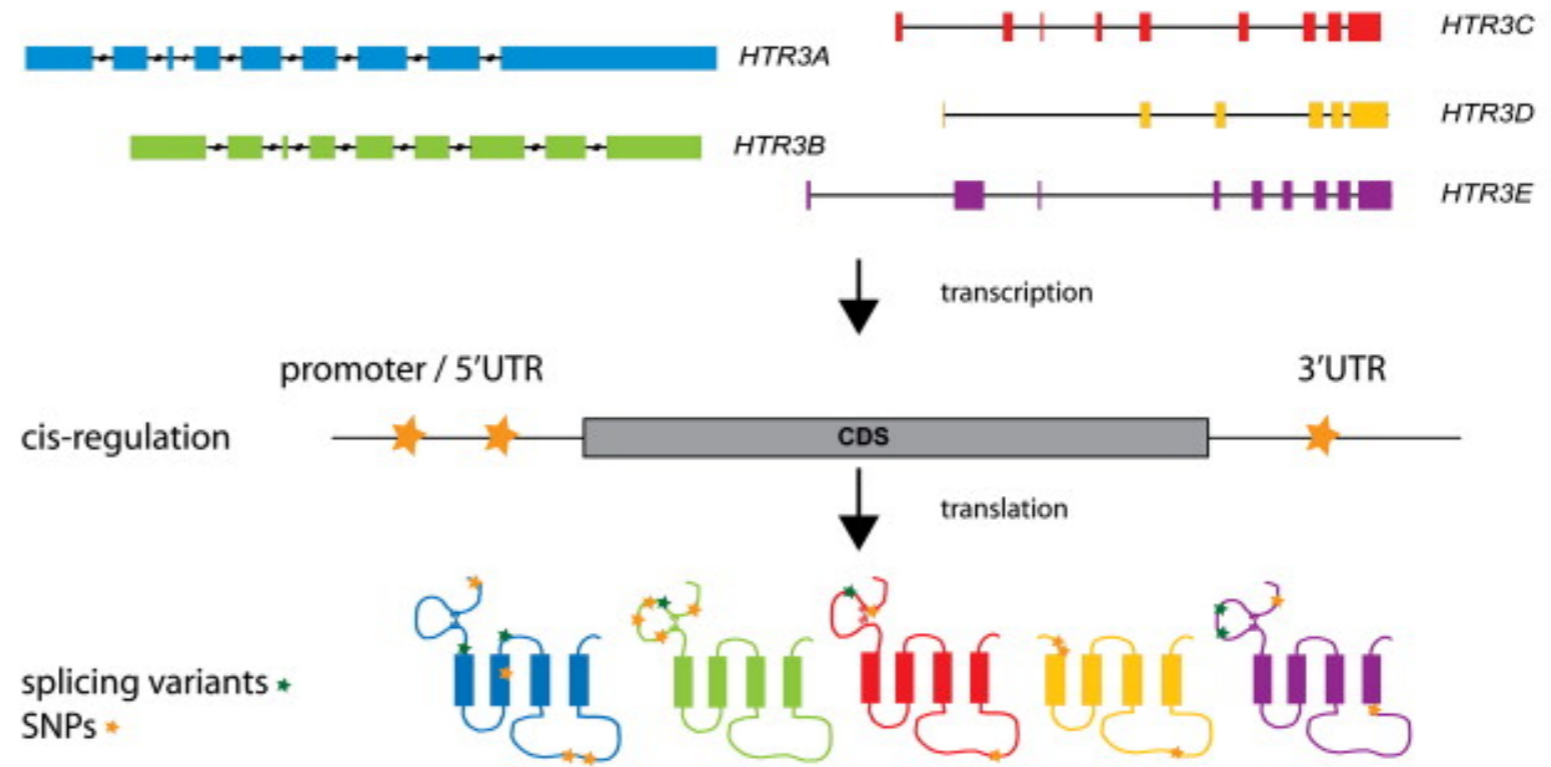


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RECEPTOR HETEROGENEITY AND SUBTYPES

Sequence variations arise at the genomic level (different genes), from alternative mRNA splicing or mRNA editing



CLASSIFICATION OF RECEPTORS (sensu stricto)

1. Ligand-gated channels

2. G-protein coupled receptors

3. Enzyme-linked receptors

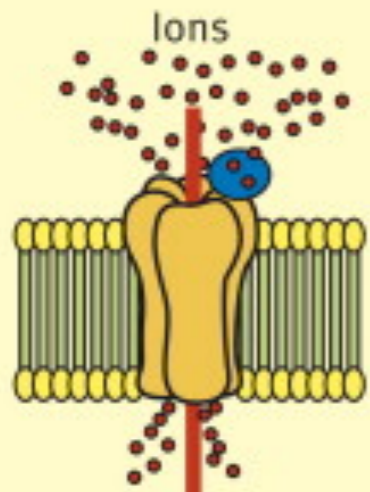
4. Nuclear receptors

This classification is primarily based on receptor structure

CLASSIFICATION OF RECEPTORS

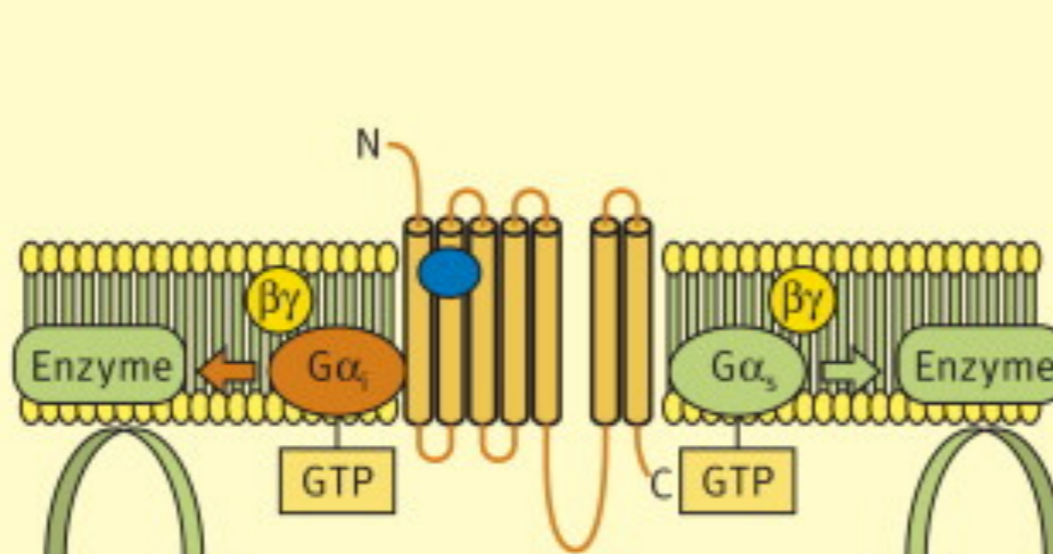
Receptor classification

Ligand-gated channels



Depolarization/
hyperpolarization

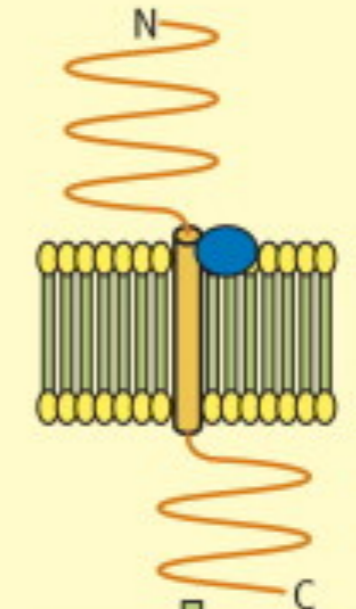
G-protein-coupled receptors



Second messenger

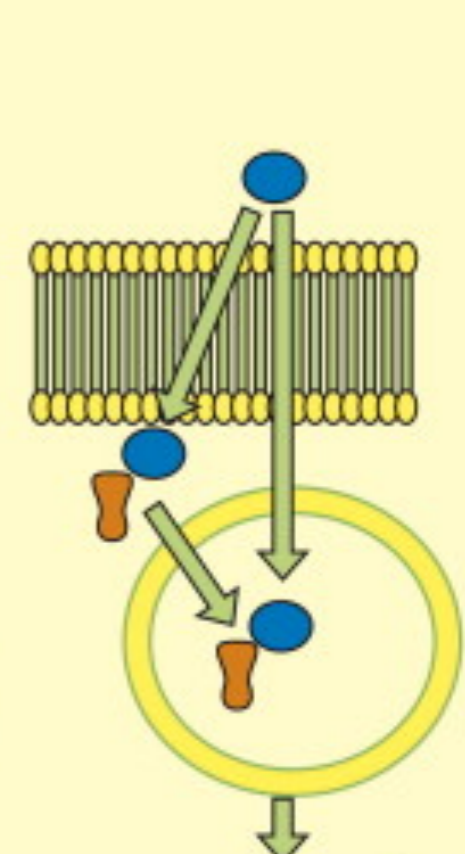
Change in $[Ca^{2+}]$
Protein kinase activity

Enzyme-linked receptors Nuclear receptors



Phosphorylation

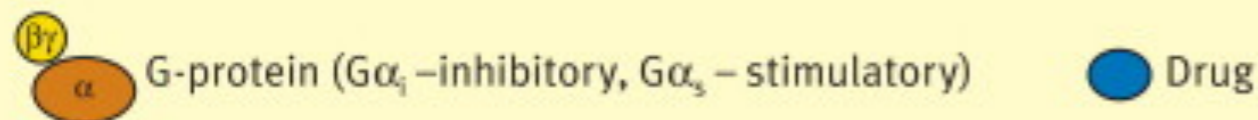
Gene transcription/protein synthesis



Timescale

Fast (msecs)

Slow (hours)

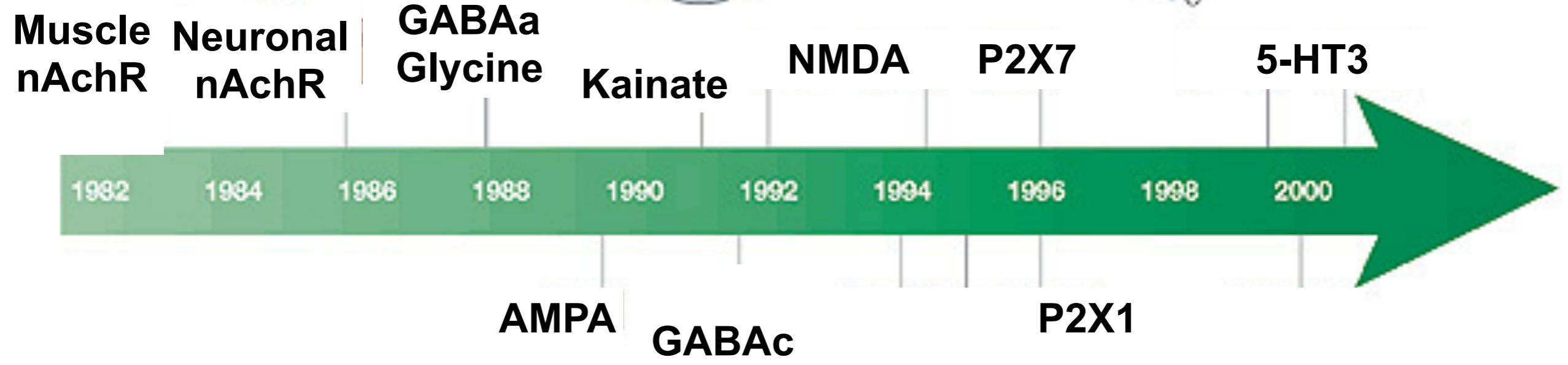
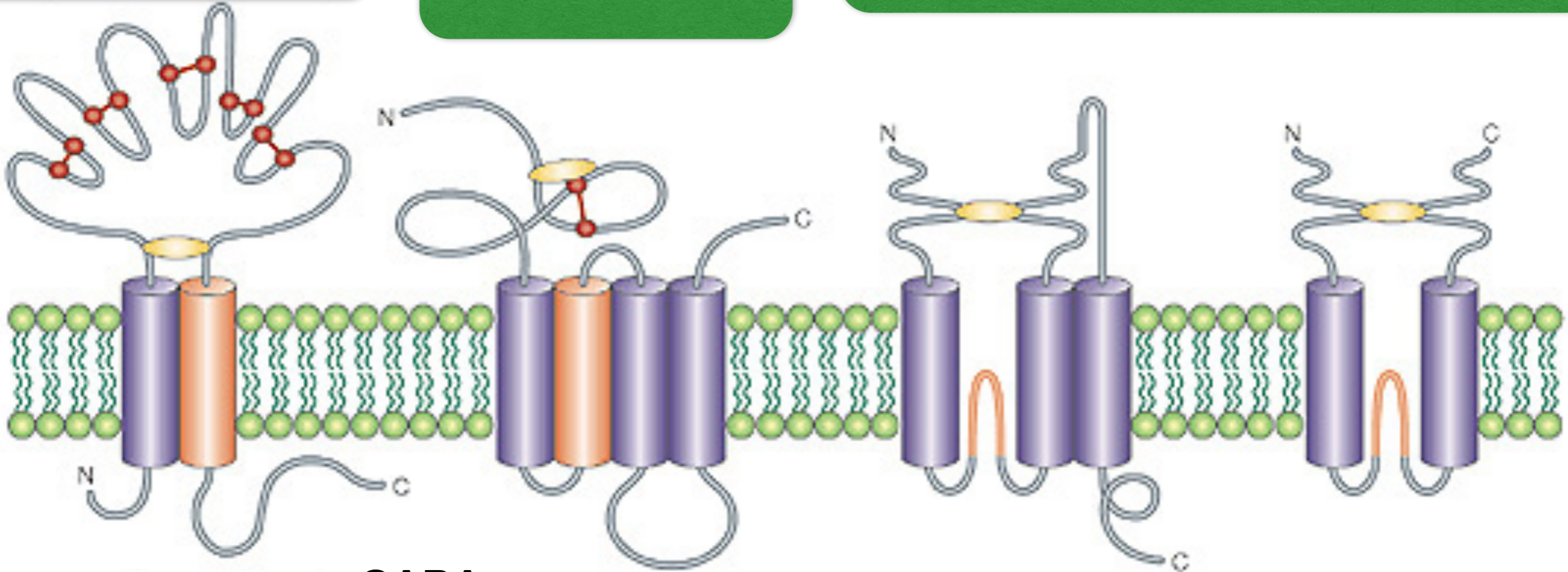


1. LIGAND-GATED CHANNELS (IONOTROPIC RECEPTORS or RECEPTOR OPERATED CHANNELS)

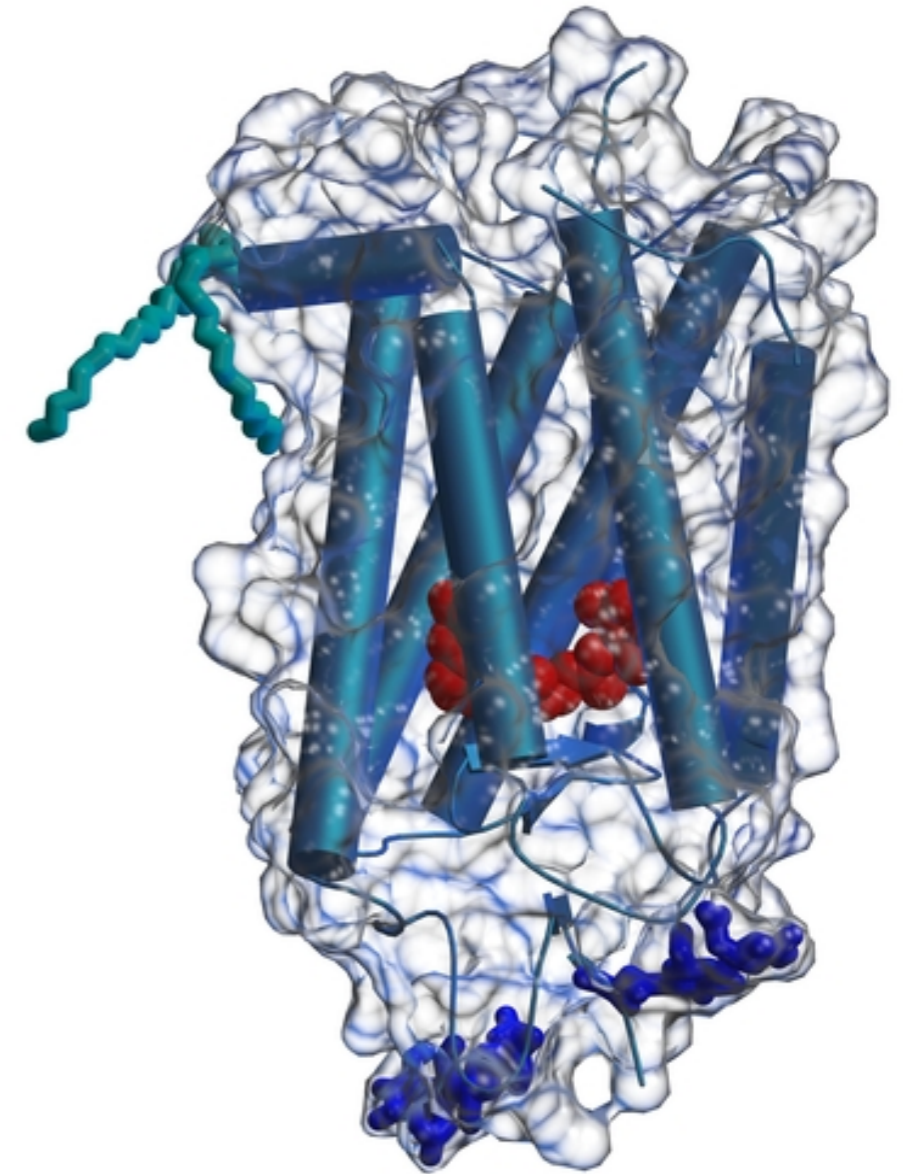
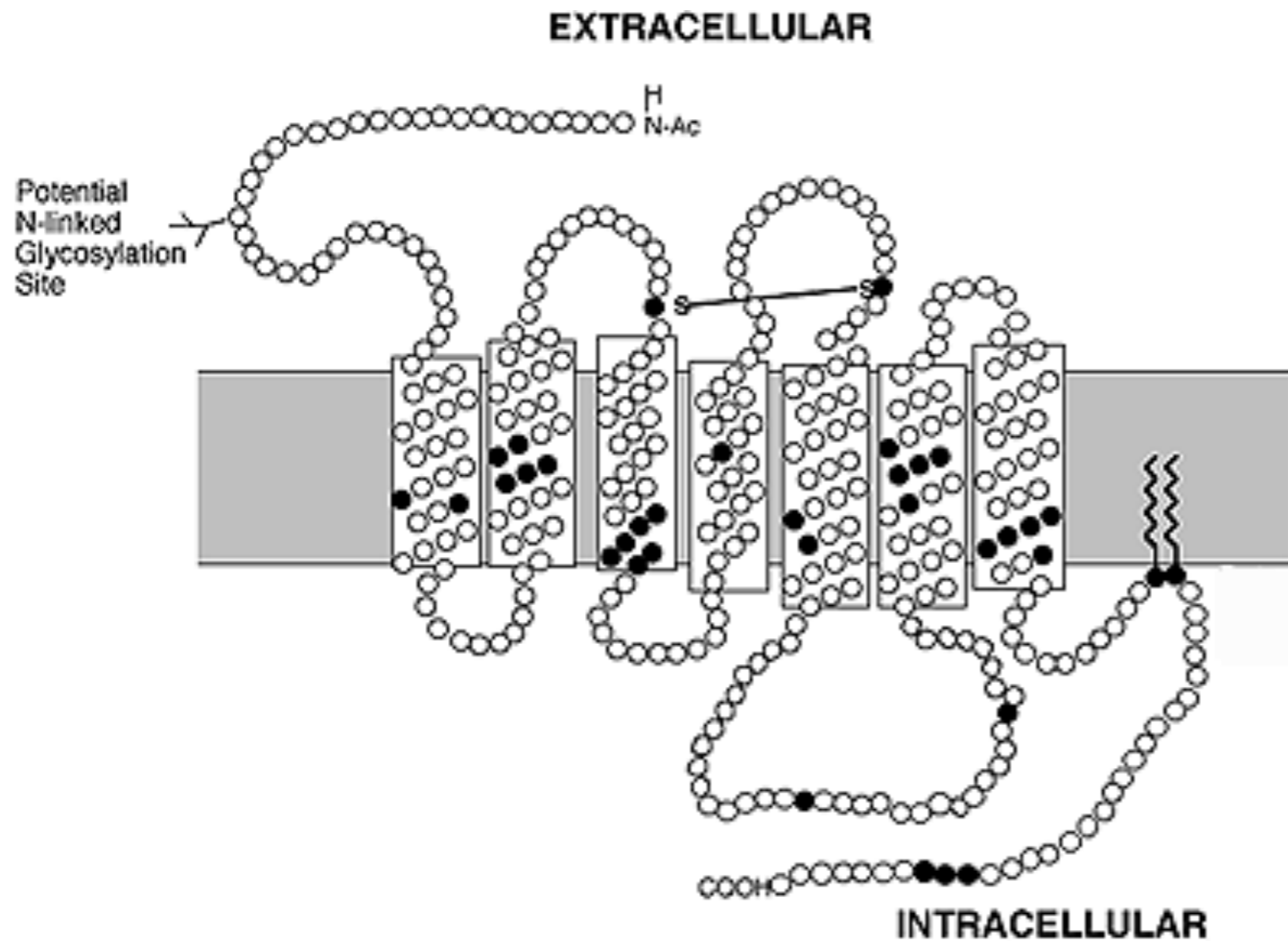
P2X-receptor- like family (ATP)

Nicotinic-receptor -like family

Glutamate-receptor-like family



2. G PROTEIN COUPLED RECEPTORS (METABOTROPIC RECEPTORS or 7 TM RECEPTORS)



β -adrenergic receptor

Target class	Number of proteins
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Receptors	193
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G protein-coupled receptors	82
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Ligand-gated ion channels	39
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Receptor tyrosine kinases	22
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Immunoglobulin-like receptors	21
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Other receptors	12
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Nuclear receptors	17
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Most common therapeutic actions	Number of drugs
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Antihypertensive, anti-allergic	563
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Antihypertensive, anti-allergic	357
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Hypnotic and sedative, anticonvulsant	84
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Antineoplastic, vasodilator	22
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Immunomodulatory, antineoplastic	28
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Immunomodulatory, platelet aggregation	11
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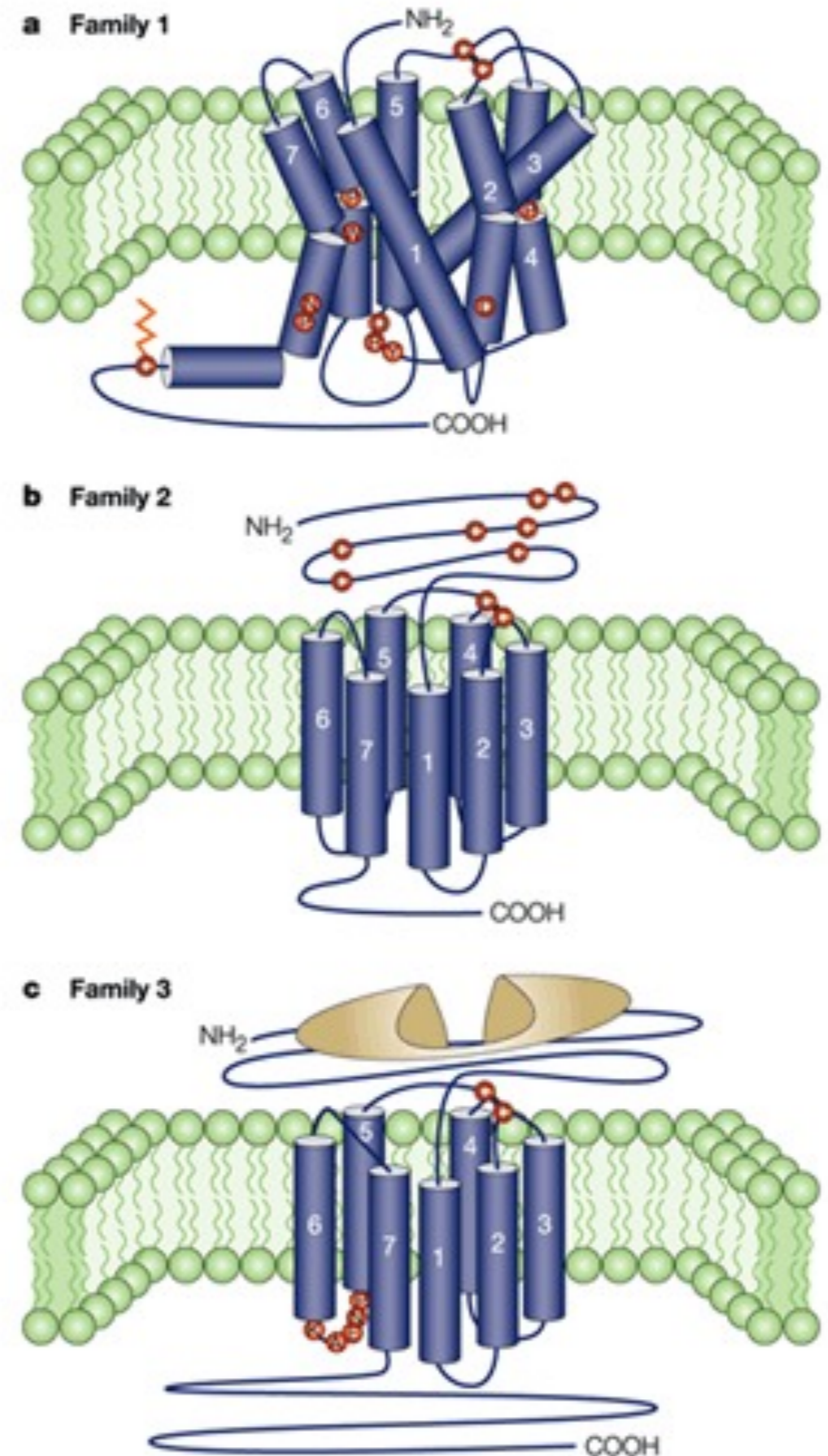
Antineoplastic, hormone replacement	76
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2. G PROTEIN COUPLED RECEPTORS

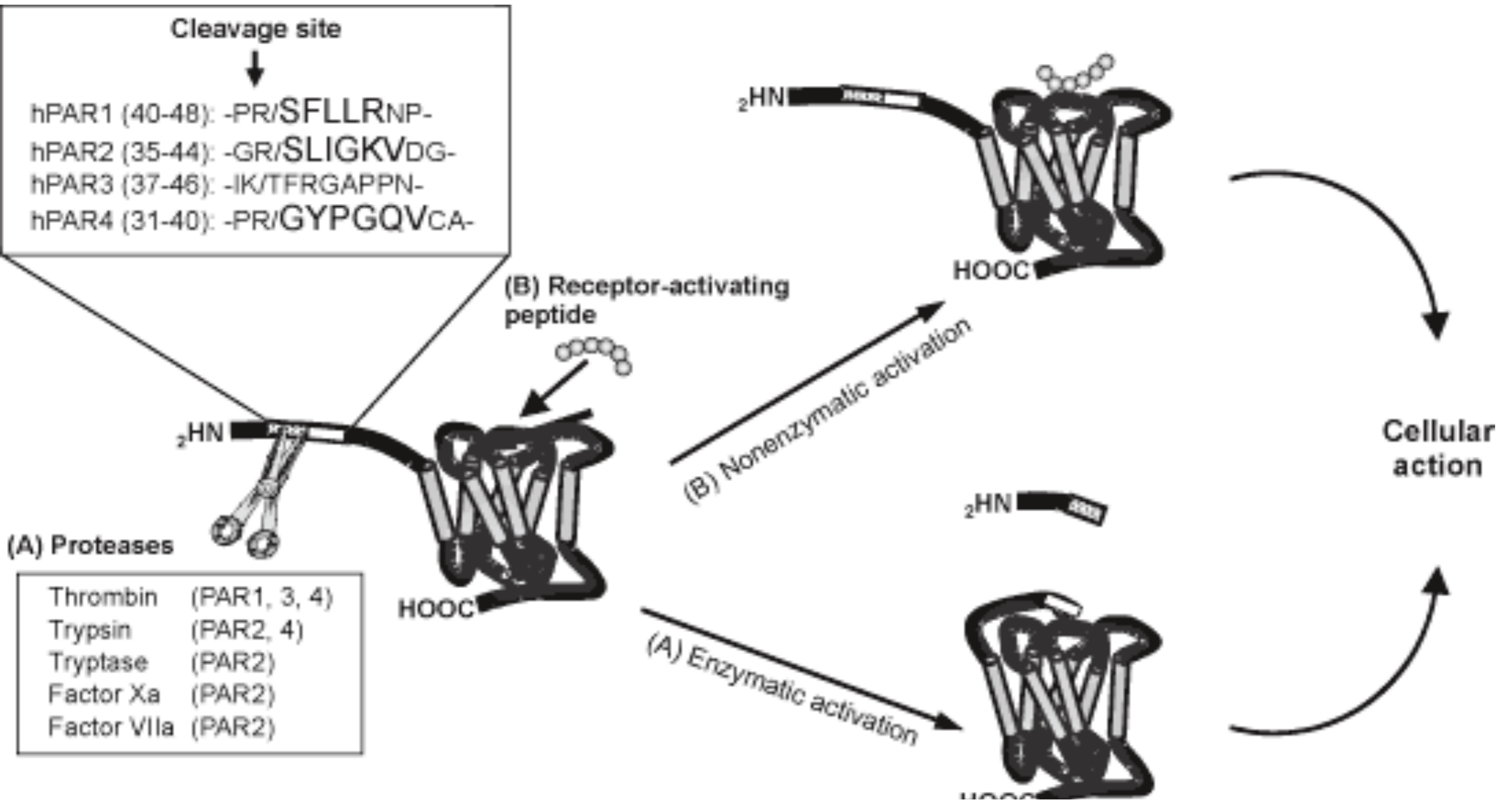
Family 1 (or A or rhodopsin-like family): odorants, small molecules such as catecholamines, some peptides and glycoprotein hormones receptors

Family 2: Secretin/Glucagon receptors

Family 3: metabotropic glutamate, the Ca^{2+} -sensing and gamma-aminobutyric acid (GABA)_B receptors



PROTEASE ACTIVATED RECEPTORS - PAR



PAR2 receptors expressed at the stomach level
 stimulate mucus secretion
 reduce acidic gastric secretion
 increase mucosal perfusion
 modulate smooth muscle activity

General regions of interaction of GPCR with other cellular proteins

different G proteins (G_i , G_s)

PDZ-, SH2- and SH3-DOMAIN
proteins

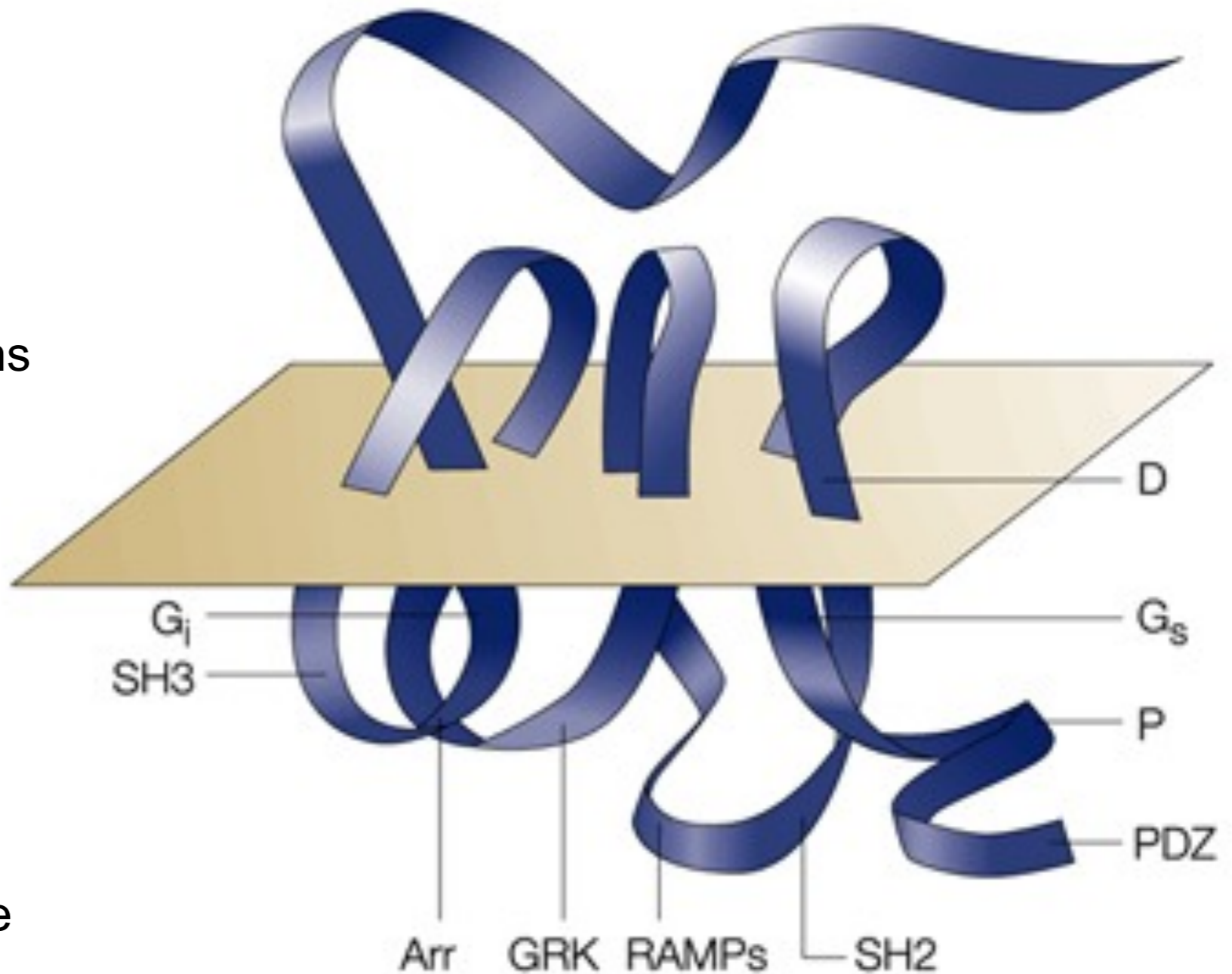
receptor-activity-modifying proteins
(RAMPs)

sites for dimerization with other
GPCRs (D)

arrestin (Arr)

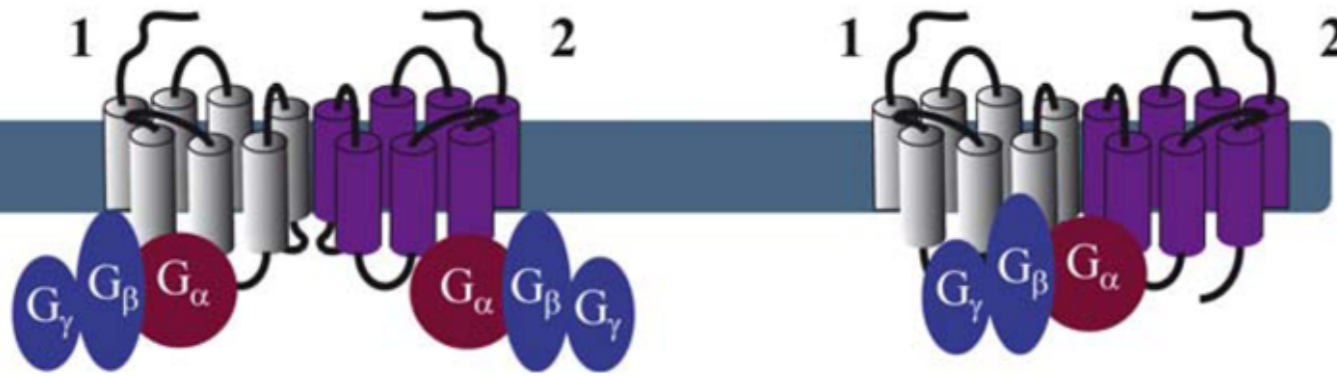
G-protein-coupled receptor kinase
(GRK)

phosphorylation sites for uncoupling
and internalization (P)

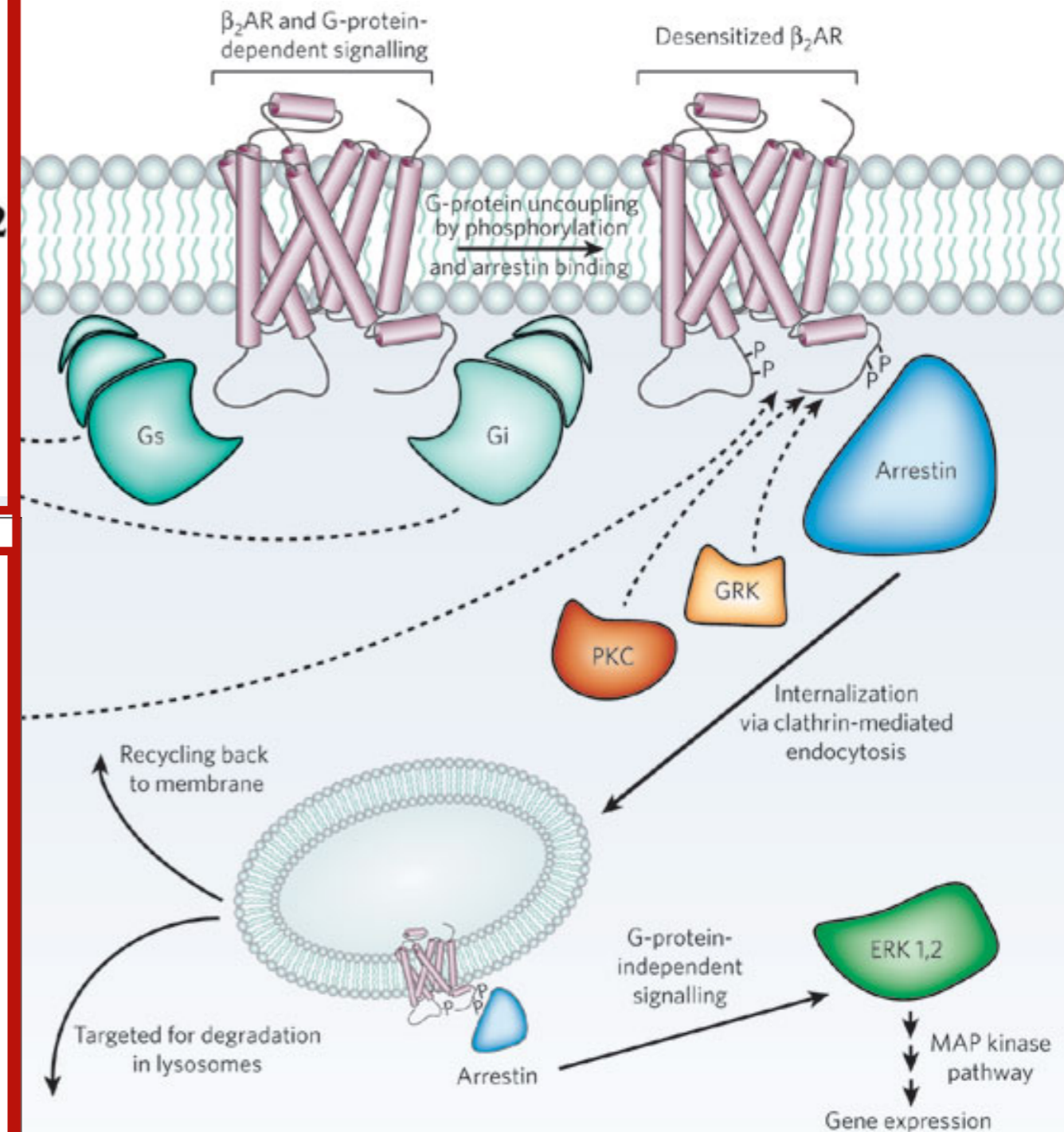
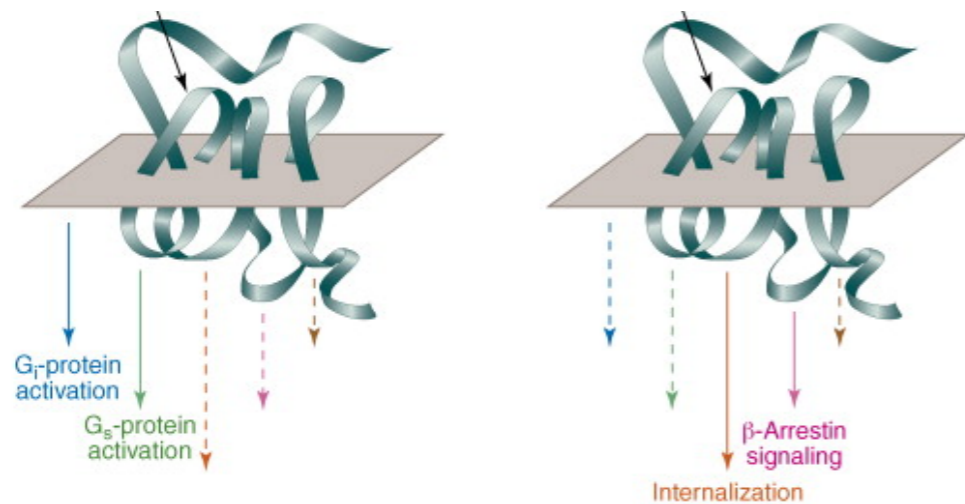


G PROTEIN-COUPLED RECEPTORS - GPCR

Can form homo- and hetero-dimers

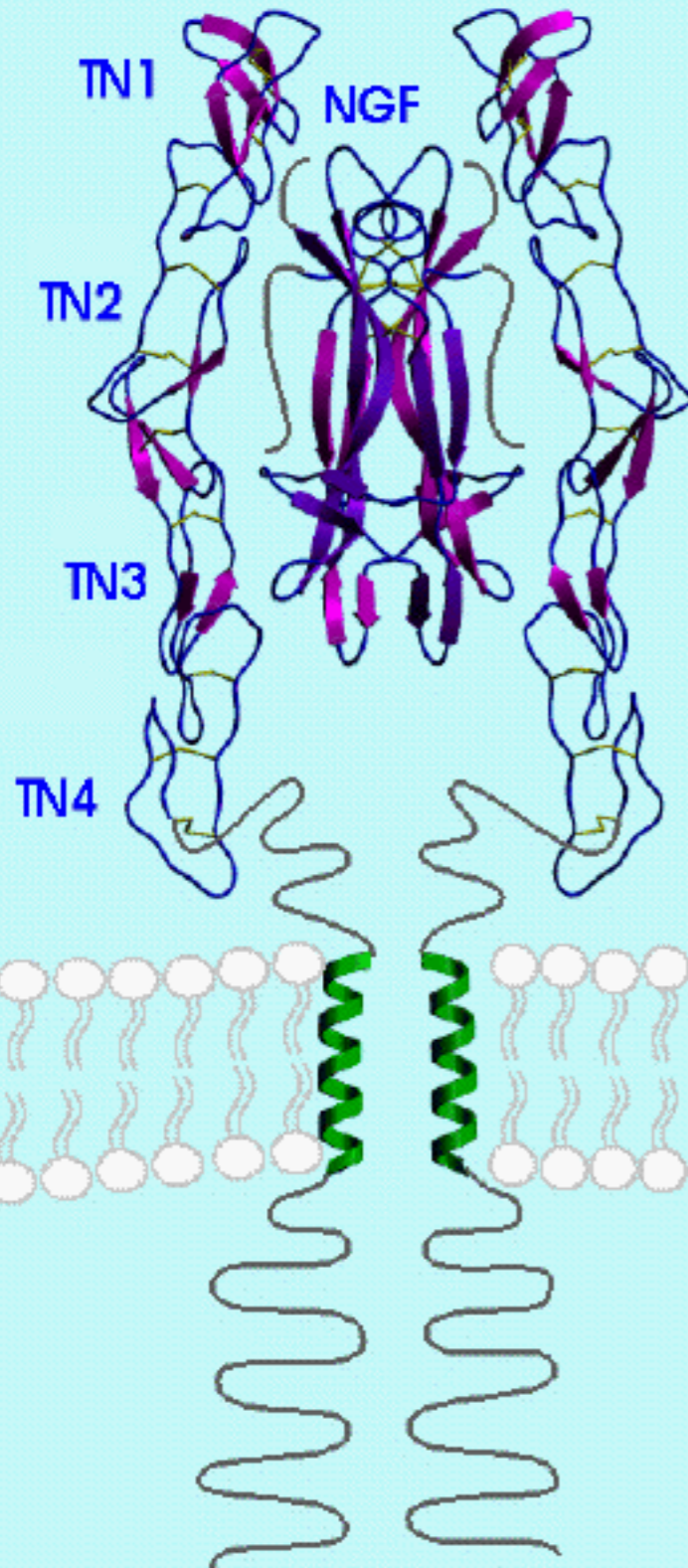


Can assume ligand-specific receptor conformation (and efficacy)



Can undergoes to desensitization and down-regulation

3. ENZYME-LINKED RECEPTORS



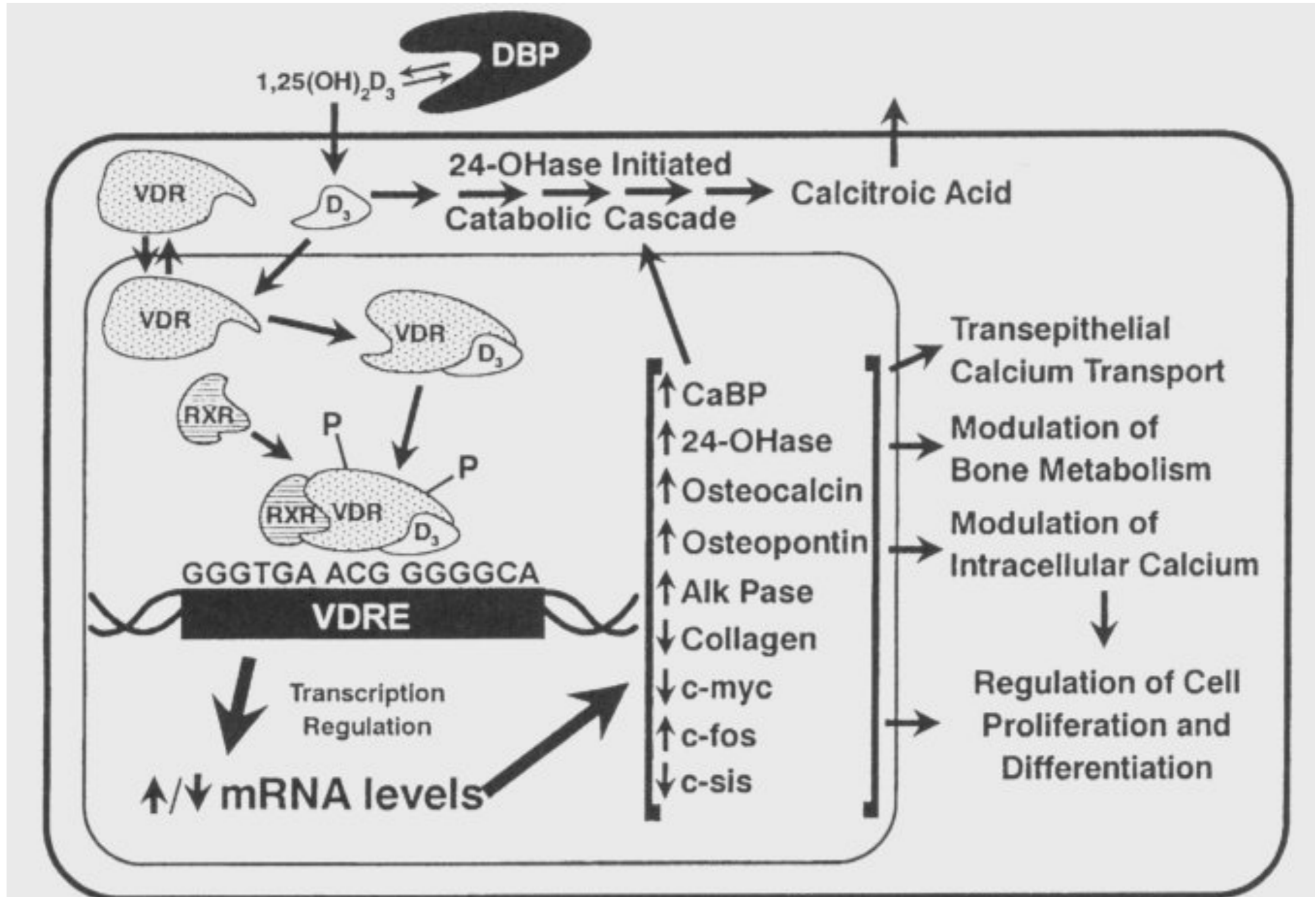
2(p75):NGF dimer

Murray-Rust 1995

Insulin receptor
Growth factors receptors
(NGF, PDGF):
Tyrosine Kinase activity

Atrial Natriuretic Peptide
(ANP) receptors:
Guanylate Cyclase activity

4. NUCLEAR RECEPTORS



Cell compartmentalizationwith a glance outside the walls

