metabotropic receptors

The Nobel Prize in Chemistry 2012

Robert J. Lefkowitz, Brian K. Kobilka

The Nobel Prize in Chemistry 2012

Robert J. Lefkowitz

Biographical

Photo Gallery

Other Resource

Brian K. Kobilka

Photo: Stewart Waller/PR Newswire. © HHMI

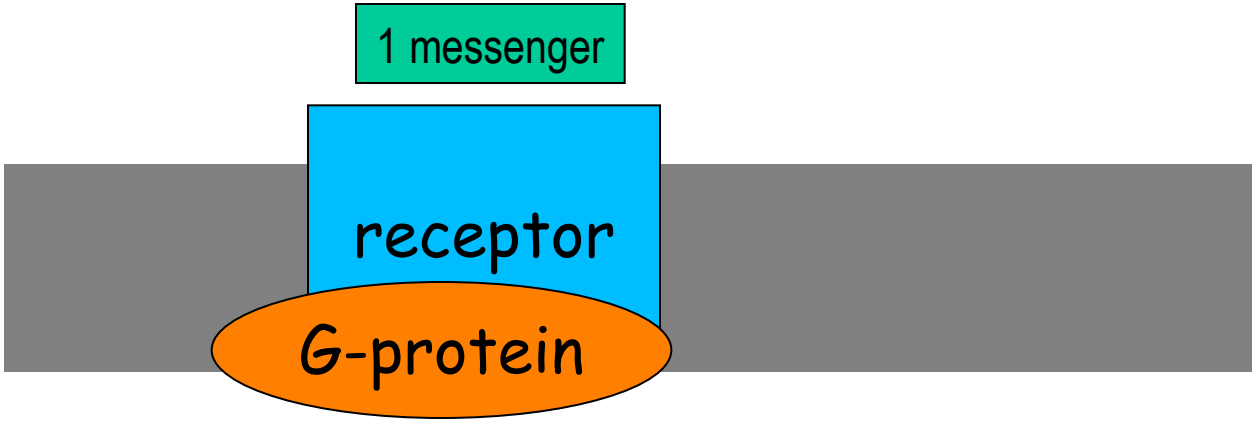
Robert J. Lefkowitz

Photo: © Stanford University

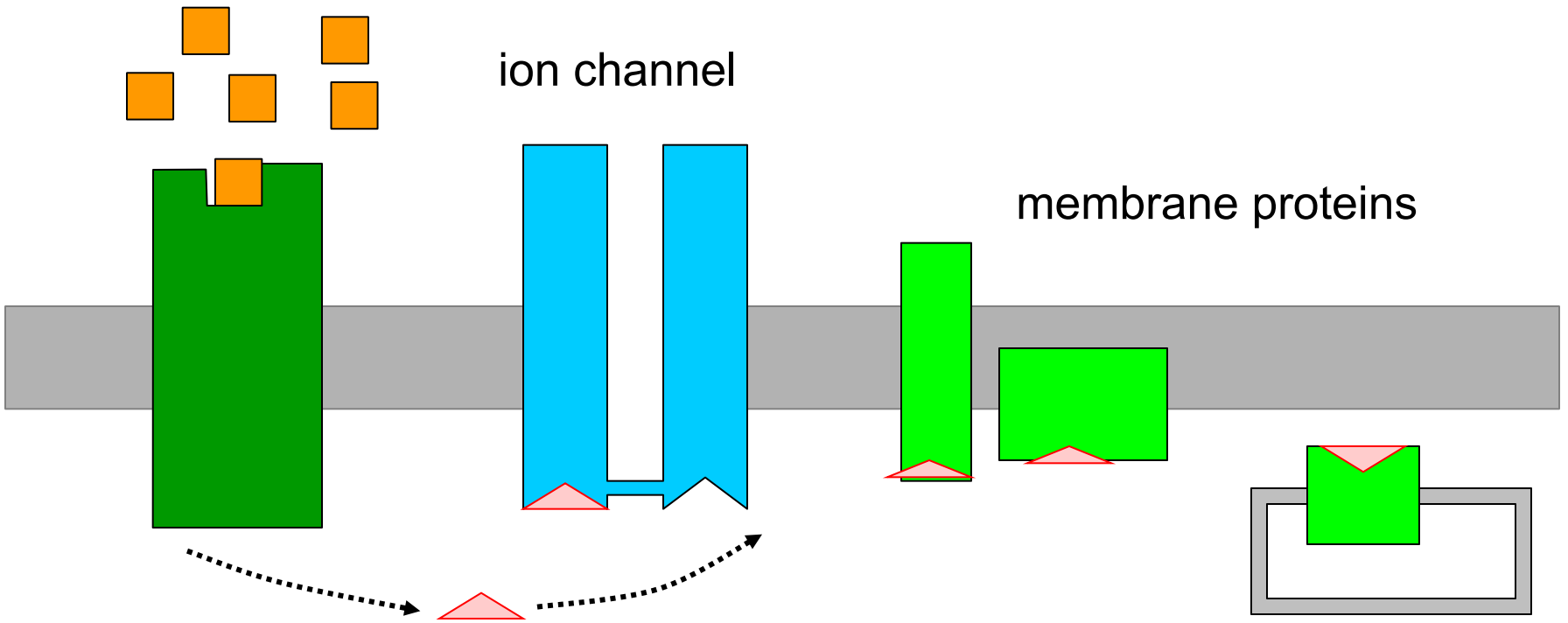
Brian K. Kobilka

G-protein coupled receptors

neurotransmitters hormones

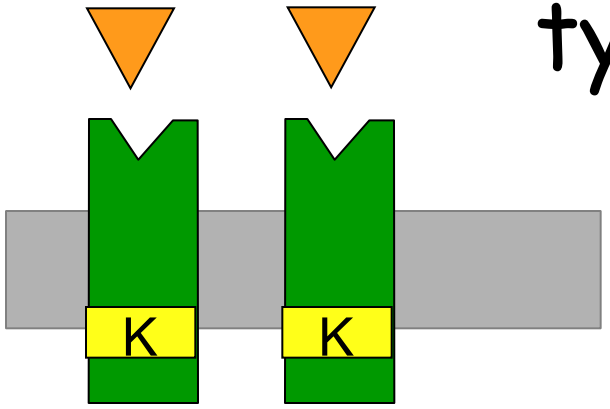


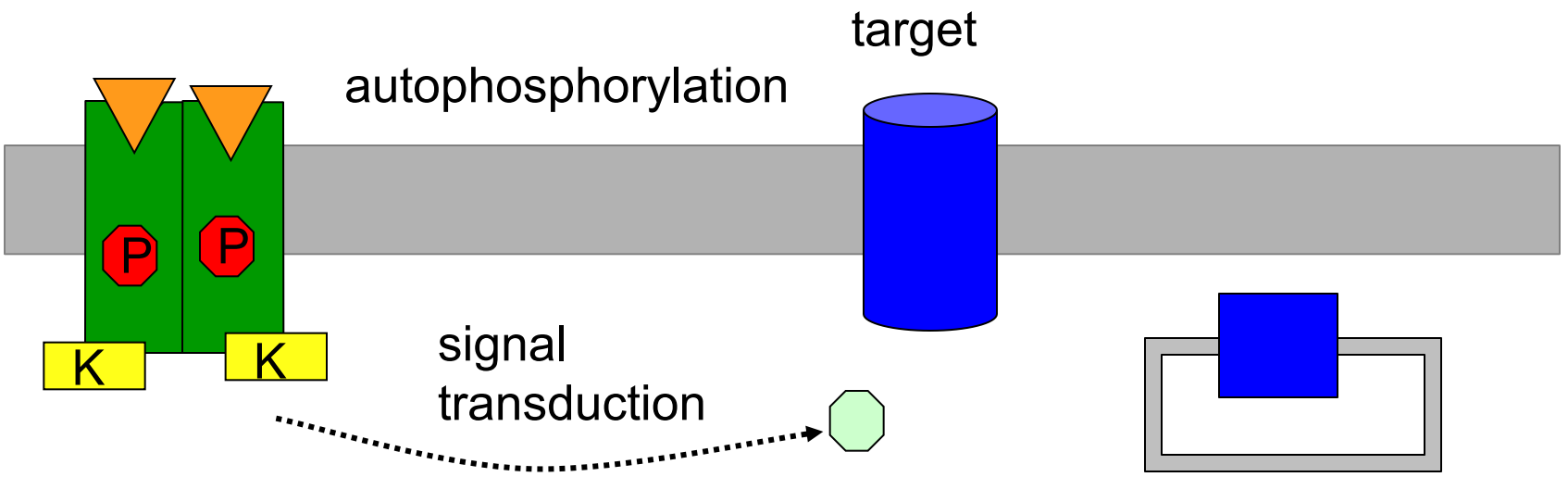
metabotropic receptors



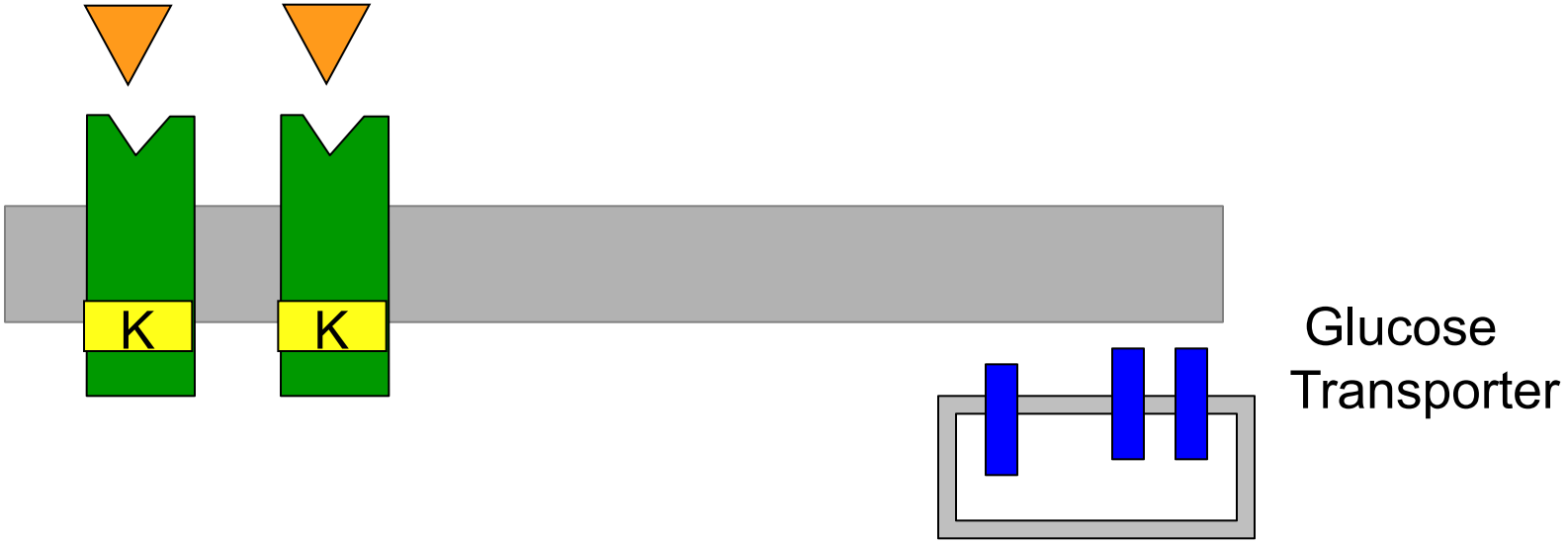
intermediate effector

tyrosine-kinase receptors

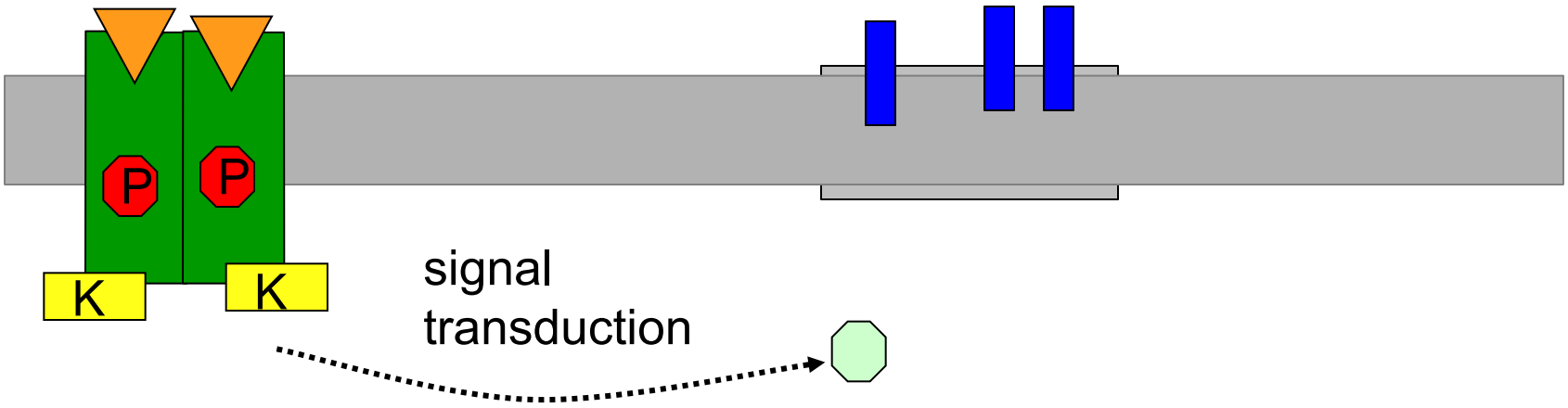




Insulin



Insulin



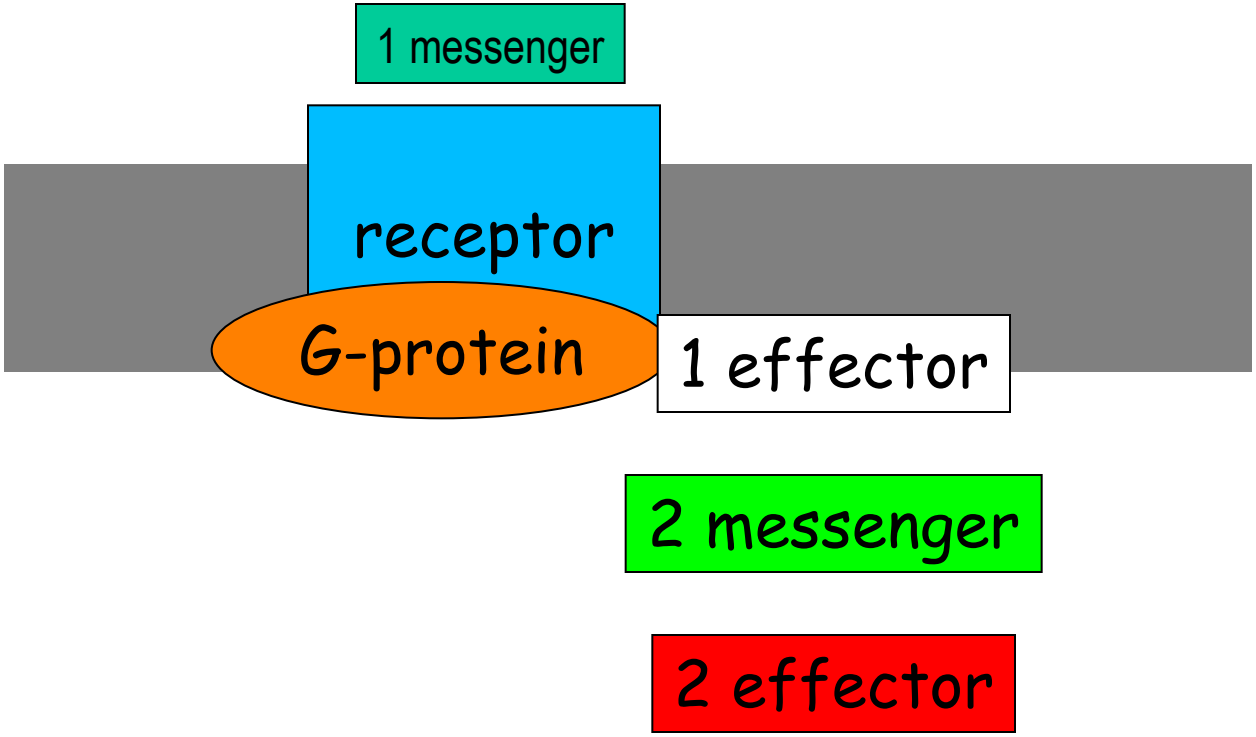
G-protein coupled receptors

> 900

1% mammalian genome

G-protein coupled receptors

neurotransmitters hormones



Which transmitters?

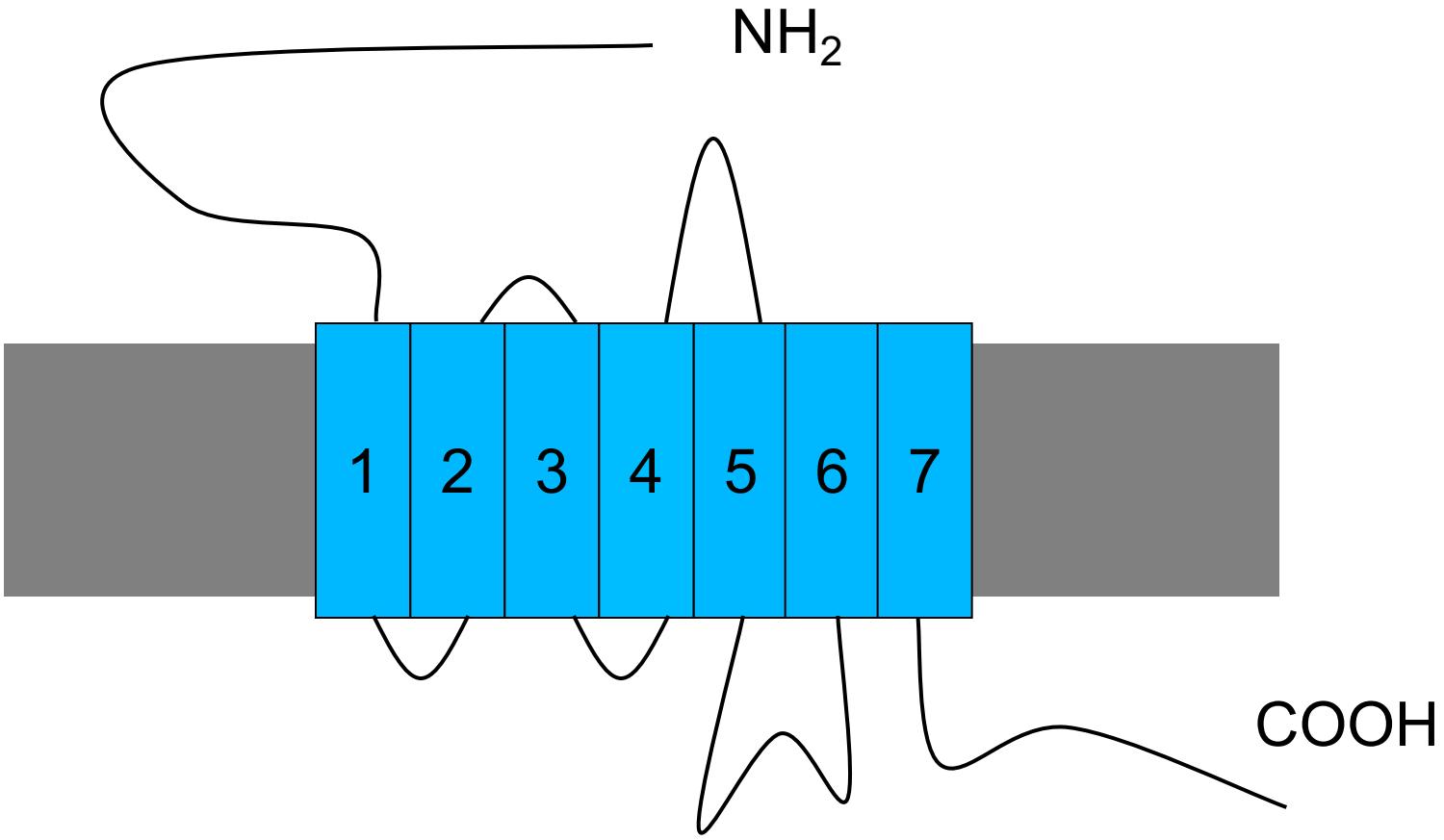
classical
ACh
Glu
GABA
5HT
DA
NA
Adrenaline
histamine
ATP

hormones
ADH
Glucagone
ET
…
…
… … …

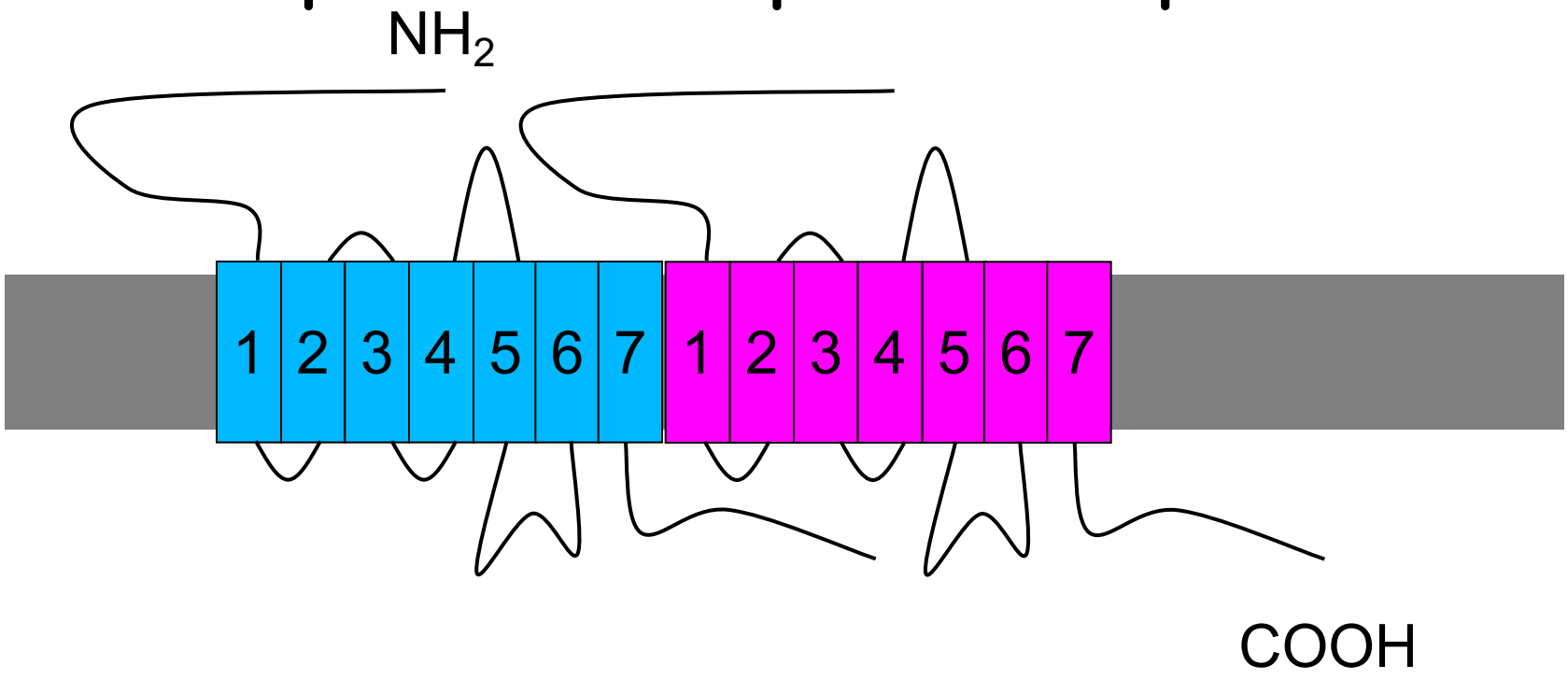
light
odorants

neuropeptides
enk
CGRP
SP
… … …
>100

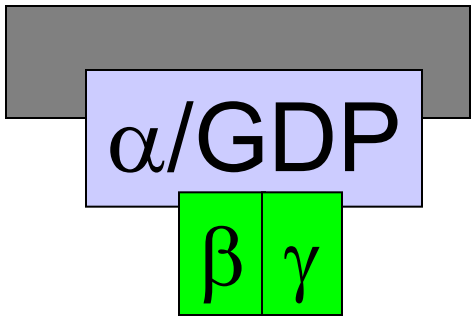
G-protein coupled receptors



G-protein coupled receptors



G-proteins

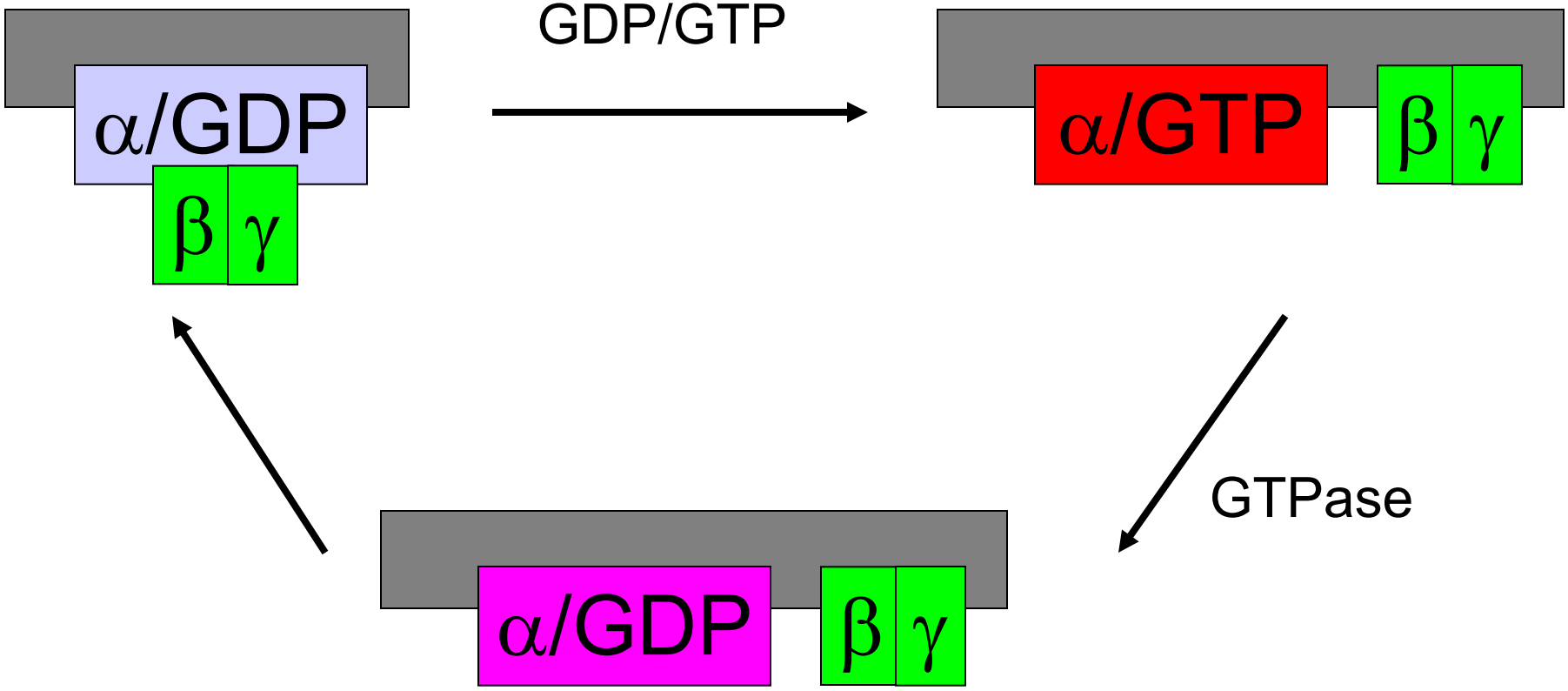


α — 20 isoforms / 16 genes

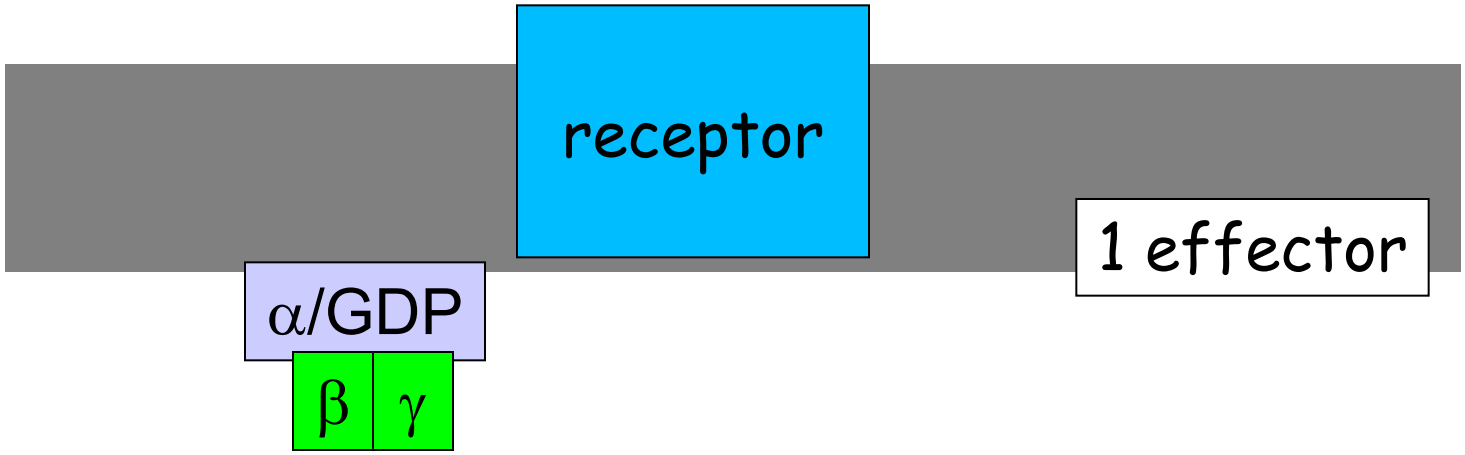
β — 6 isoforms

γ — 12 isoforms

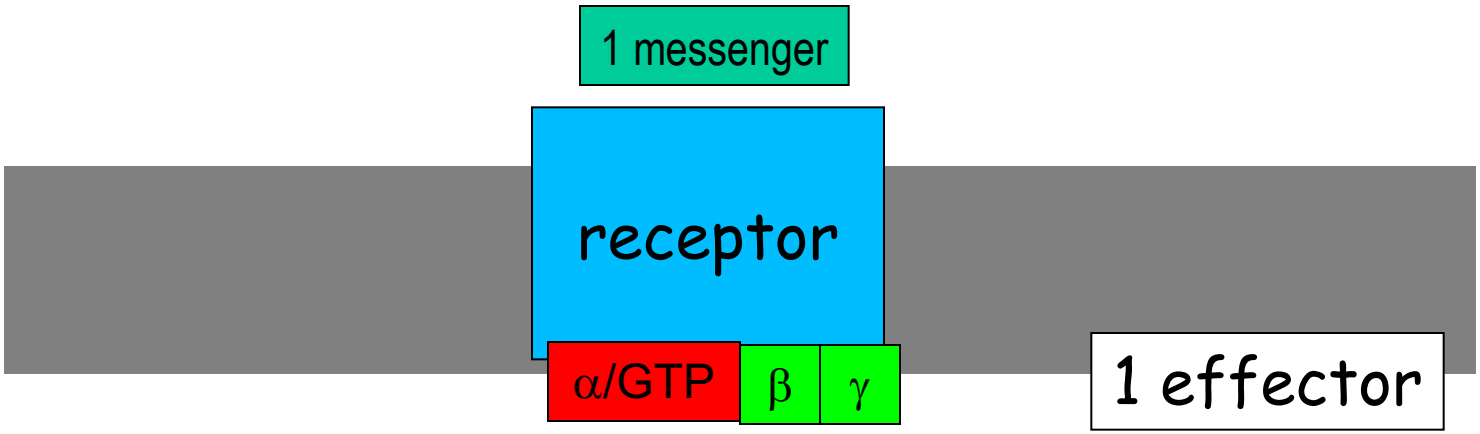
G-proteins



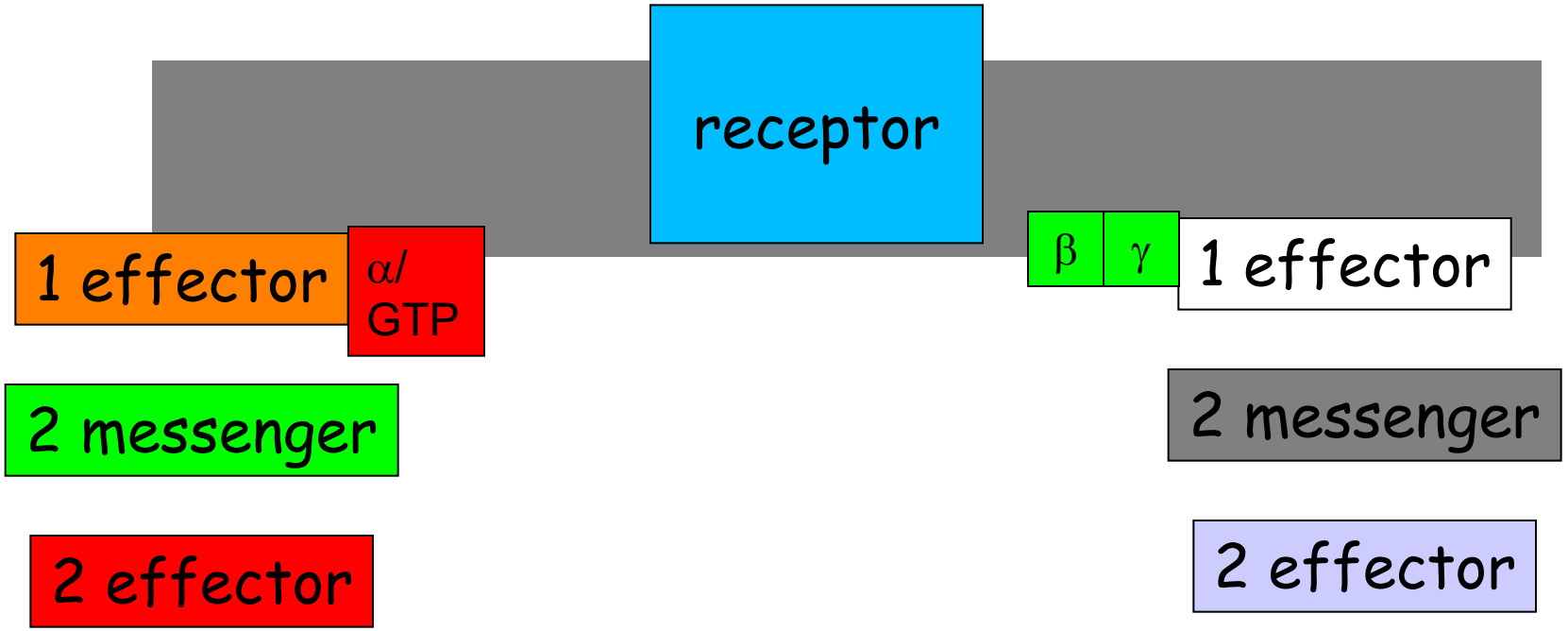
1: resting condition



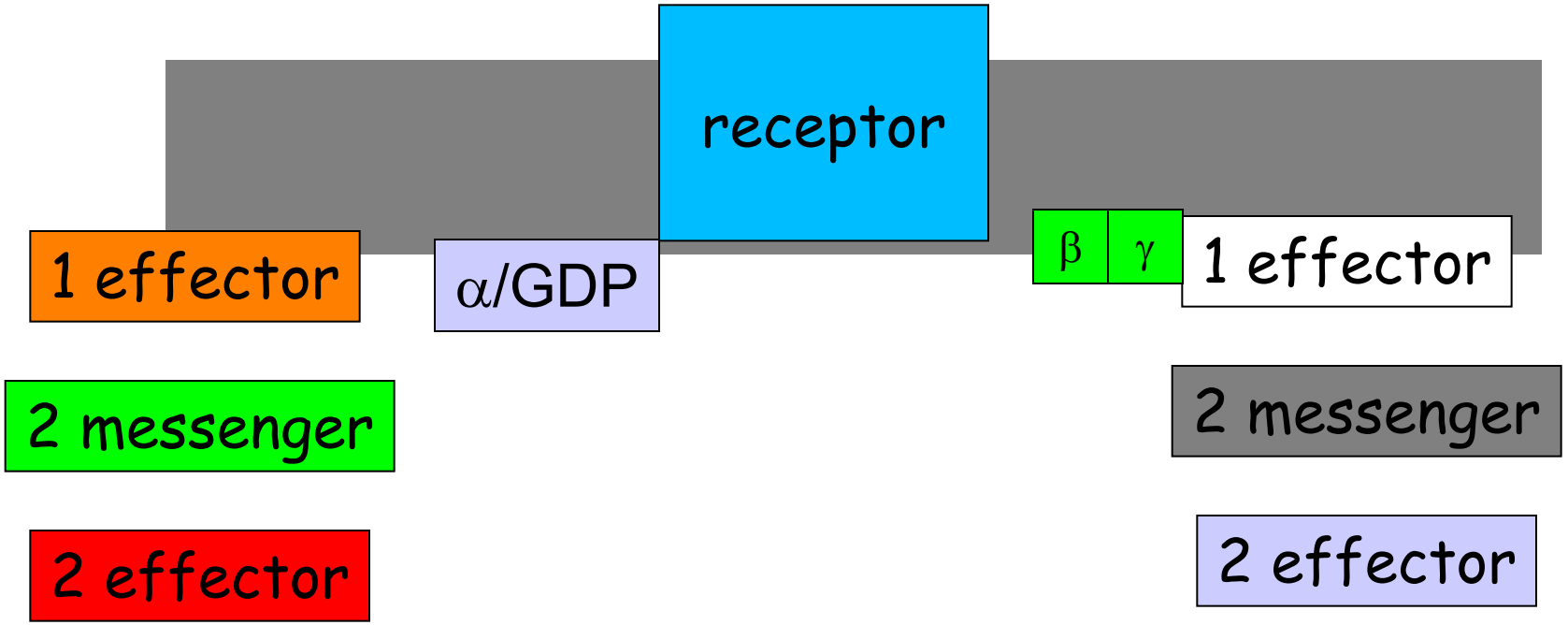
2: activation



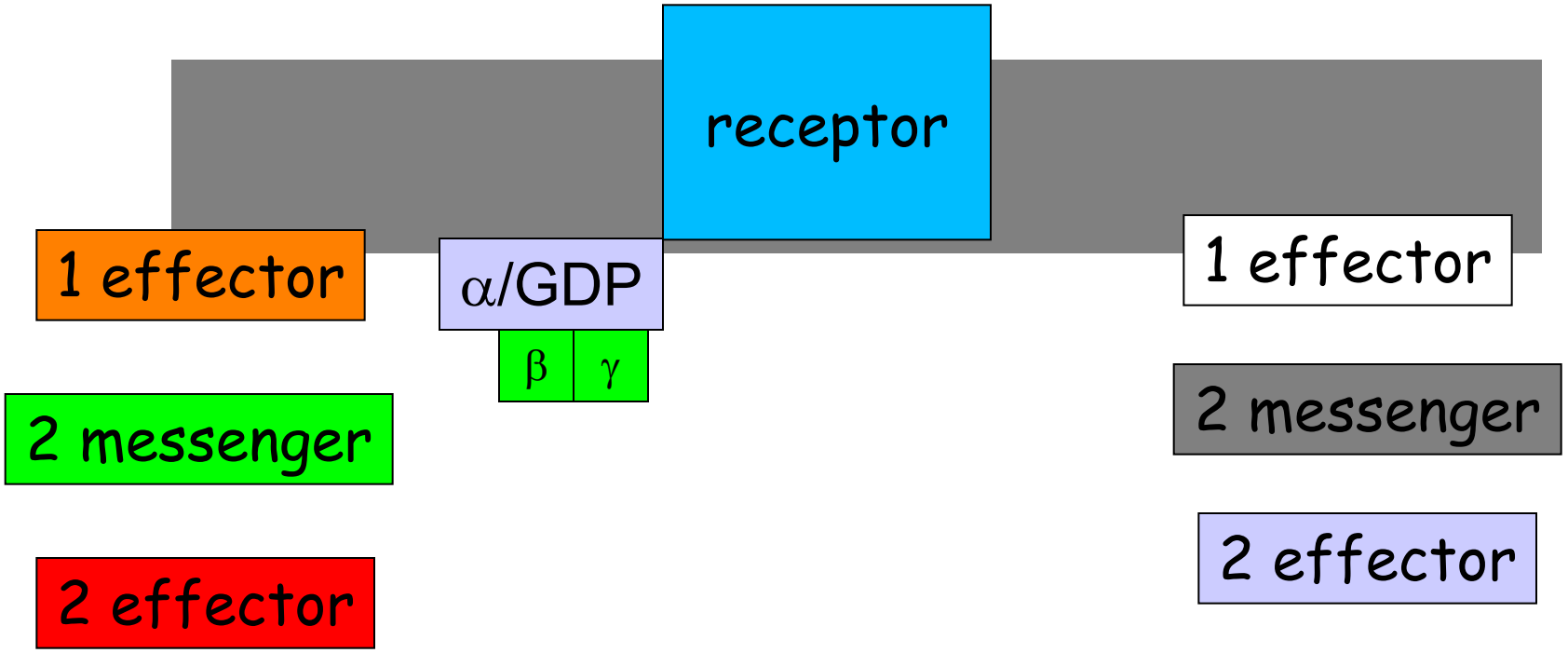
3: activity


receptor
1 effector
α/
GTP
2 messenger
2 effector
β
γ
1 effector
2 messenger
2 effector

4.1: deactivation

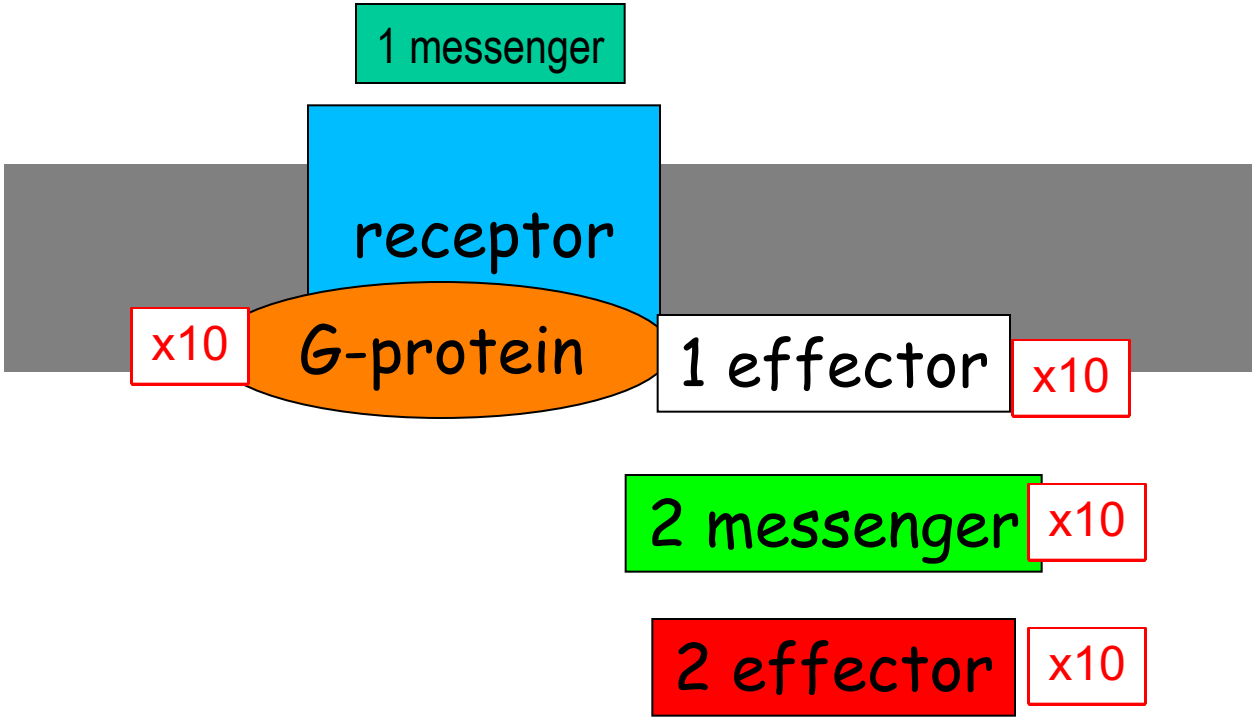


4.2: deactivation

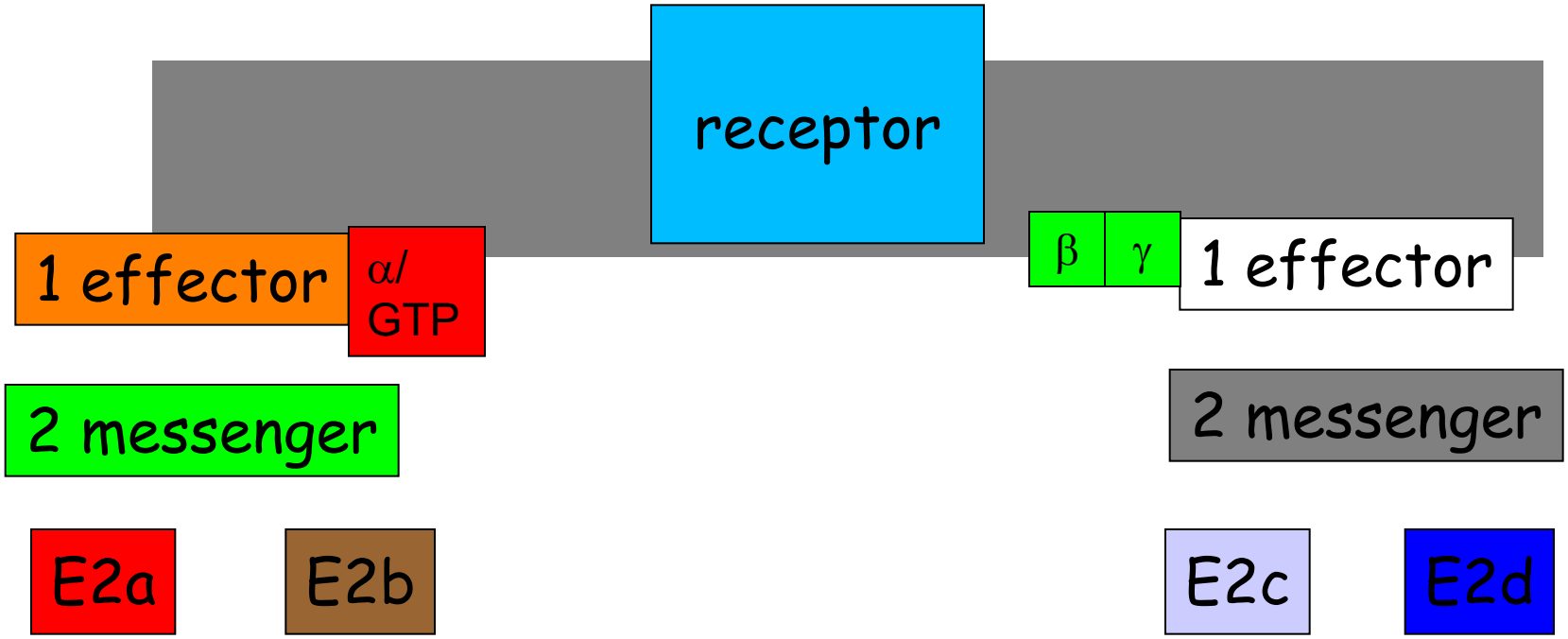


Function

amplification



Plurality of effects



Examples

G-proteins

G_s: stimulate adenylate cyclase

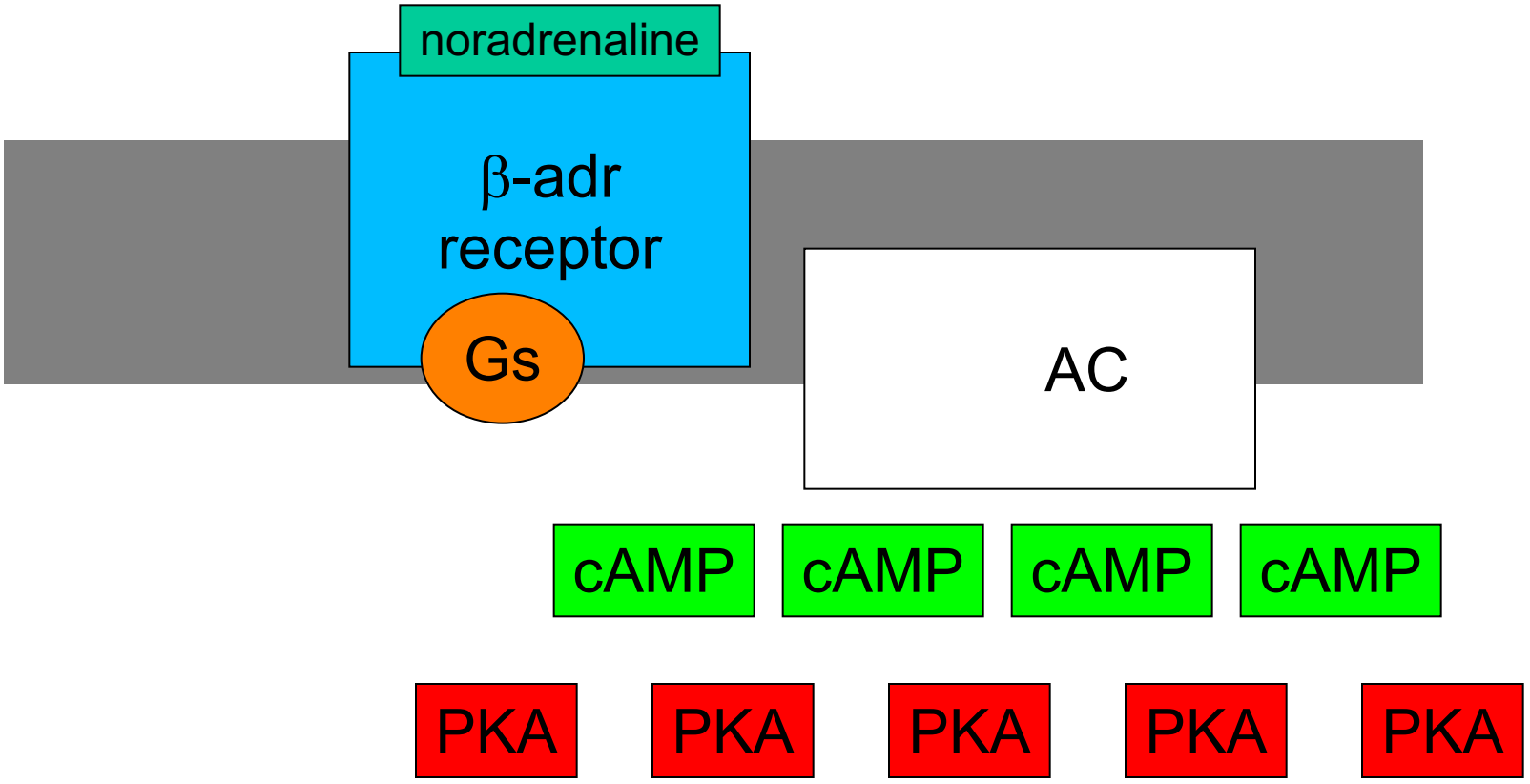
G_i: inhibit *AC*

G_q: stimulate phospholipase *C*

$G_{??}$: stimulate phospholipase *A*

Others in specific cell types

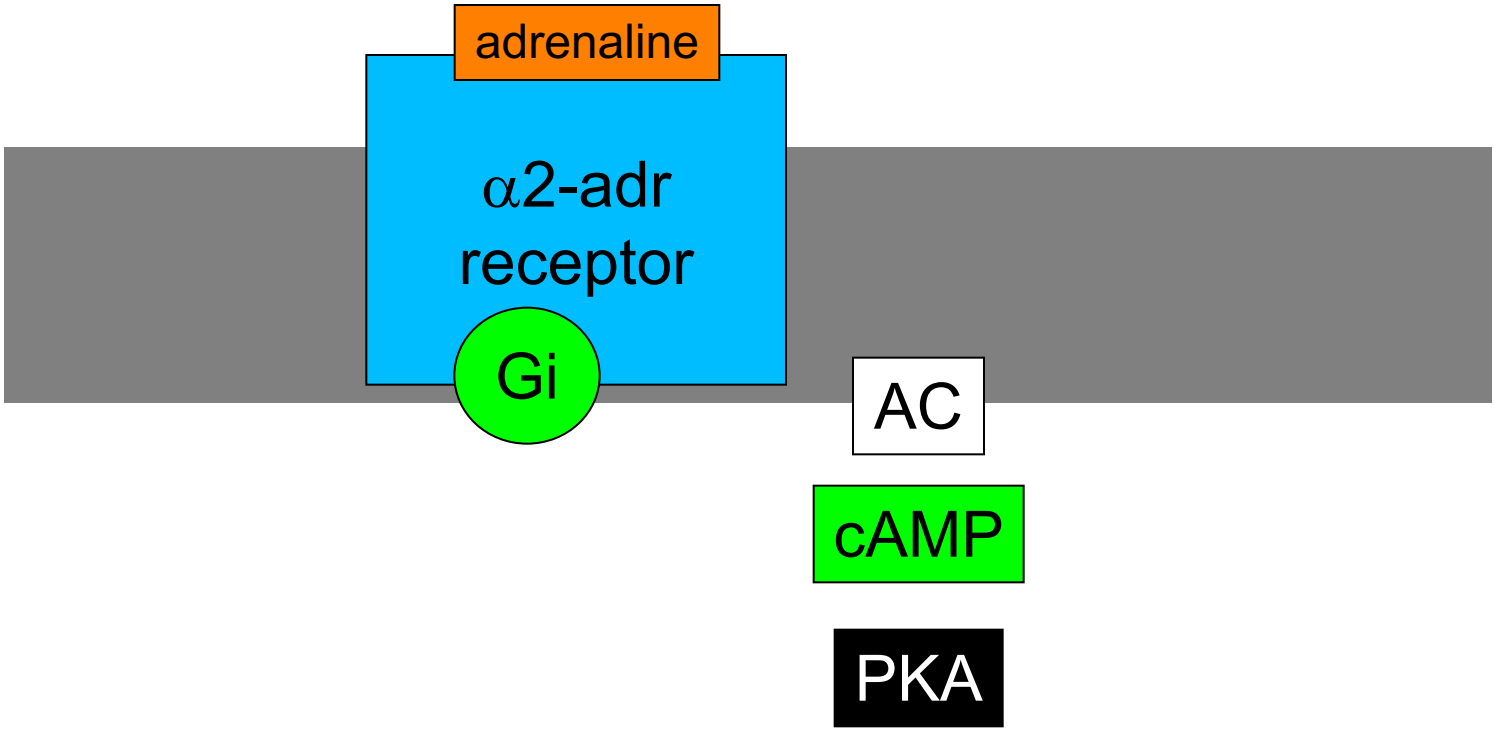
cAMP stimulation



$AR\beta_1$, $AR\beta_2$, $5\text{-}HT_{4,6,7}$

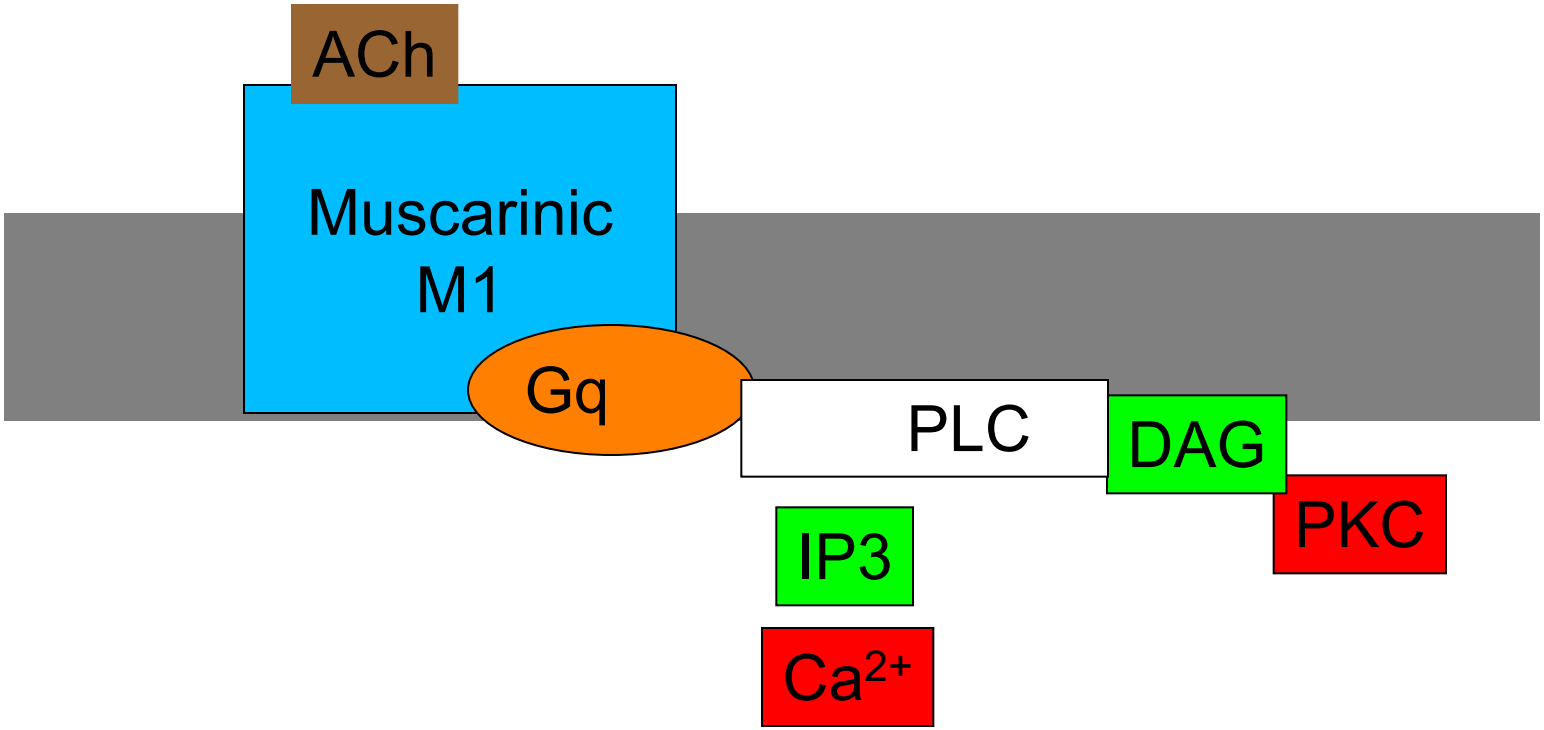
ADH

cAMP inhibition



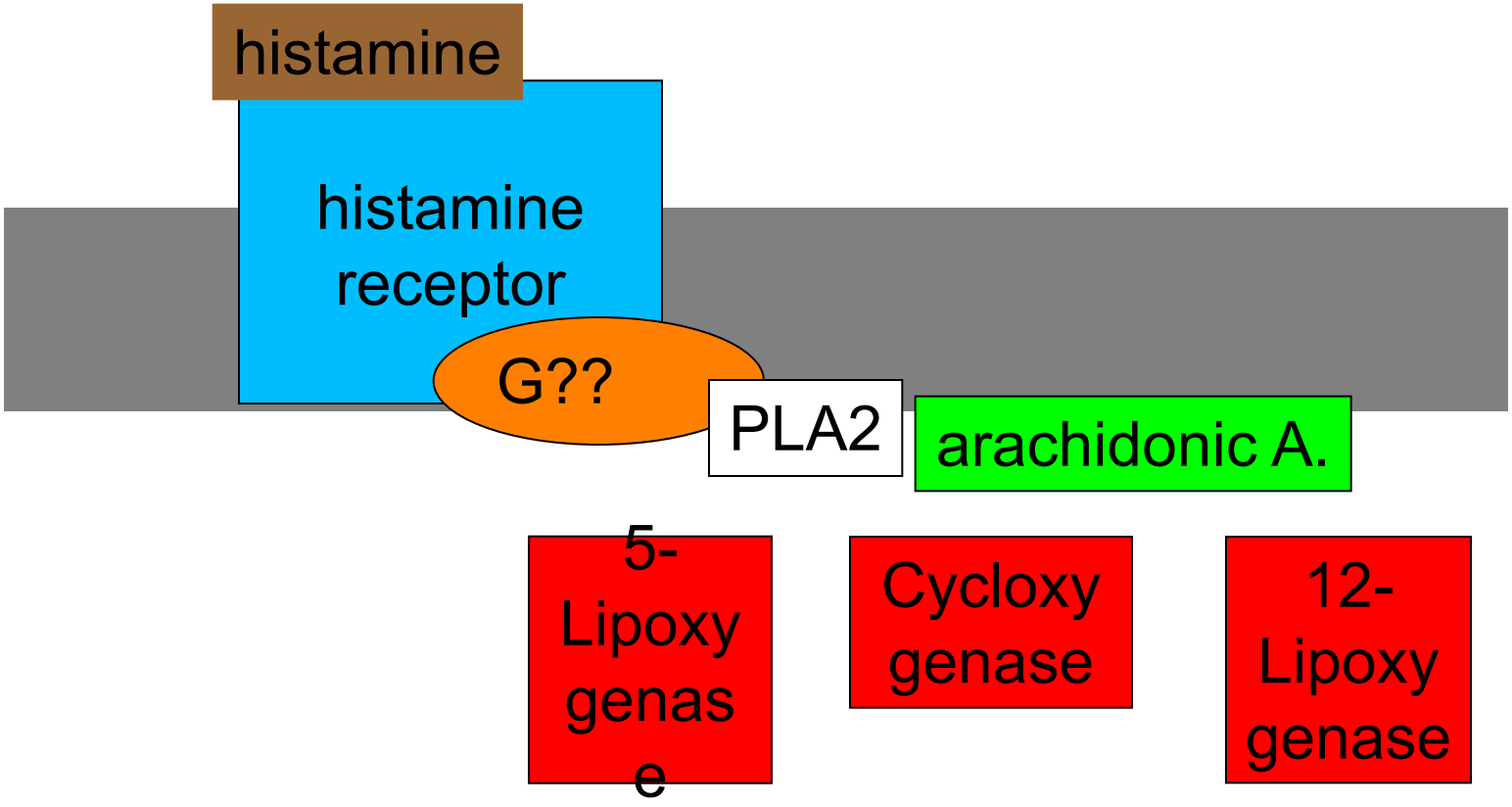
$AR\alpha_2$, $M_{2,4}$, $GABA_B$, $mGluR_{2\text{-}4,6\text{-}8}$, $5\text{-}HT_1$

IP3/diacylglyerol

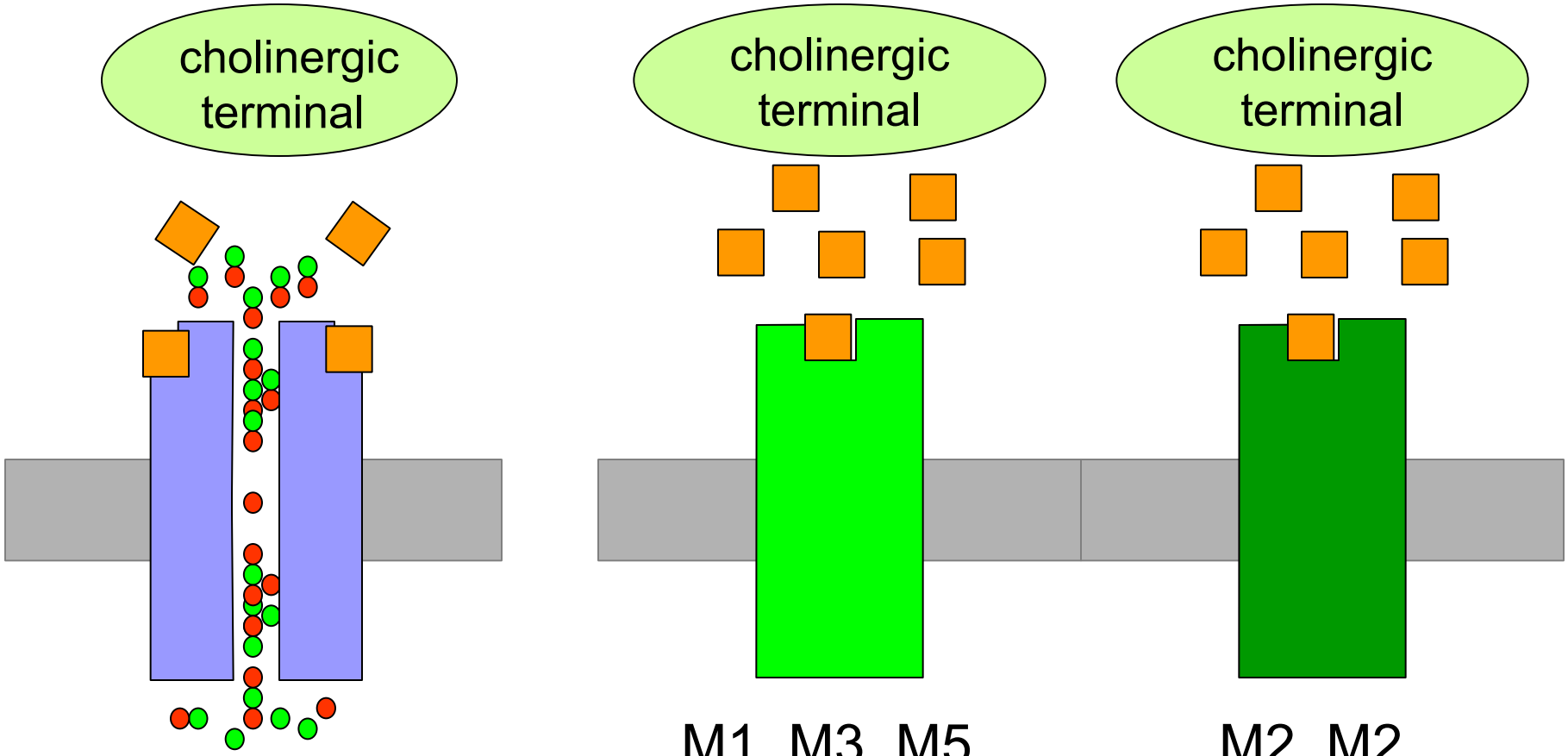


$AR\alpha_1$, $M_{1,3,5}$, $mGluR_{1,5}$, $5\text{-}HT_2$

Arachidonic acid

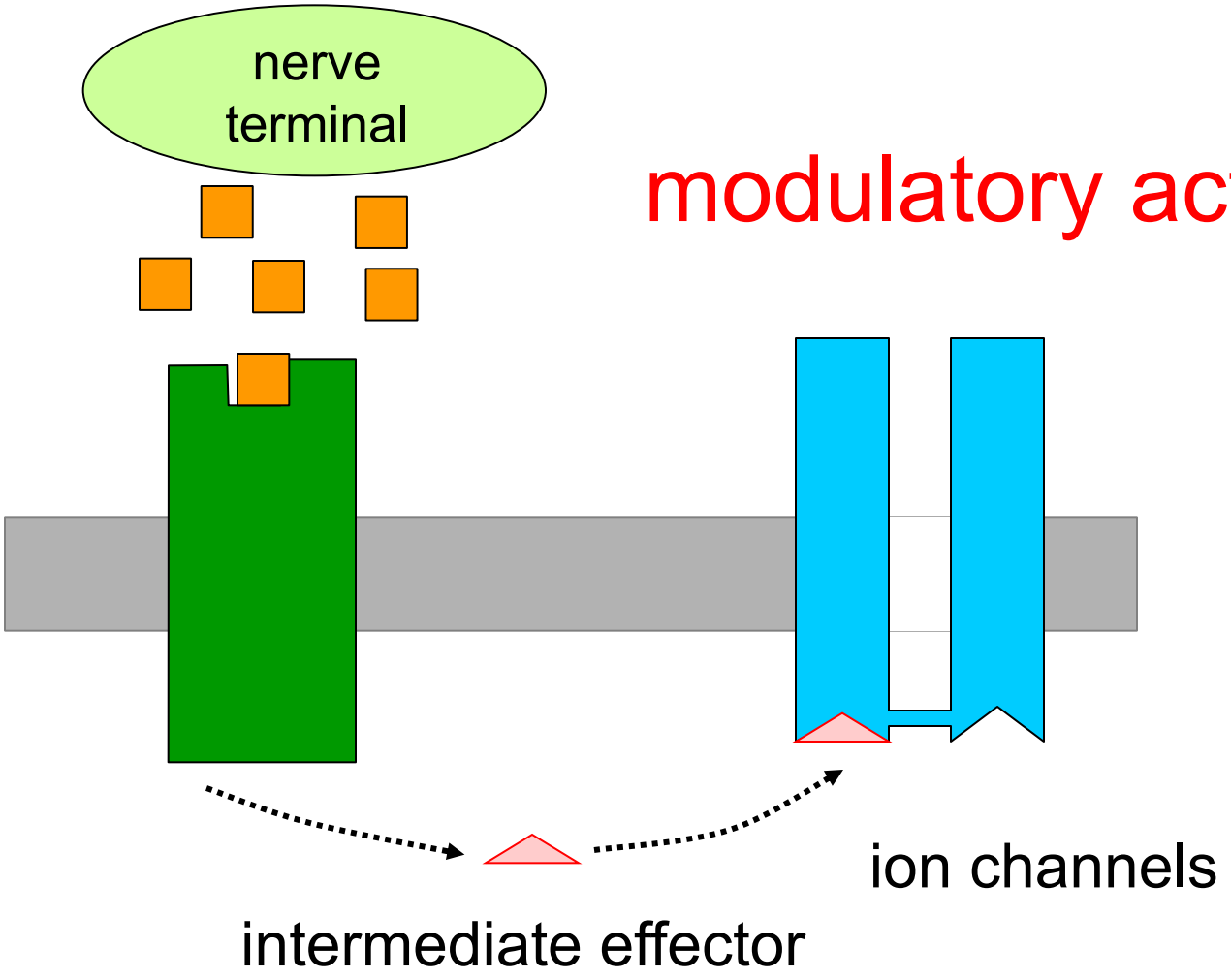


Promiscuity

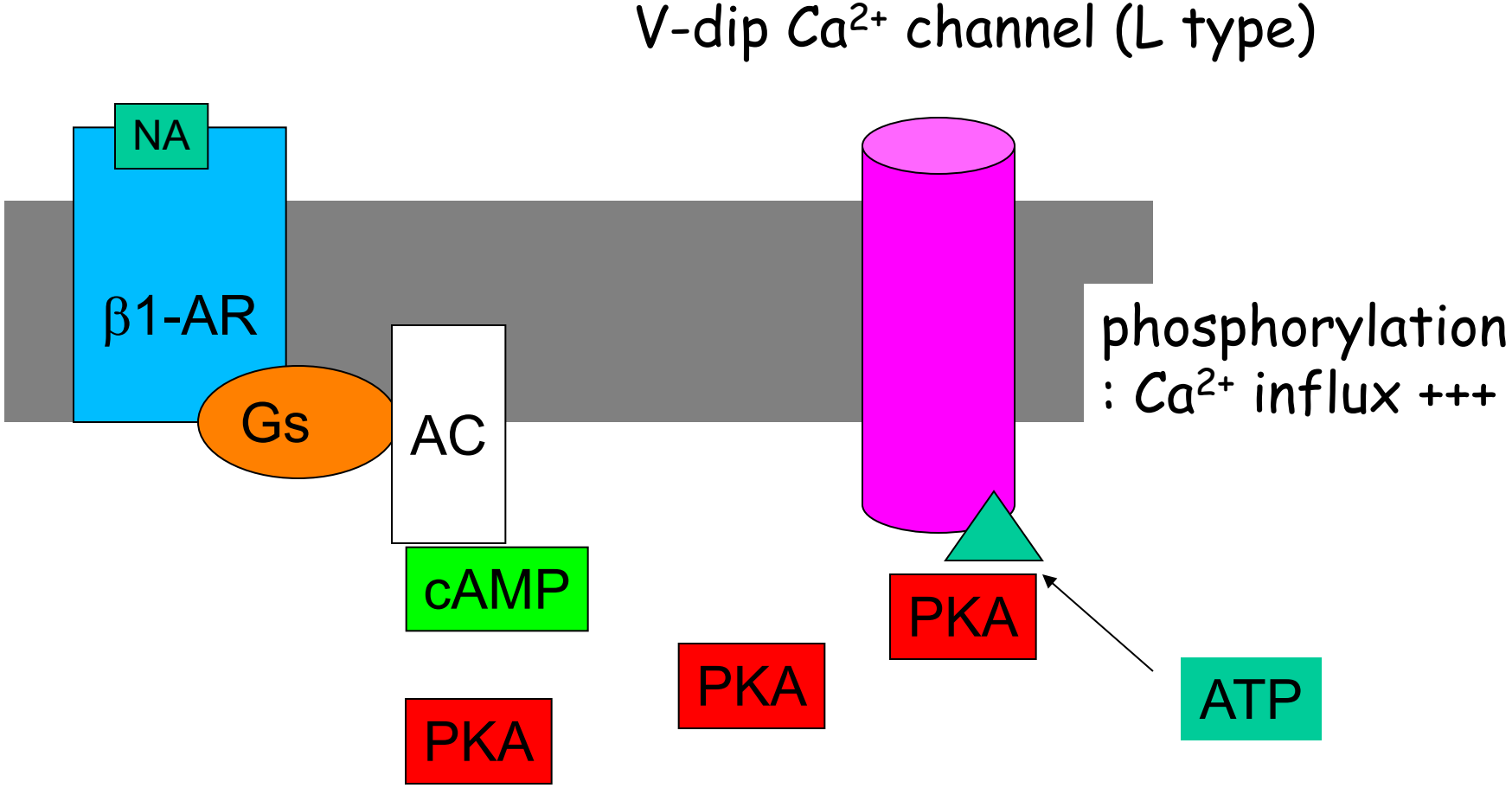


Interactions with ion channels

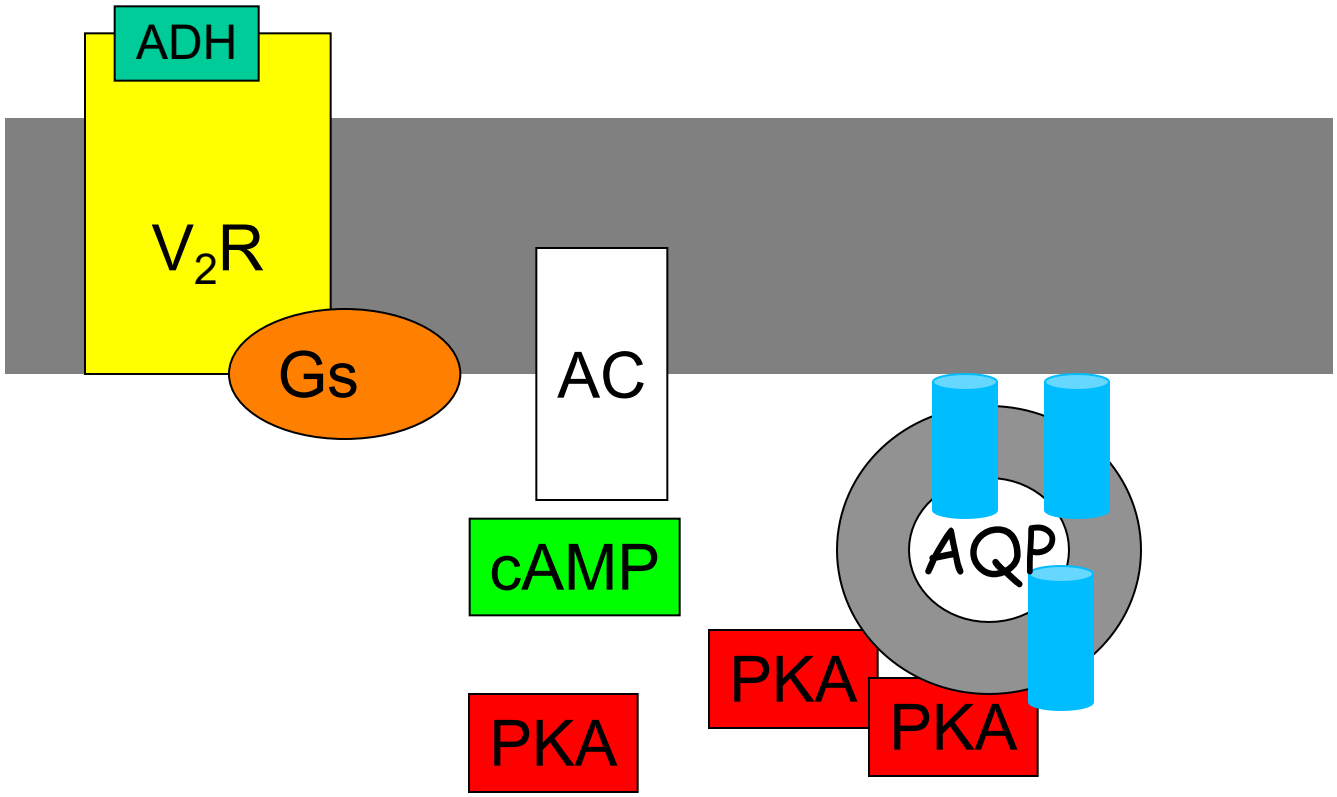
metabotropic receptors



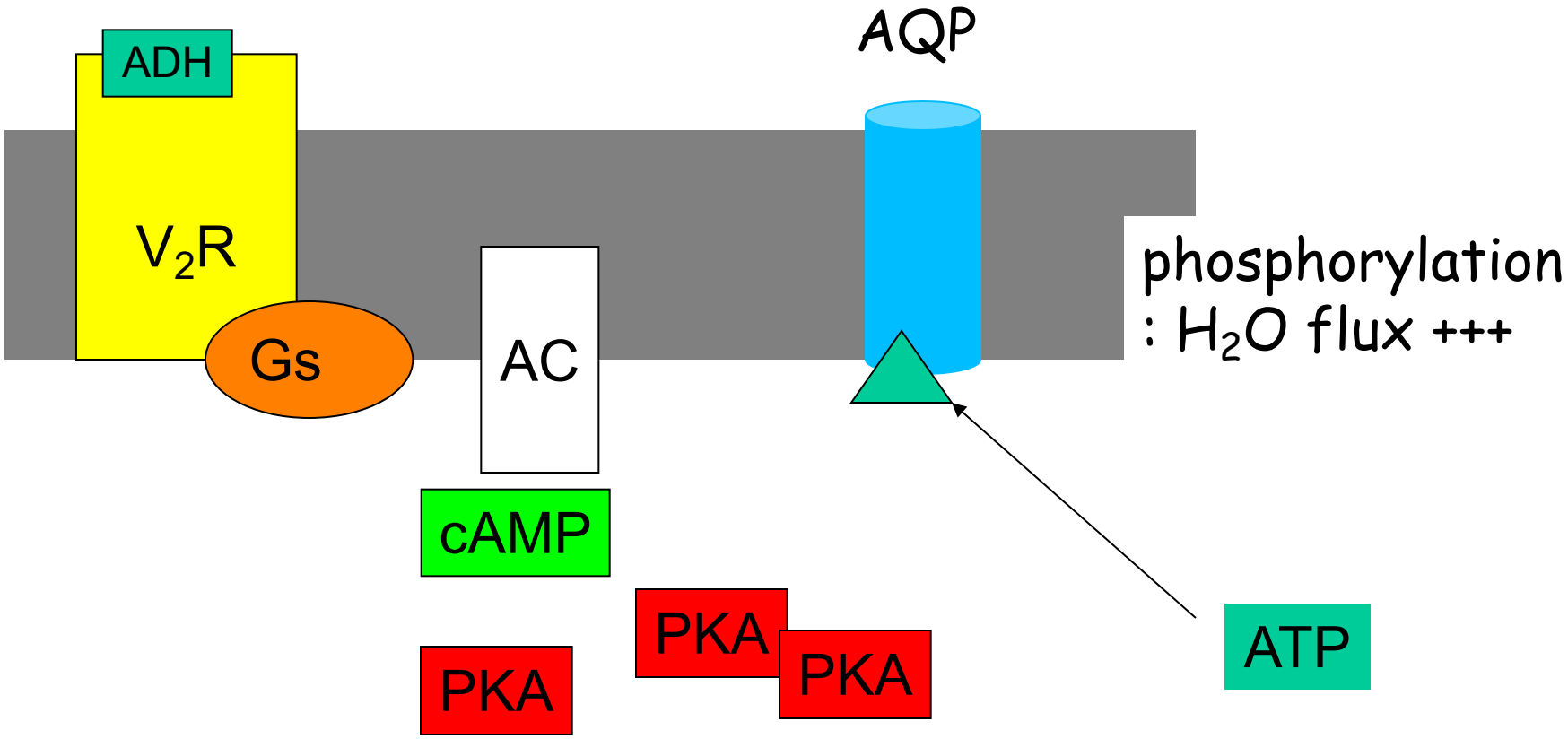
phosphorylation: indirect action

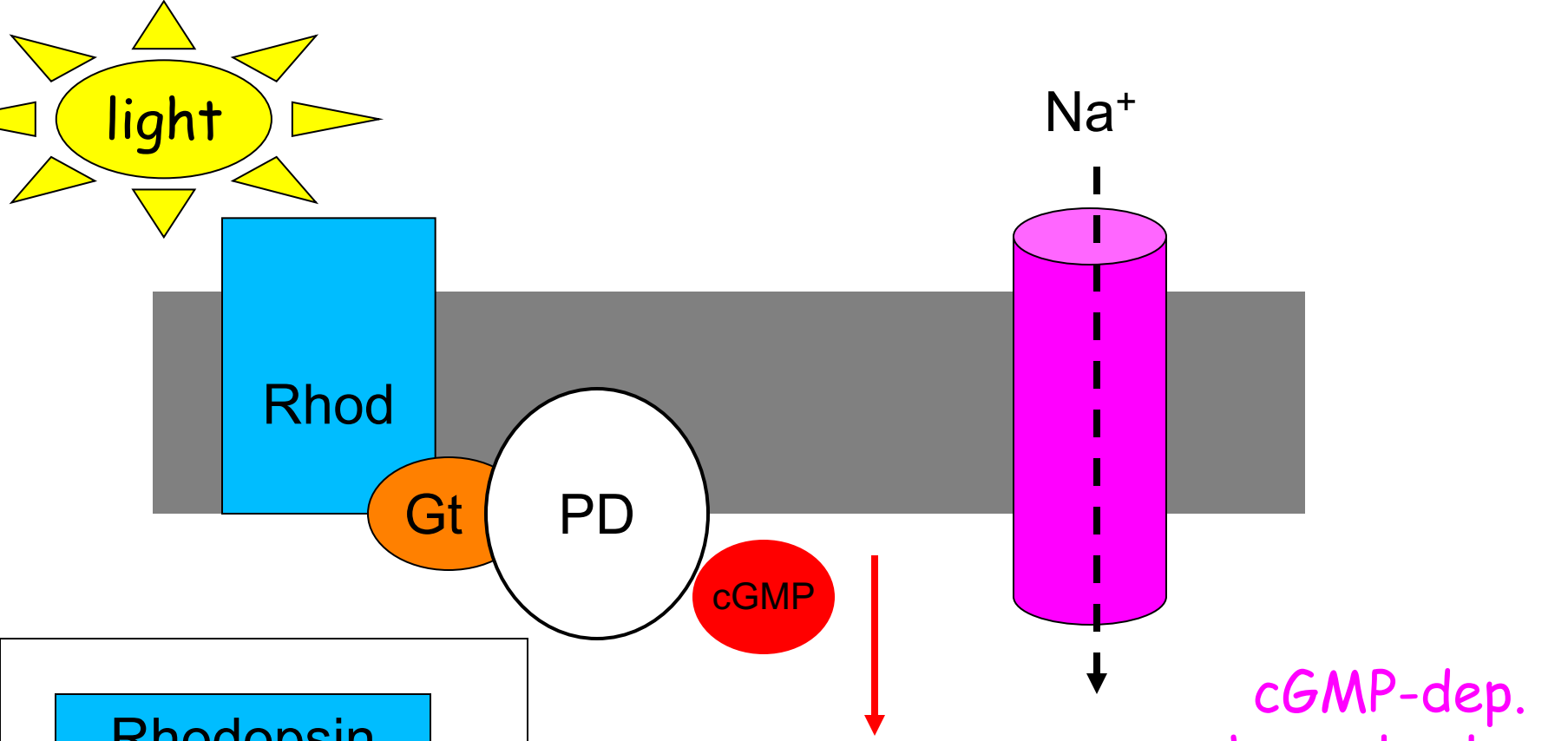


phosphorylation: indirect action



phosphorylation: indirect action





Rhodopsin

Transducine

phosphodiesterase

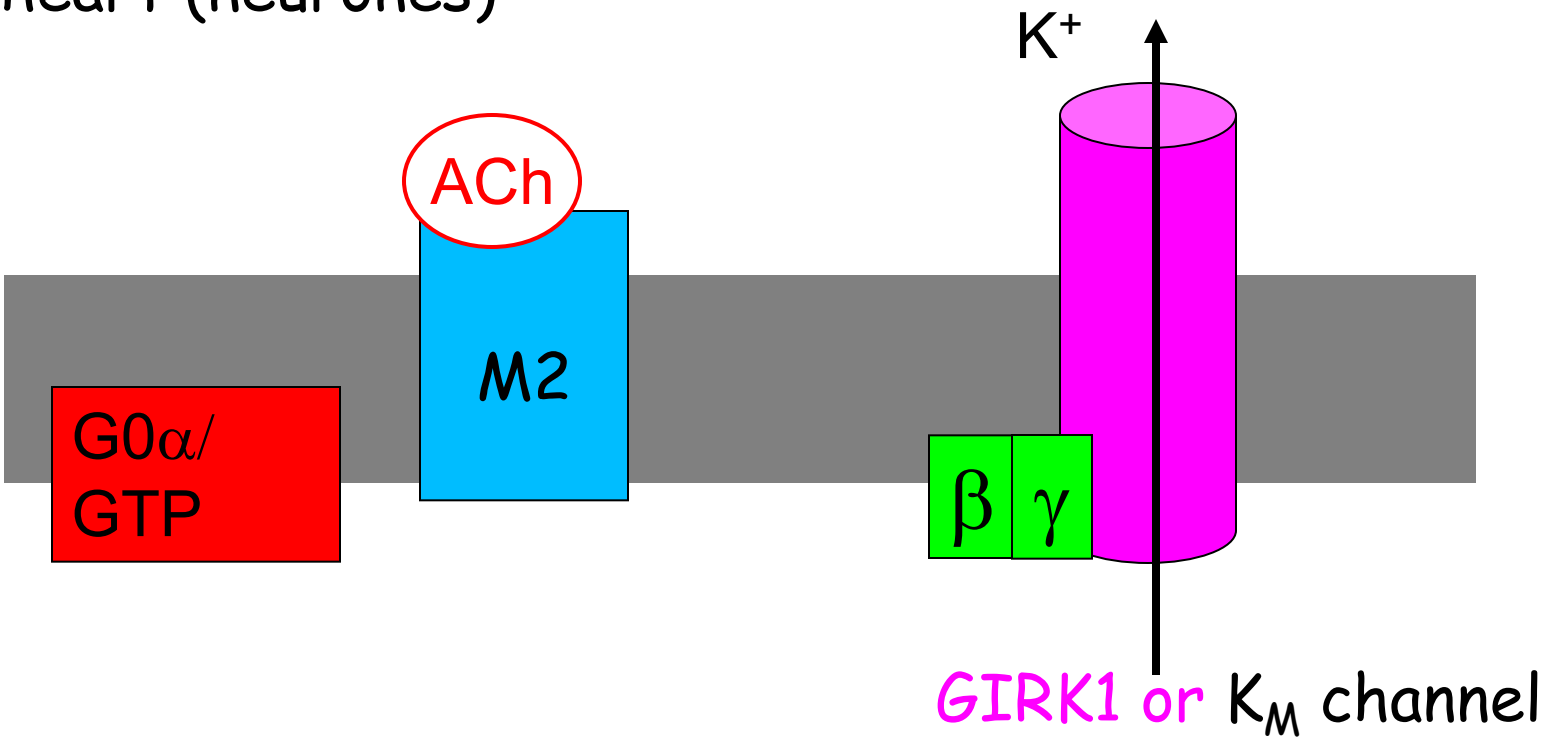
cGMP → 5'GMP

cGMP-dep. channels close

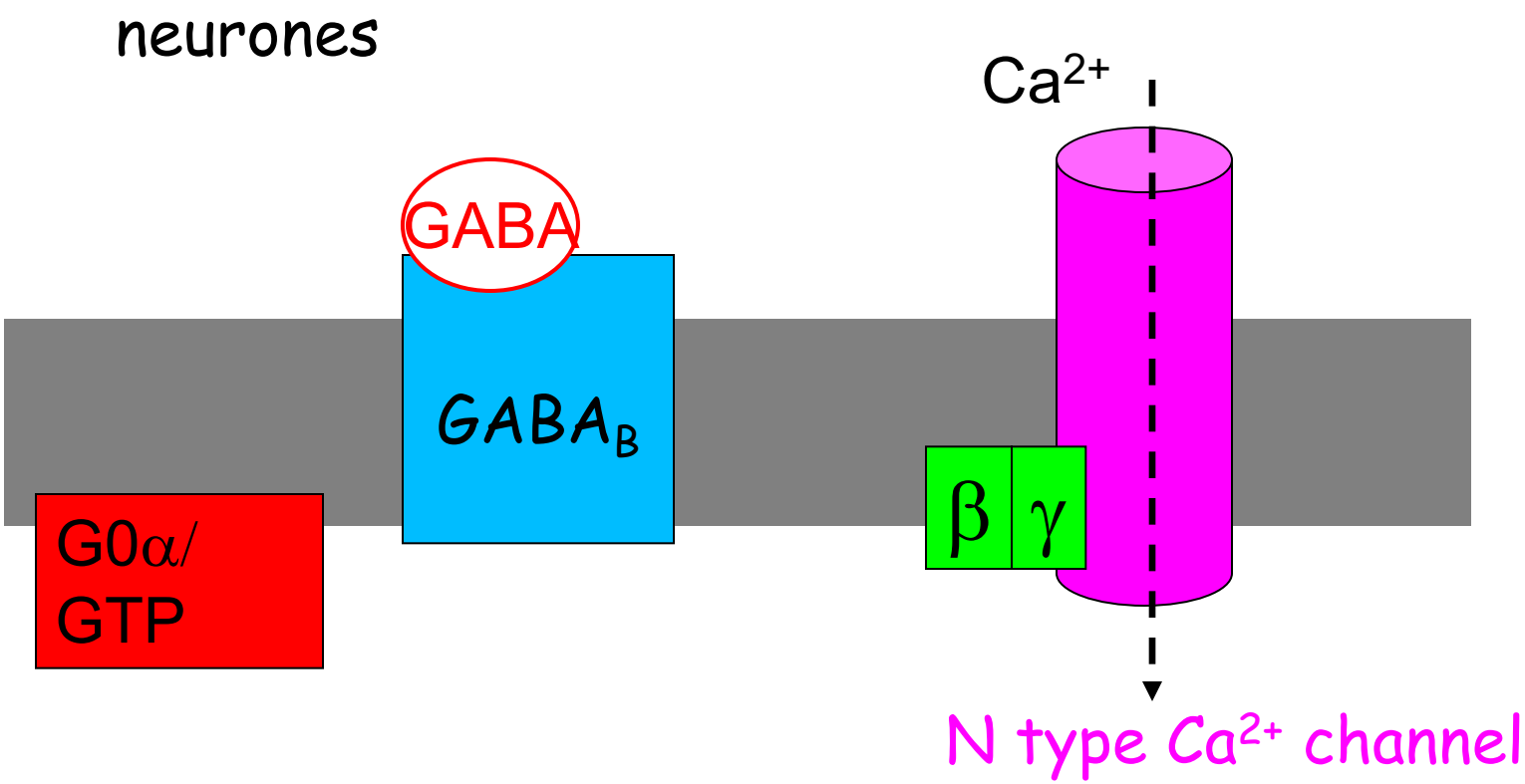
via cGMP

membrane pathway

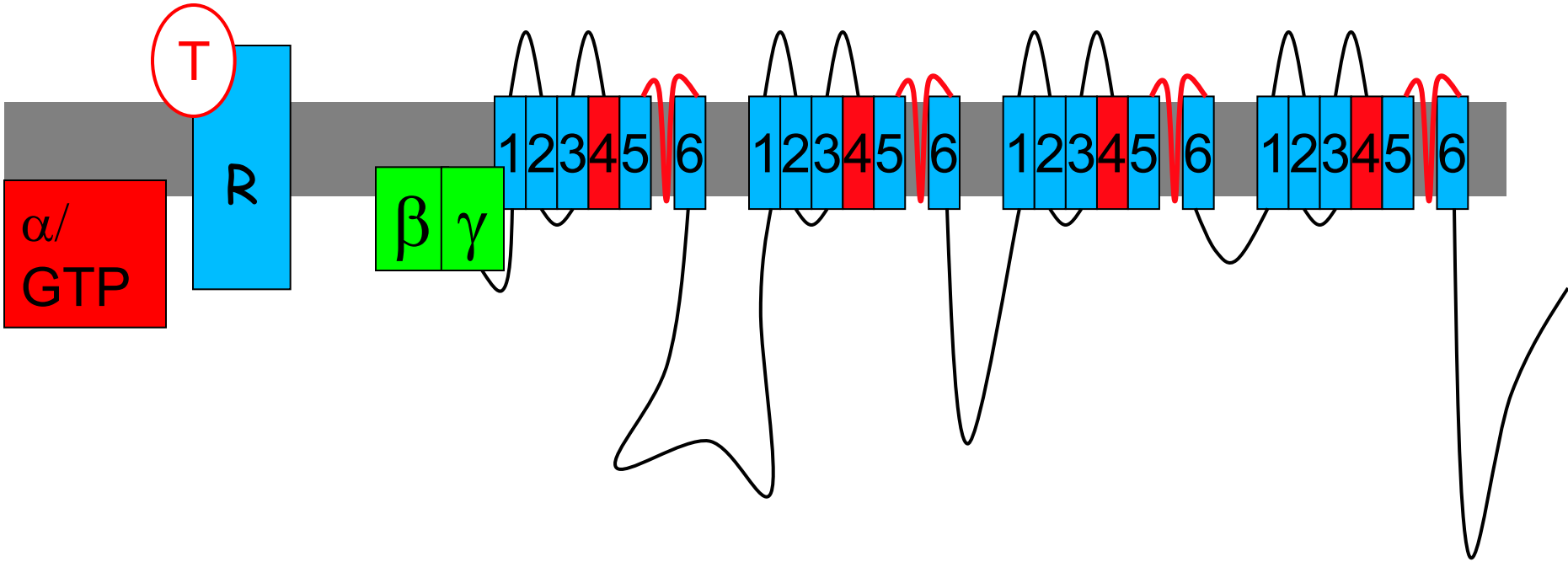
heart (neurones)



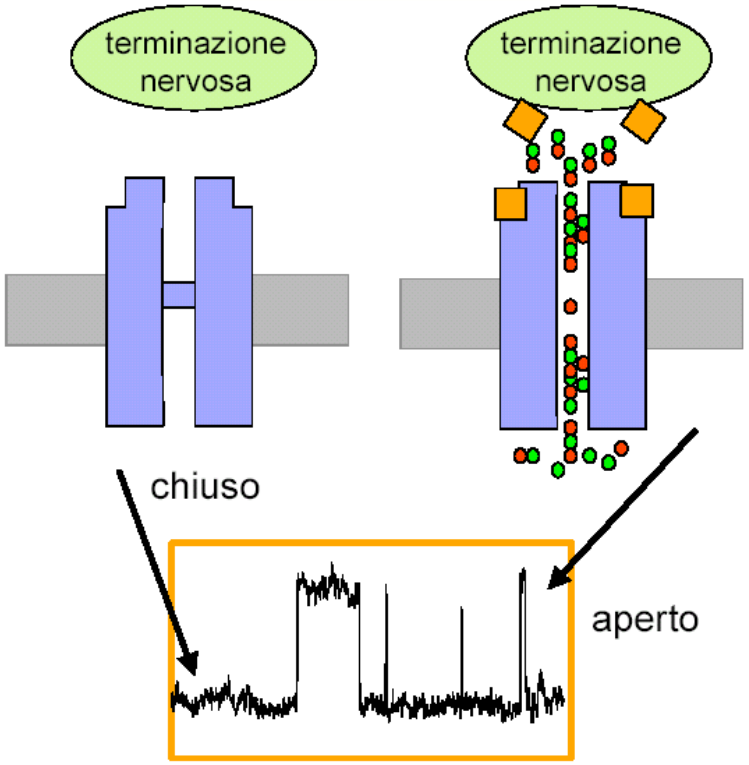
membrane pathway

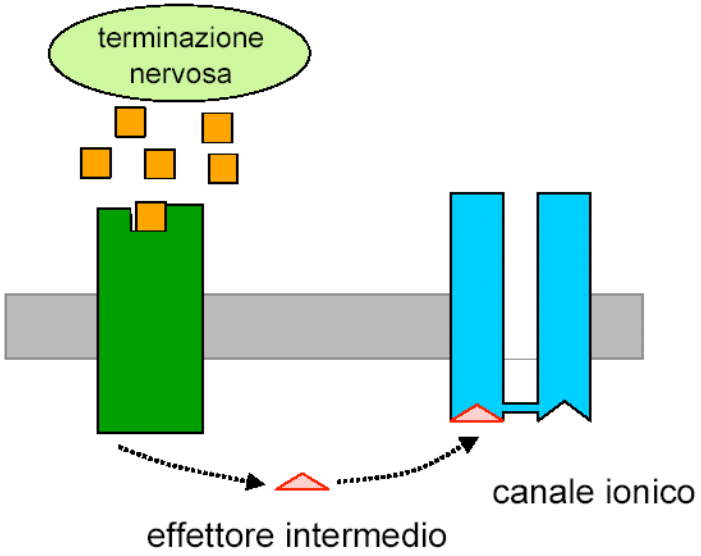


All voltage-gated channels



receptors

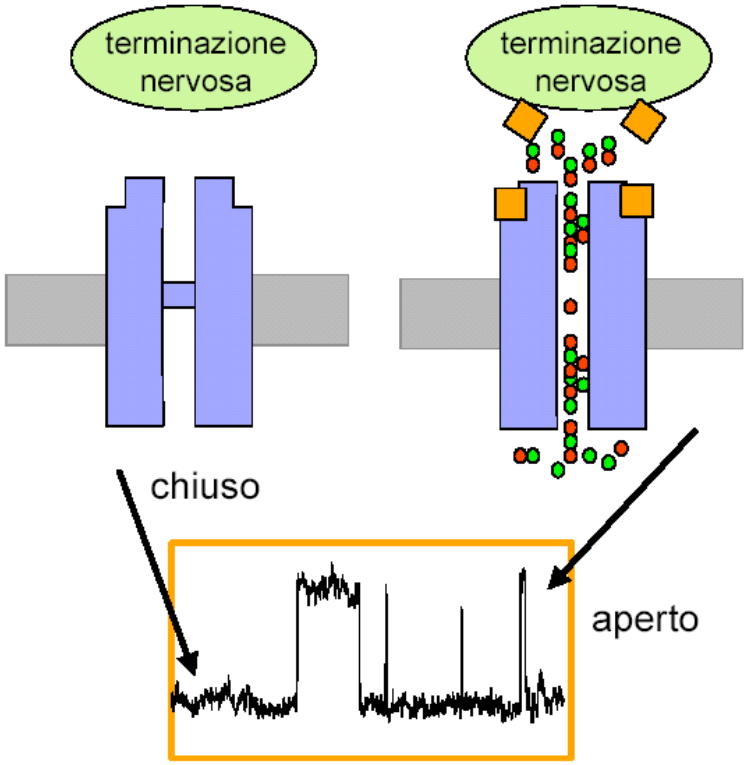


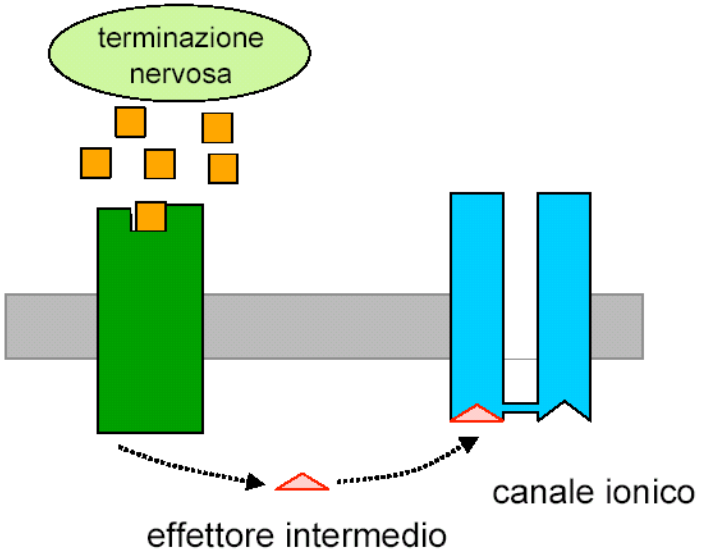


ionotropic = ligand-gated channels

metabotropic

receptors





FAST synaptic transmission

SLOW synaptic transmission

Long lasting effect

Tcl= classical NT
Npep= neuropeptide