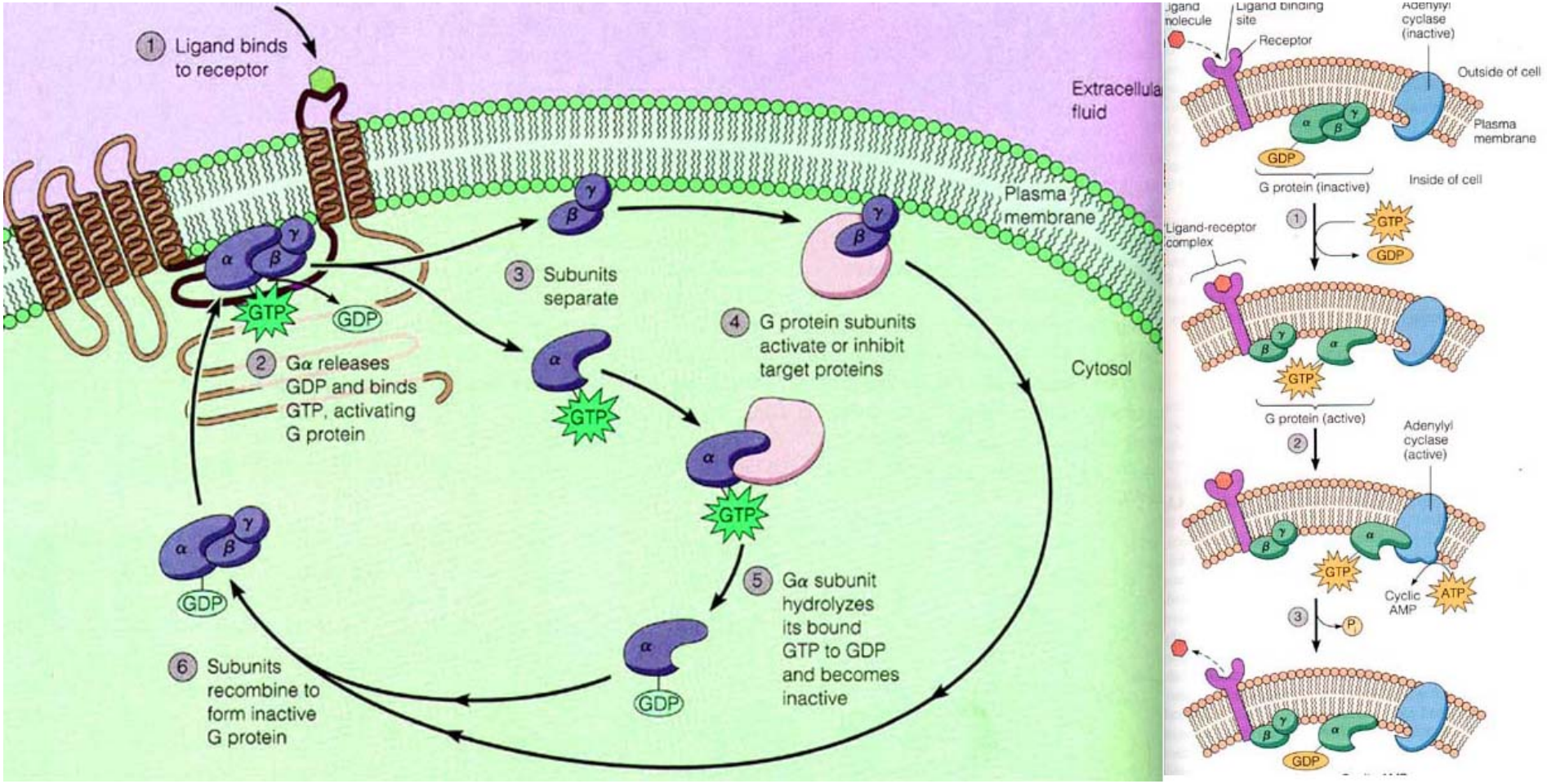
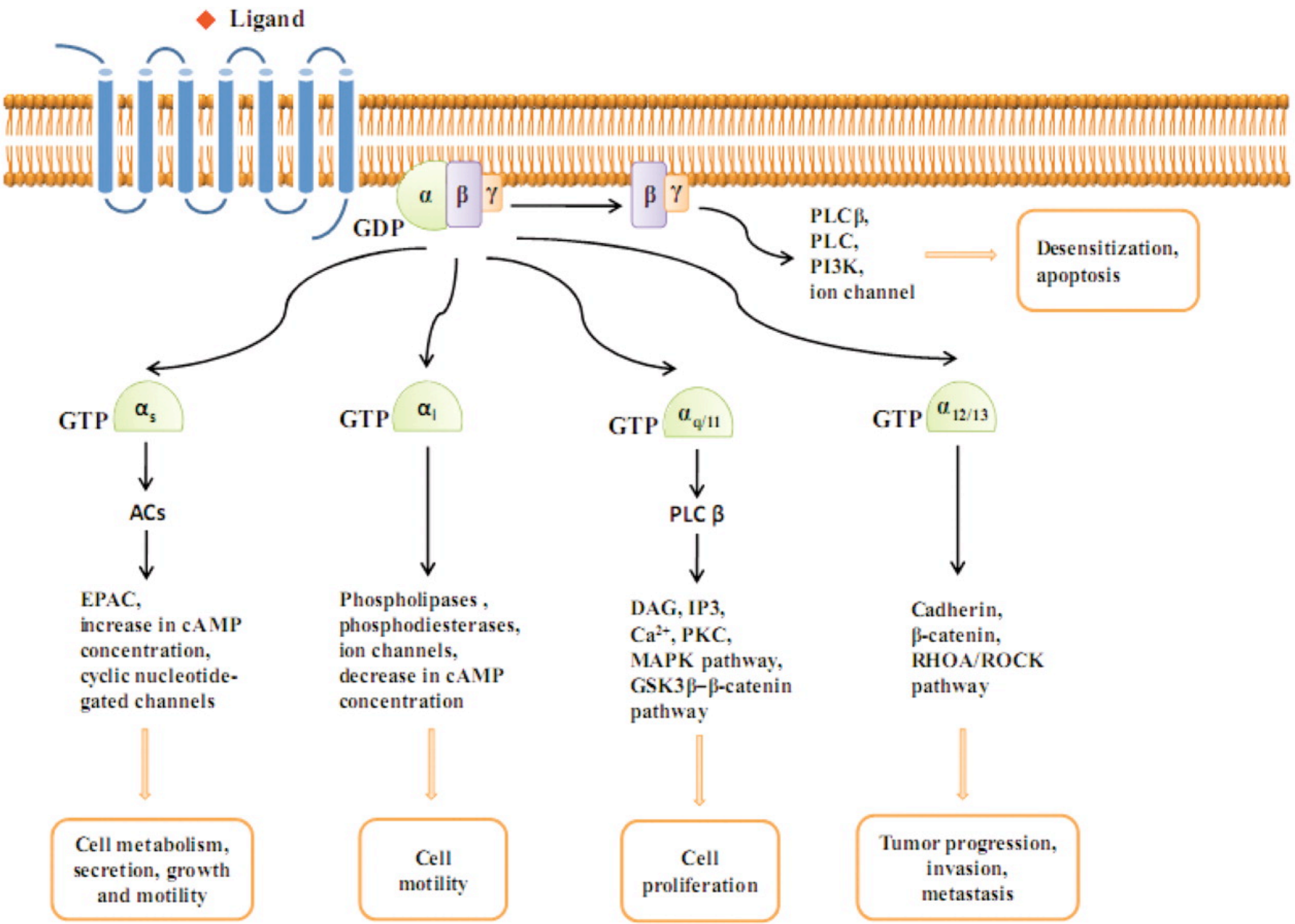
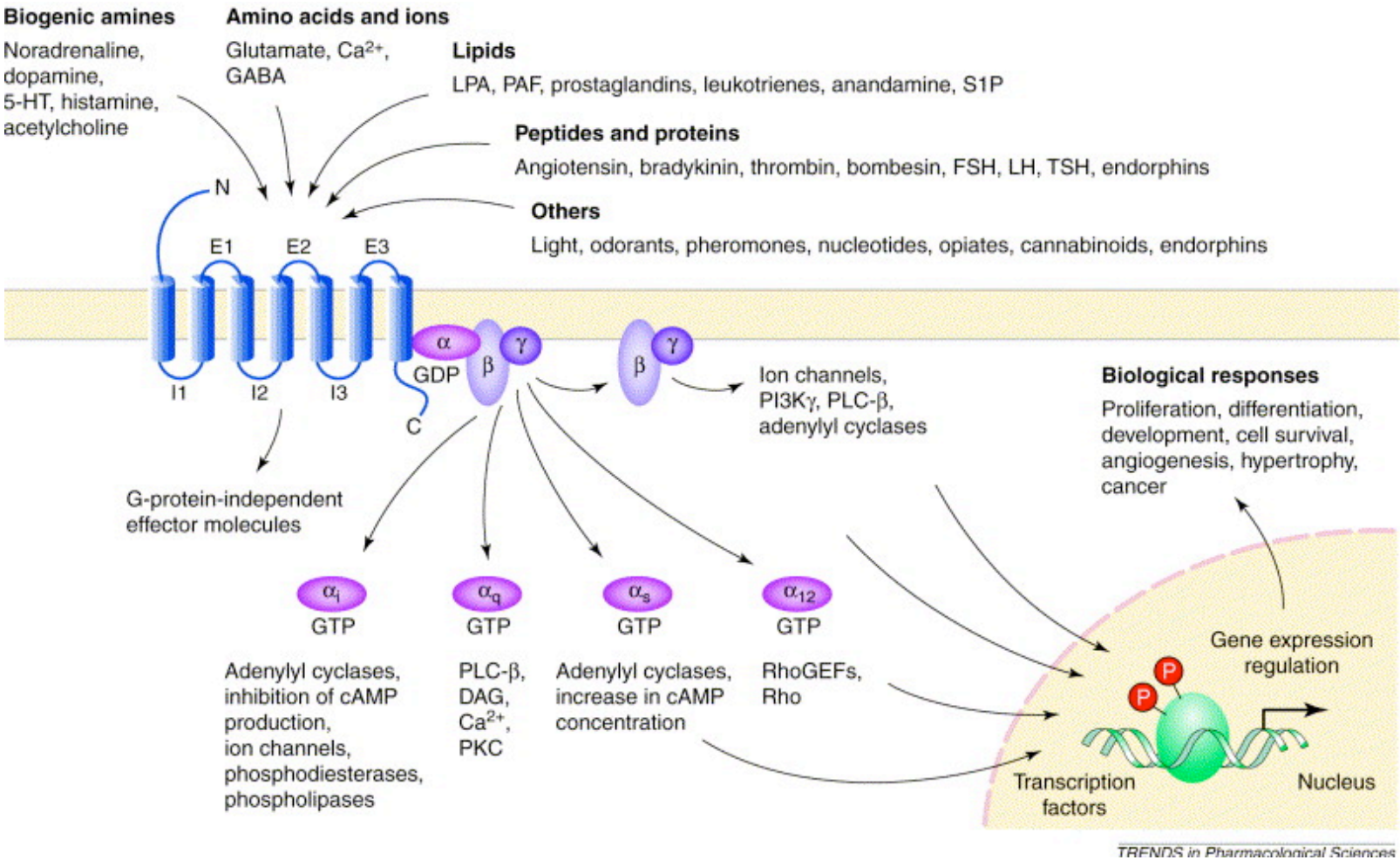
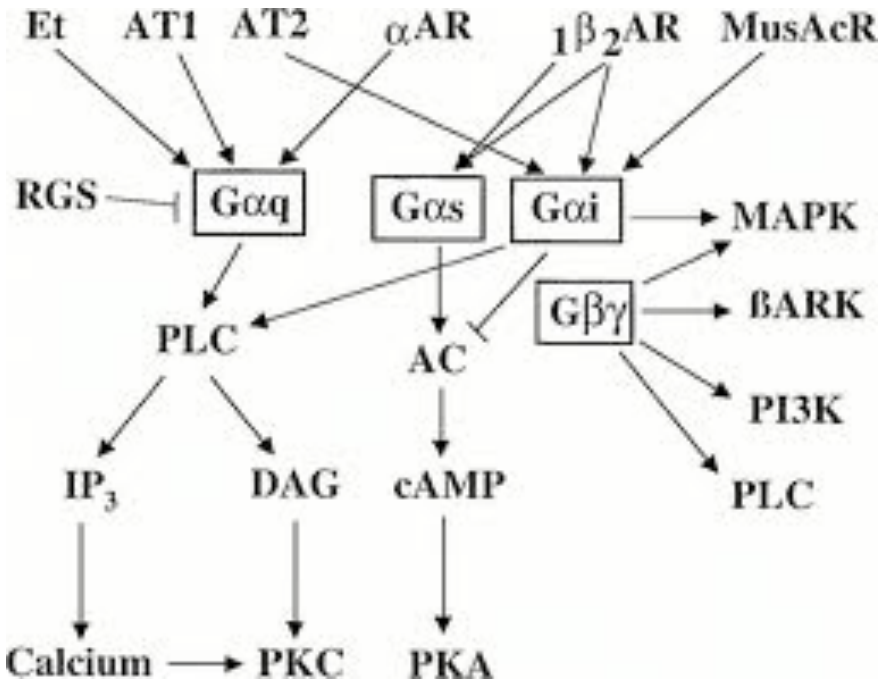
G-protein signaling pathways

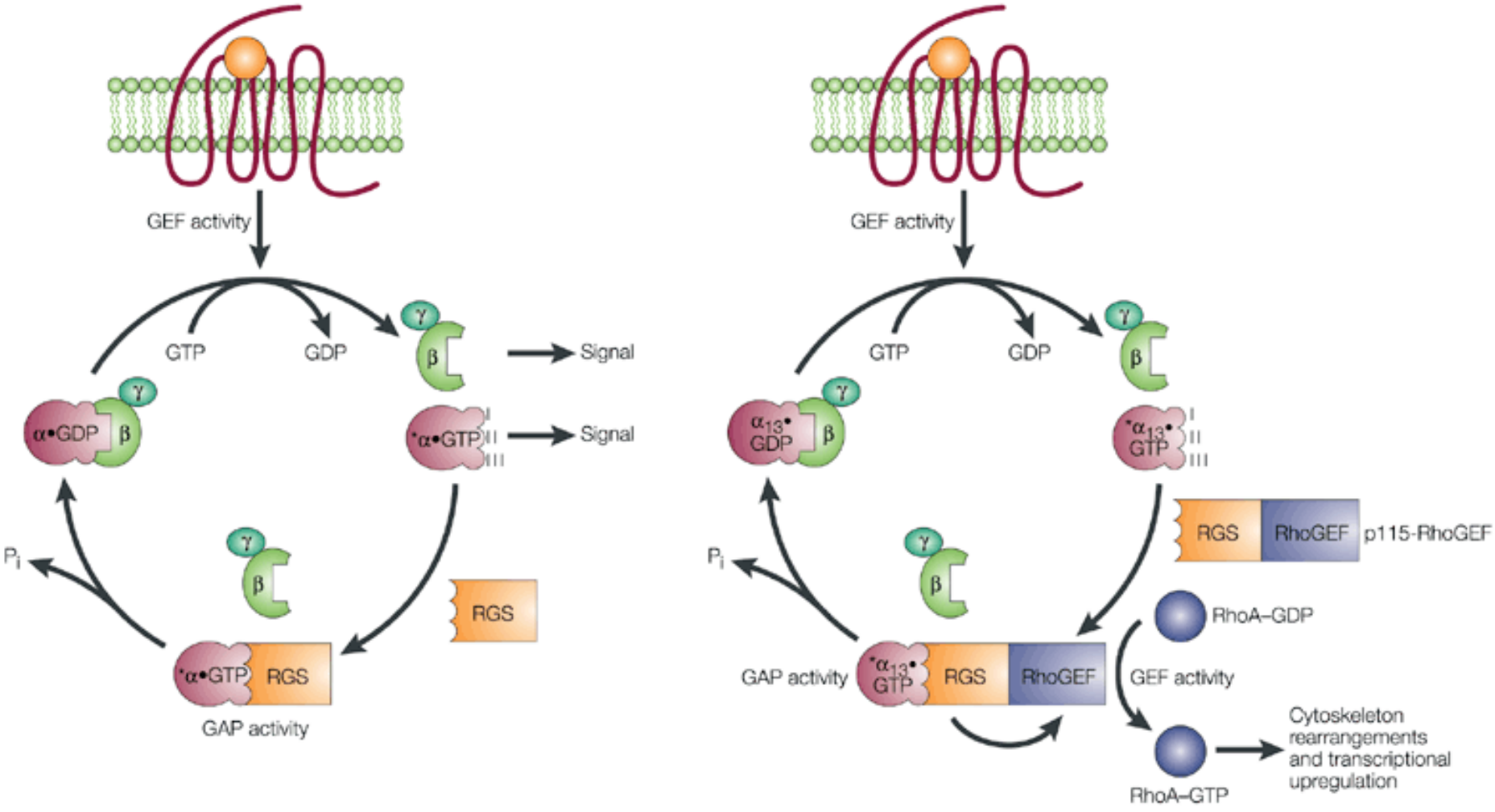
General mechanism




Ligand
α
β
γ
GDP
β
γ
PLCβ,
PLC,
PI3K,
ion channel
Desensitization,
apoptosis
GTP
α_s
ACs
EPAC,
increase in cAMP
concentration,
cyclic nucleotide-
gated channels
Cell metabolism,
secretion, growth
and motility
GTP
α_i
Phospholipases ,
phosphodiesterases,
ion channels,
decrease in cAMP
concentration
Cell
motility
GTP
$\alpha_{q/11}$
PLC β
DAG, IP3,
Ca^{2+}, PKC,
MAPK pathway,
GSK3β–β-catenin
pathway
Cell
proliferation
GTP
$\alpha_{12/13}$
Cadherin,
β-catenin,
RHOA/ROCK
pathway
Tumor progression,
invasion,
metastasis


Biogenic amines
Noradrenaline, dopamine, 5-HT, histamine, acetylcholine
Amino acids and ions
Glutamate, Ca2+, GABA
Lipids
LPA, PAF, prostaglandins, leukotrienes, anandamine, S1P
Peptides and proteins
Angiotensin, bradykinin, thrombin, bombesin, FSH, LH, TSH, endorphins
Others
Light, odorants, pheromones, nucleotides, opiates, cannabinoids, endorphins
N
E1
E2
E3
I1
I2
I3
C
α
β
γ
GDP
Ion channels, PI3Kγ, PLC-β, adenylyl cyclases
Biological responses
Proliferation, differentiation, development, cell survival, angiogenesis, hypertrophy, cancer
G-protein-independent effector molecules
αi GTP
αq GTP
αs GTP
α12 GTP
Adenylyl cyclases, inhibition of cAMP production, ion channels, phosphodiesterases, phospholipases
PLC-β, DAG, Ca2+, PKC
Adenylyl cyclases, increase in cAMP concentration
RhoGEFs, Rho
Gene expression regulation
P
P
Transcription factors
Nucleus
TRENDS in Pharmacological Sciences


Et
AT1
AT2
αAR
1β2AR
MusAcR
RGS
Gαq
Gαs
Gαi
MAPK
Gβγ
ßARK
PLC
AC
PI3K
IP3
DAG
cAMP
PLC
Calcium
PKC
PKA


GEF activity
GTP
GDP
γ
β
Signal
α•GDP
*α•GTP
I
II
III
Signal
Pi
RGS
*α•GTP
RGS
GAP activity
GEF activity
GTP
GDP
α13• GDP
*α13• GTP
RGS
RhoGEF
p115-RhoGEF
Pi
RhoA–GDP
GAP activity
*α13• GTP
RGS
RhoGEF
GEF activity
Cytoskeleton rearrangements and transcriptional upregulation
RhoA–GTP

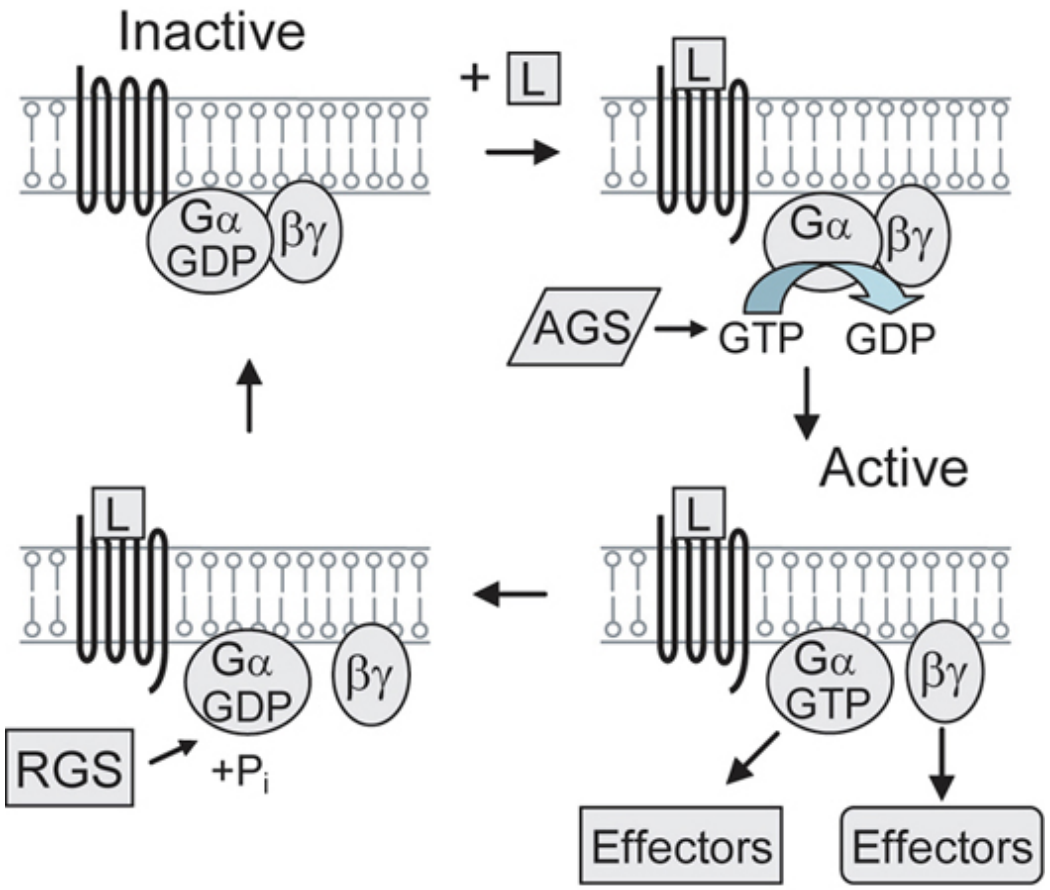


Figure 1. Heterotrimeric G-protein mechanism. The activation of the G-protein coupled receptor by a ligand (L) causes the exchange of GDP for GTP on the α subunit. This switches Gα to the active conformation and results in the release of Gα and Gβγ from the receptor to signal to downstream effectors. The switch is turned off by the intrinsic GTP hydrolysis (GTPase) activity of Gα, which leads to its reassociation with Gβγ and the receptor. The regulators of G-protein signaling (RGS) play key roles in inactivating G-protein signaling. The activators of G-protein signaling (AGS) activate G-proteins by several mechanisms.

Regulation of neurite outgrowth by $G_{i/o}$ signaling pathways

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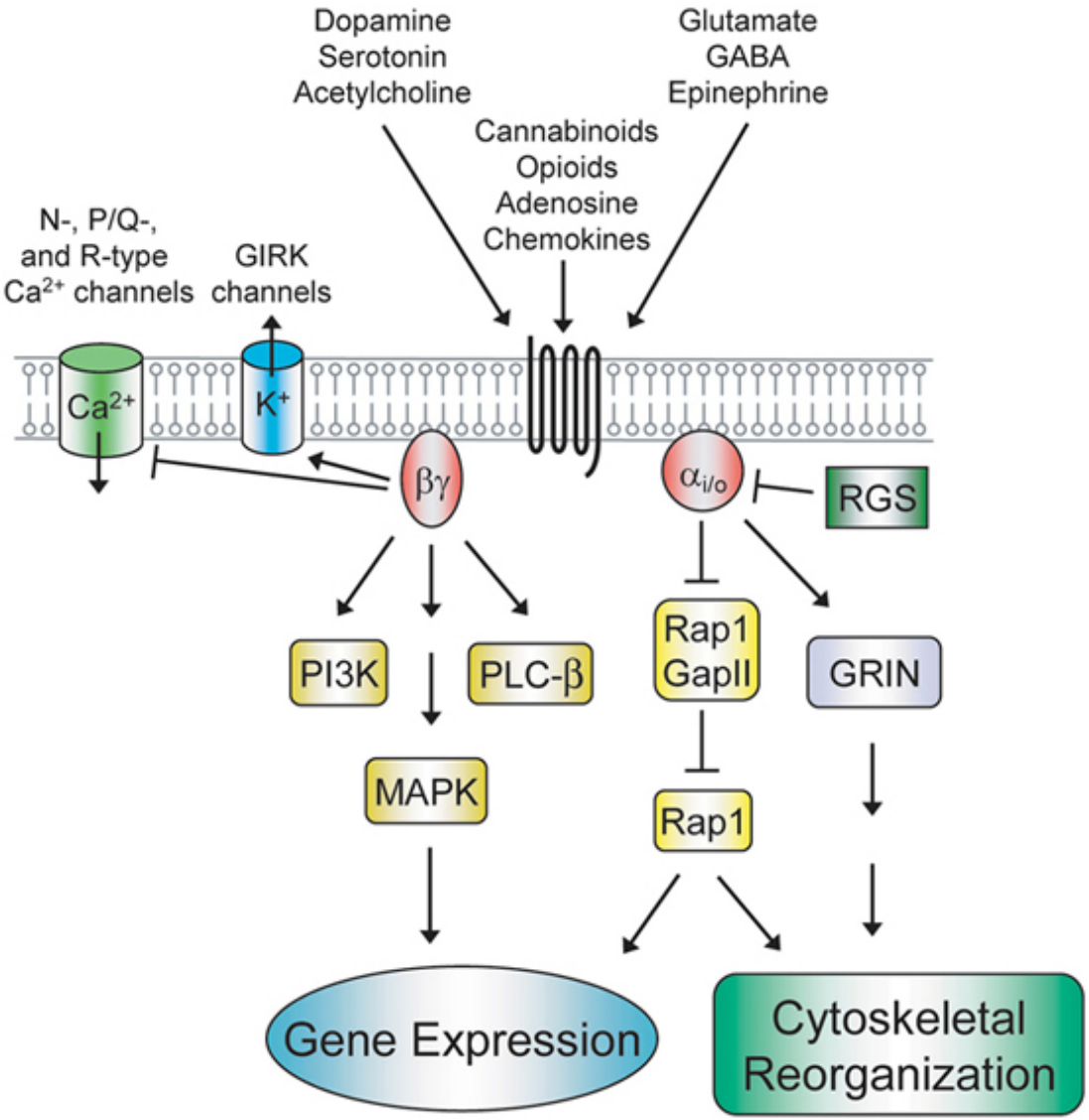


Figure 2. Effector pathways activated by $G_{i/o}$ signaling. Signals from a wide array of hormones,neurotransmitters, and chemokines are transduced into intracellular responses by $G_{i/o}$-coupled receptors. Depicted are pathways that are stimulated by Gα and Gβγ and lead to changes in gene expression and cytoskeletal reorganization. See text for further details. GIRK, G-protein-coupled inward rectifying potassium channels.

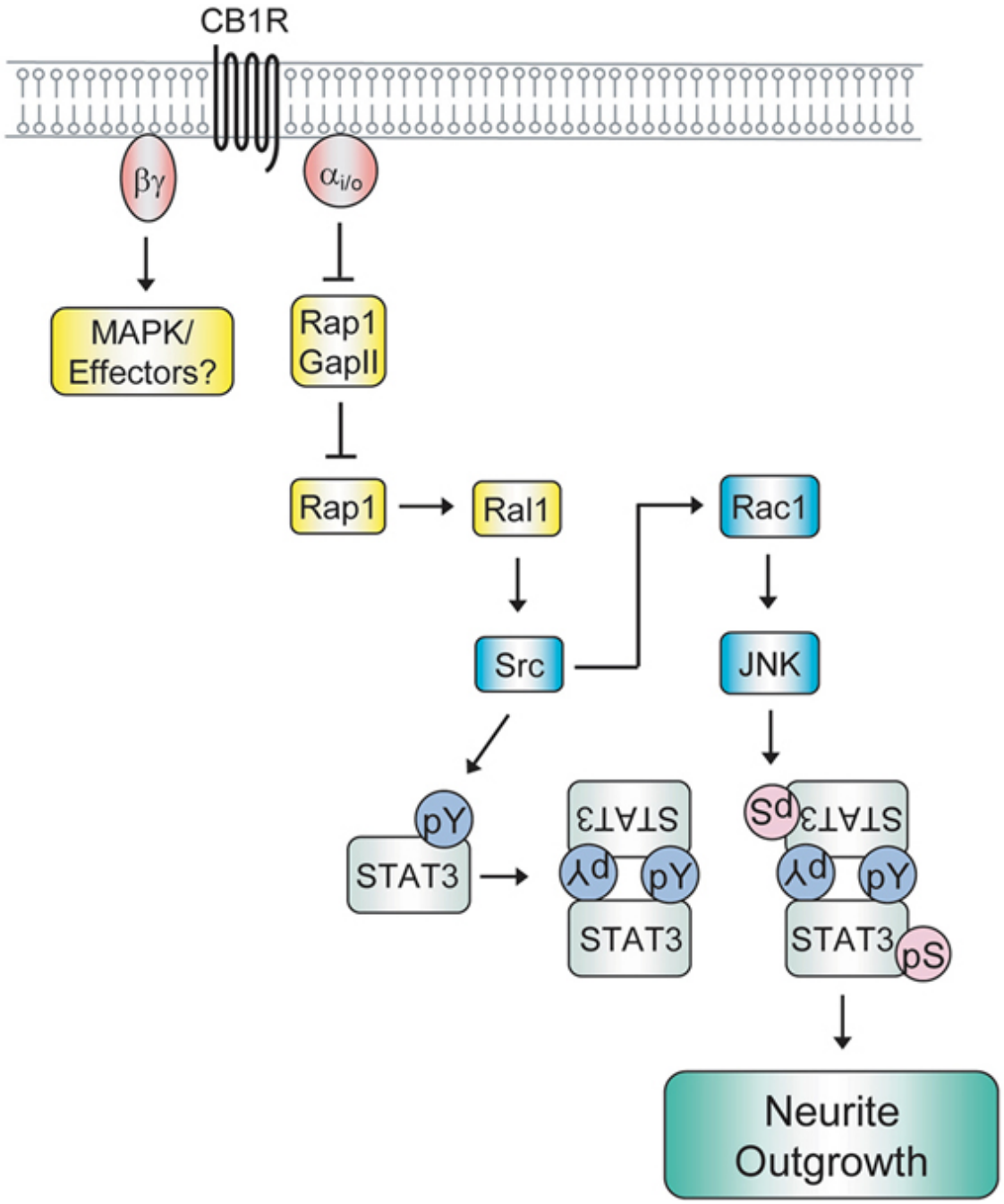


Figure 3. $G_{i/o}$ signaling to the nucleus during the induction of neurite outgrowth. Signal flow emanating from stimulation of the $G_{i/o}$-coupled cannabinoid receptor 1 (CB1R) to the activation of the transcription factor STAT3 is depicted in the schematic. It is likely that Gβγ also signals to downstream effectors to change patterns of gene expression, possibly through p42/44 mitogen activated protein kinase (MAPK). See text for further details. pY, phospho-tyrosine; pS, phospho-serine.

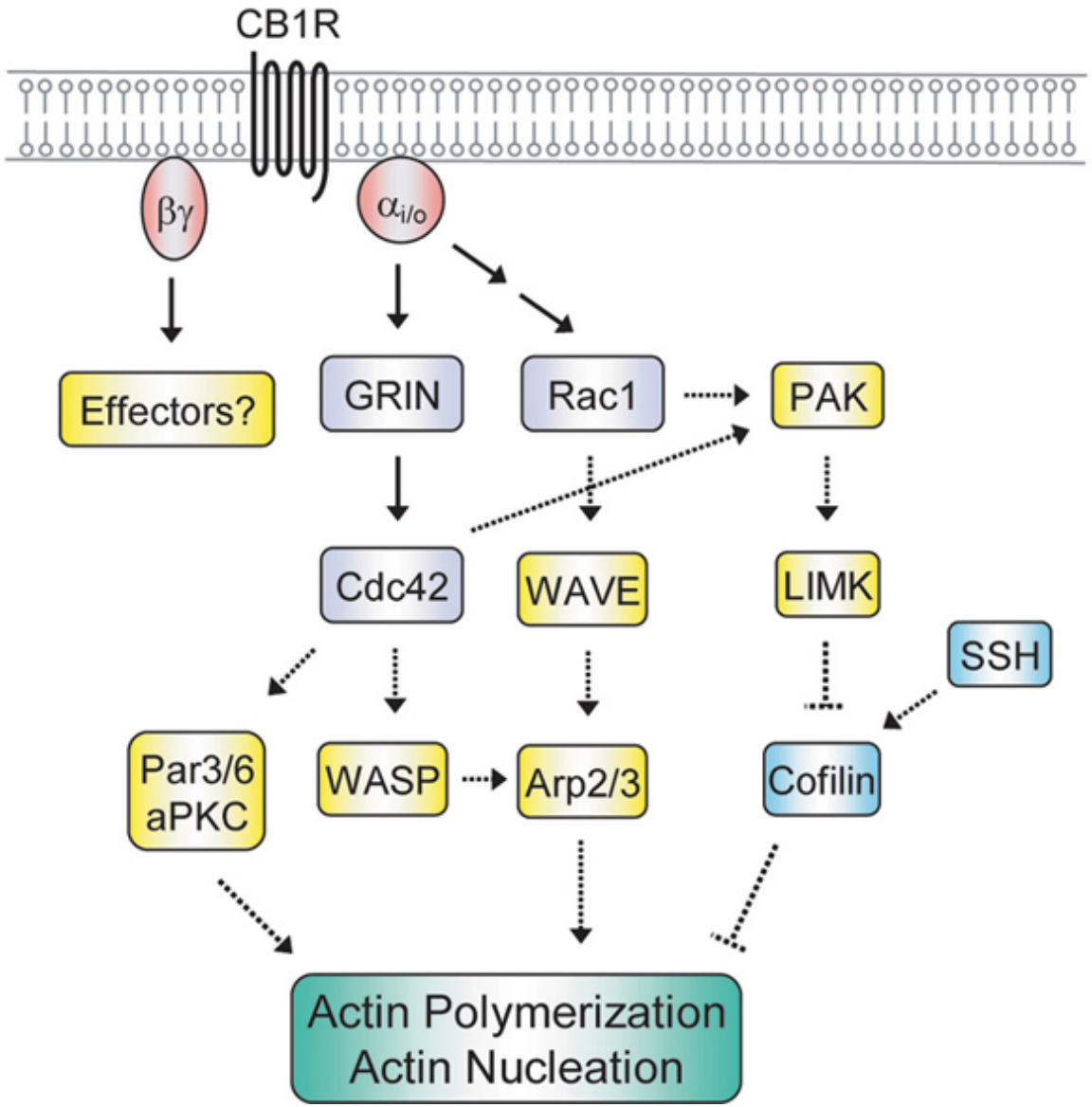
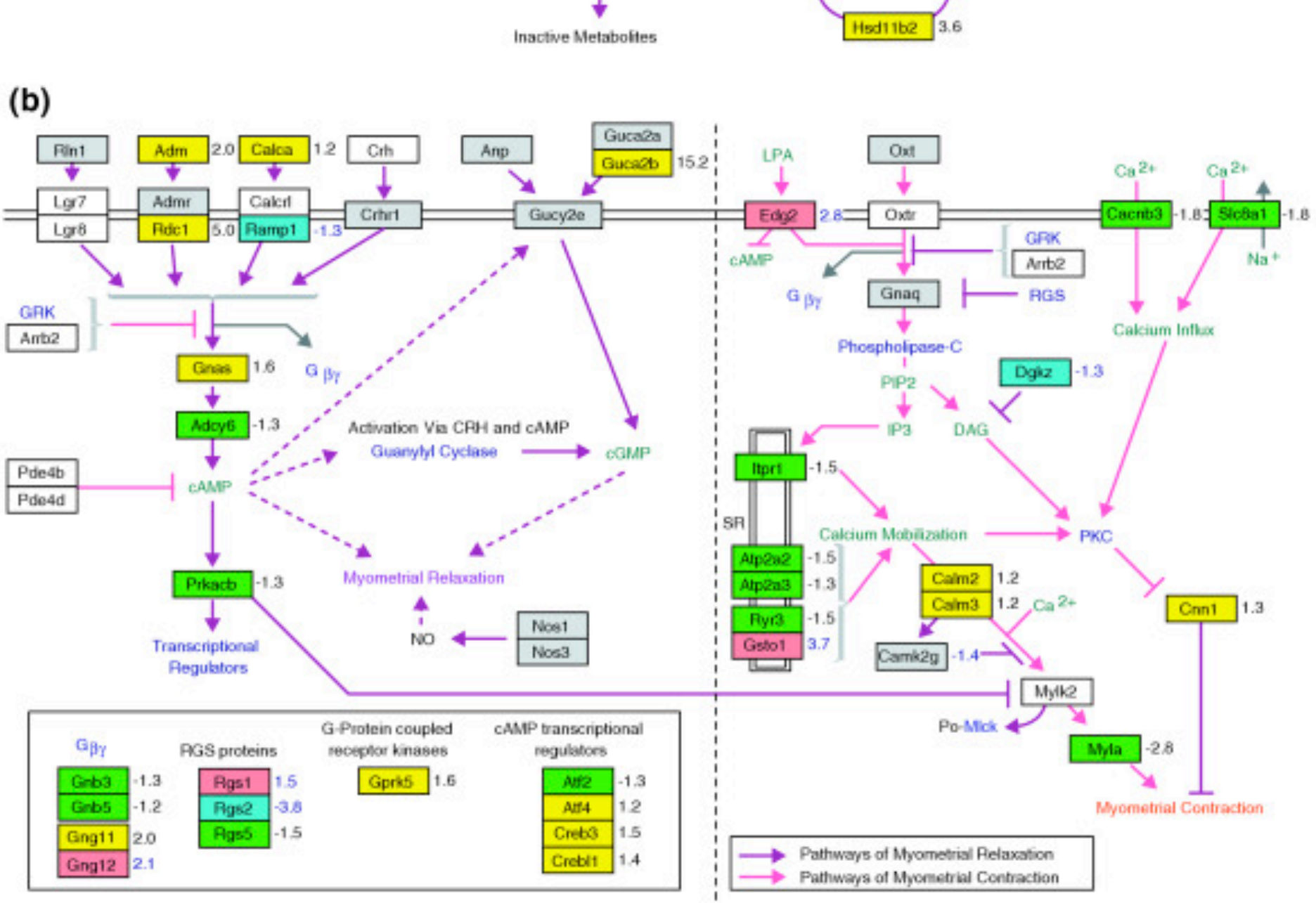
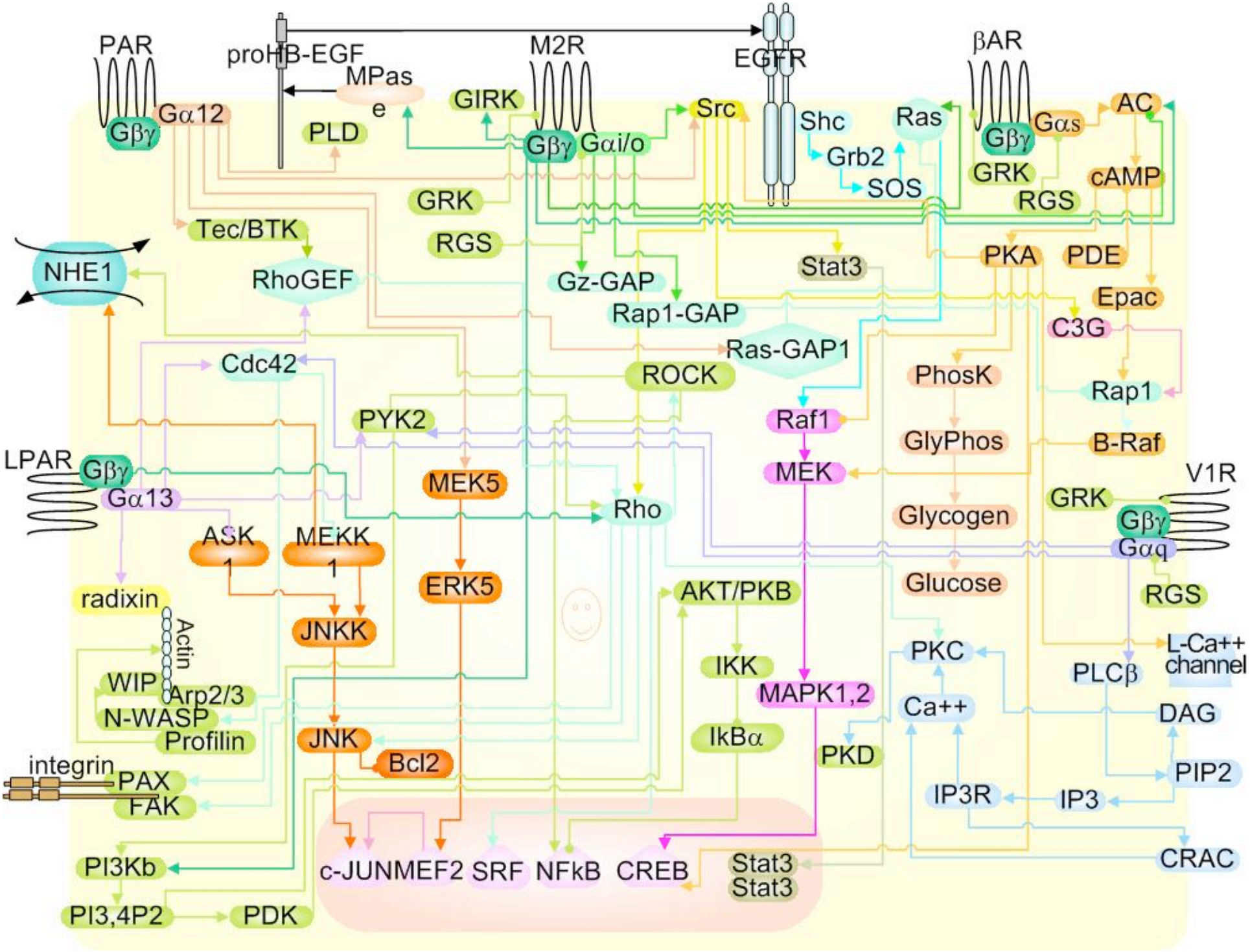
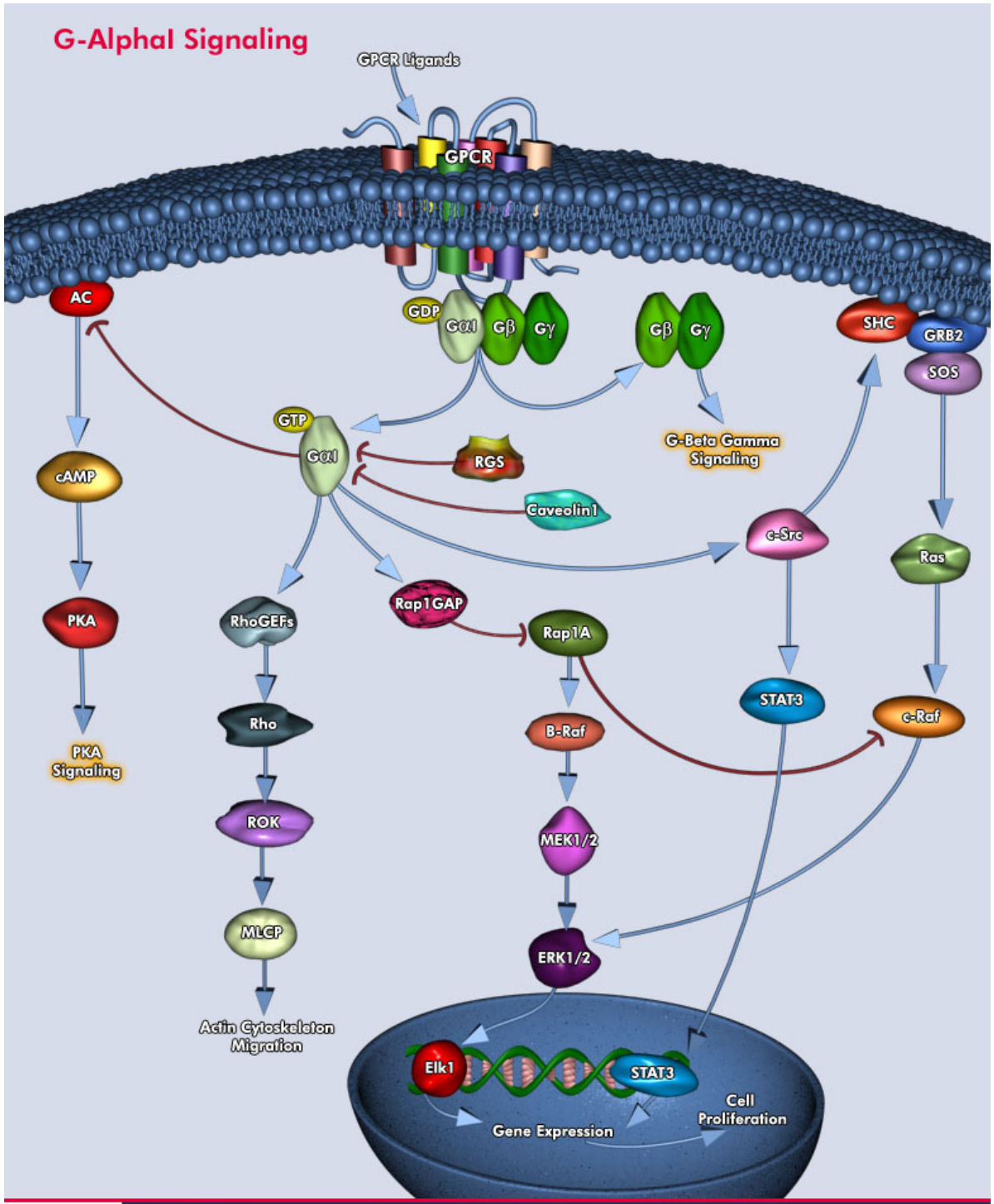


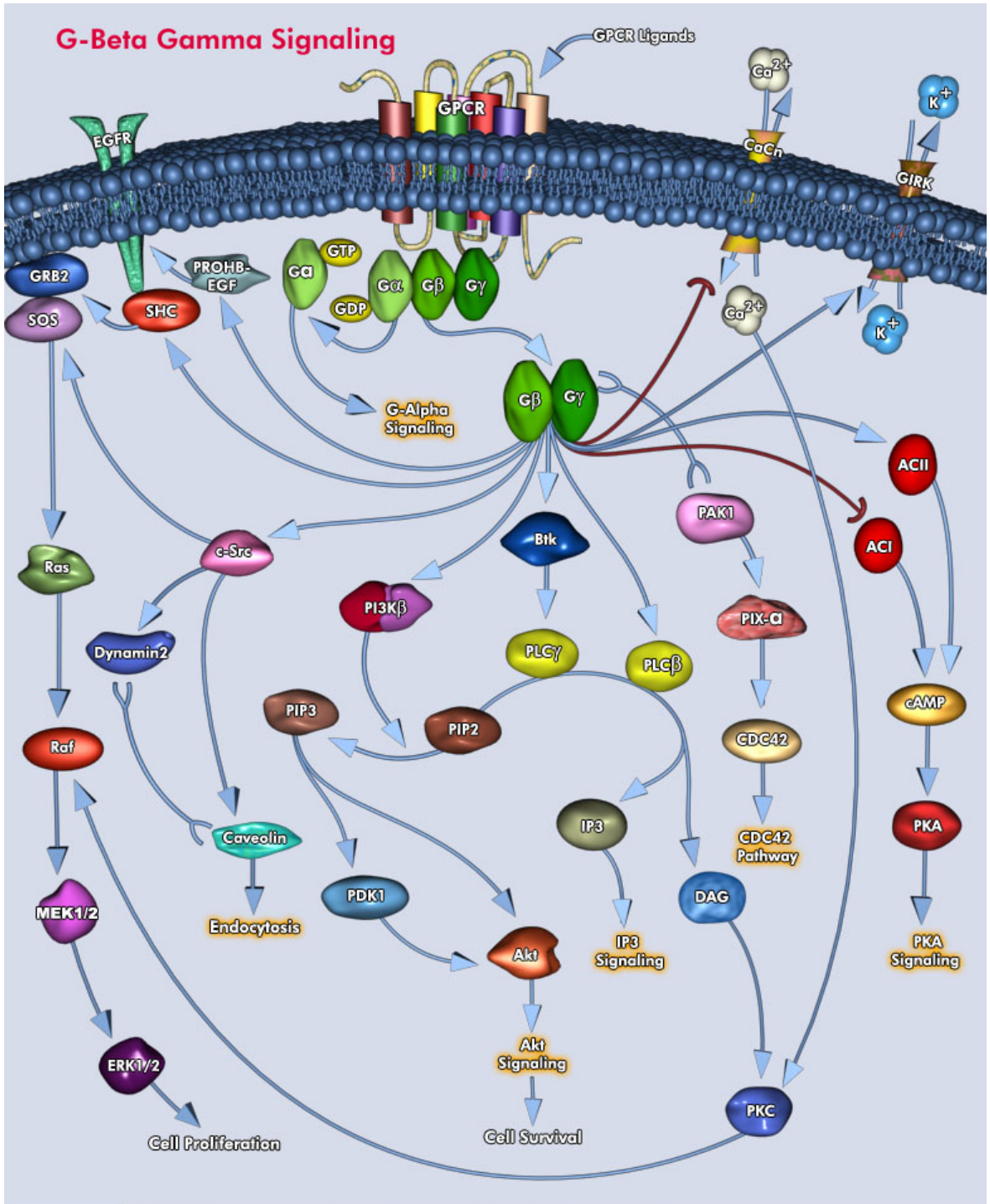
Figure 4. $G_{i/o}$ signaling to the actin cytoskeleton during the induction of neurite outgrowth. Signalingfrom the $G_{i/o}$-coupled CB1R to its effectors GRIN, Cdc42 and Rac1 and their potential downstream targets is shown in the schematic. The intermediate molecules between CB1R and Rac1 have been omitted for clarity. It is likely that Gβγ also signals to yet to be identified downstream effectors to reorganize the actin cytoskeleton. Known interactions are depicted by solid arrows, putative interactions by dashed arrows. See text for further details. PAK, p21-activated kinase; SSH, Slingshot; WASP, Wiskott-Aldrich-syndrome protein.

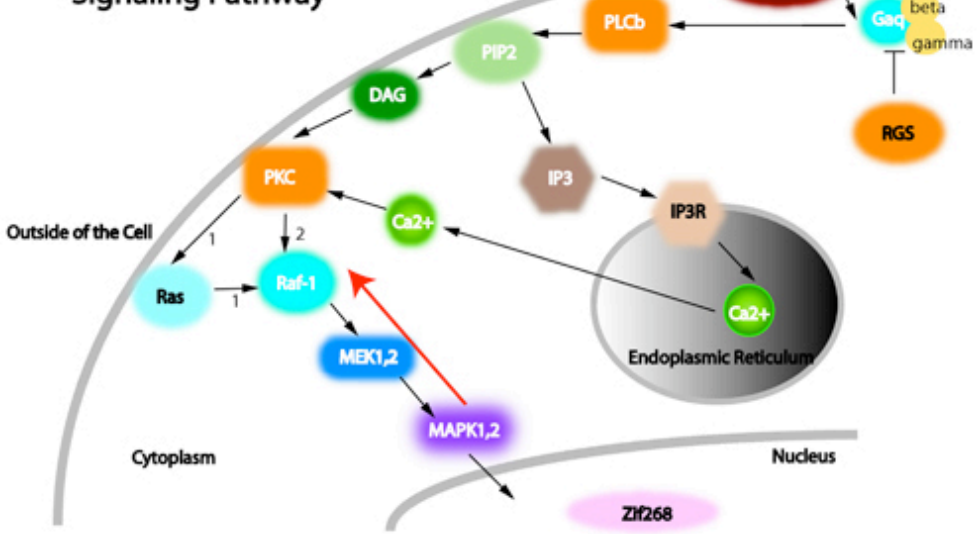

Inactive Metabolites
Hsd11b2
3.6
(b)
Rln1
Adm
2.0
Calca
1.2
Crh
Anp
Guca2a
Guca2b
15.2
Lgr7
Lgr8
Admr
Rdc1
5.0
Calcrl
Ramp1
-1.3
Crhr1
Gucy2e
LPA
Edg2
2.8
Oxt
Oxtr
Ca 2+
Cacnb3
-1.8
Ca 2+
Slc8a1
-1.8
Na +
cAMP
GRK
Arrb2
G βγ
Gnaq
RGS
Calcium Influx
Phospholipase-C
PtP2
Dgkz
-1.3
IP3
DAG
Gnas
1.6
G βγ
Adcy6
-1.3
Activation Via CRH and cAMP
Guanylyl Cyclase
cGMP
Pde4b
Pde4d
cAMP
Itpr1
-1.5
SR
Calcium Mobilization
PKC
Atp2a2
-1.5
Atp2a3
-1.3
Ryr3
-1.5
Gsto1
3.7
Calm2
1.2
Calm3
1.2
Ca 2+
Cnn1
1.3
Camk2g
-1.4
Prkacb
-1.3
Myometrial Relaxation
NO
Nos1
Nos3
Transcriptional Regulators
Mylk2
Po-Mlck
Myla
-2.8
Myometrial Contraction
Gβγ
Gnb3
-1.3
Gnb5
-1.2
Gng11
2.0
Gng12
2.1
RGS proteins
Rgs1
1.5
Rgs2
-3.8
Rgs5
-1.5
G-Protein coupled receptor kinases
Grk5
1.6
cAMP transcriptional regulators
Atf2
-1.3
Atf4
1.2
Creb3
1.5
Crebl1
1.4
Pathways of Myometrial Relaxation
Pathways of Myometrial Contraction


PAR
Gβγ
Gα12
proHB-EGF
MPase
PLD
M2R
GIRK
Gβγ
Gαi/o
Src
EGFR
Shc
Grb2
SOS
Ras
βAR
Gβγ
Gαs
AC
GRK
cAMP
RGS
GRK
RGS
Tec/BTK
RhoGEF
NHE1
Gz-GAP
Rap1-GAP
Stat3
PKA
PDE
Epac
C3G
Ras-GAP1
Cdc42
ROCK
PhosK
Rap1
PYK2
Raf1
GlyPhos
B-Raf
LPAR
Gβγ
Gα13
MEK5
MEK
V1R
GRK
Gβγ
Gαq
Rho
Glycogen
ASK1
MEKK1
ERK5
Glucose
RGS
radixin
Actin
JNKK
AKT/PKB
PKC
L-Ca++ channel
WIP
Arp2/3
N-WASP
Profilin
IKK
MAPK1,2
PLCβ
Ca++
DAG
JNK
Bcl2
IkBα
PKD
integrin
PAX
FAK
IP3R
IP3
PIP2
PI3Kb
c-JUNMEF2
SRF
NFkB
CREB
Stat3
Stat3
CRAC
PI3,4P2
PDK

This schematic was prepared by R. Iyengar's laboratory to provide a sense of the complexity of heterotrimeric G protein signaling. Each canonical G protein pathway is represented in the diagram.

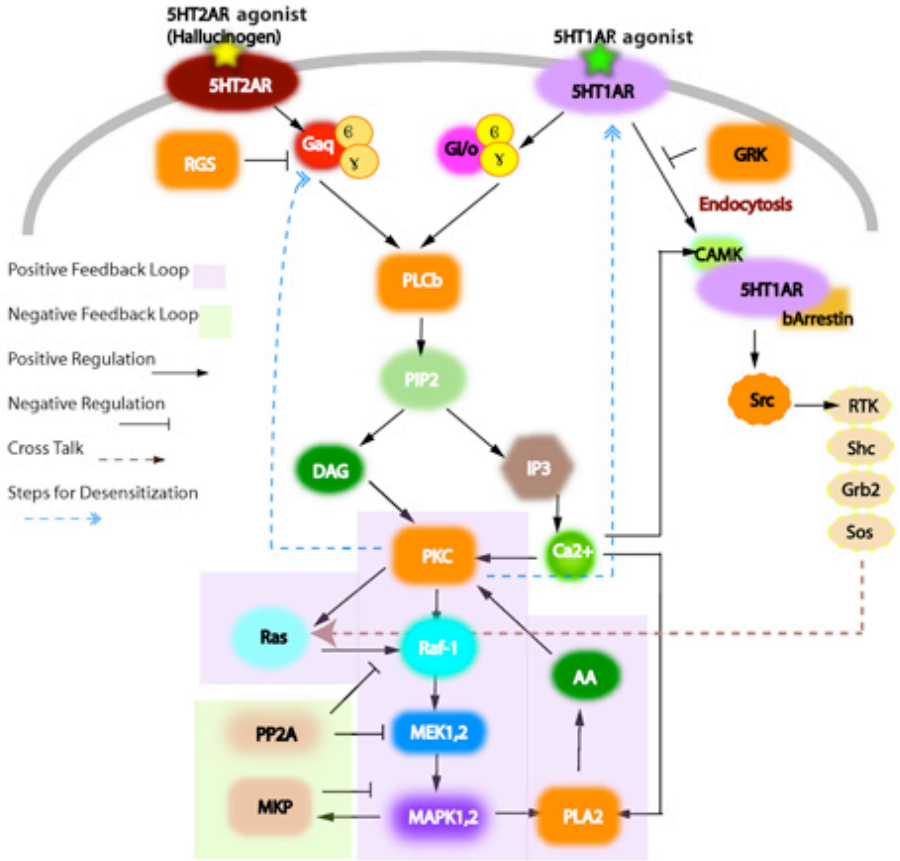

G-Alphal Signaling
GPCR Ligands
GPCR
AC
GDP
Gαi
Gβ
Gγ
Gβ
Gγ
SHC
GRB2
SOS
GTP
Gαi
RGS
G-Beta Gamma Signaling
cAMP
Caveolin1
c-Src
Ras
PKA
RhoGEFs
Rap1GAP
Rap1A
STAT3
c-Raf
PKA Signaling
Rho
B-Raf
ROK
MEK1/2
MLCP
ERK1/2
Actin Cytoskeleton Migration
Elk1
STAT3
Cell Proliferation
Gene Expression

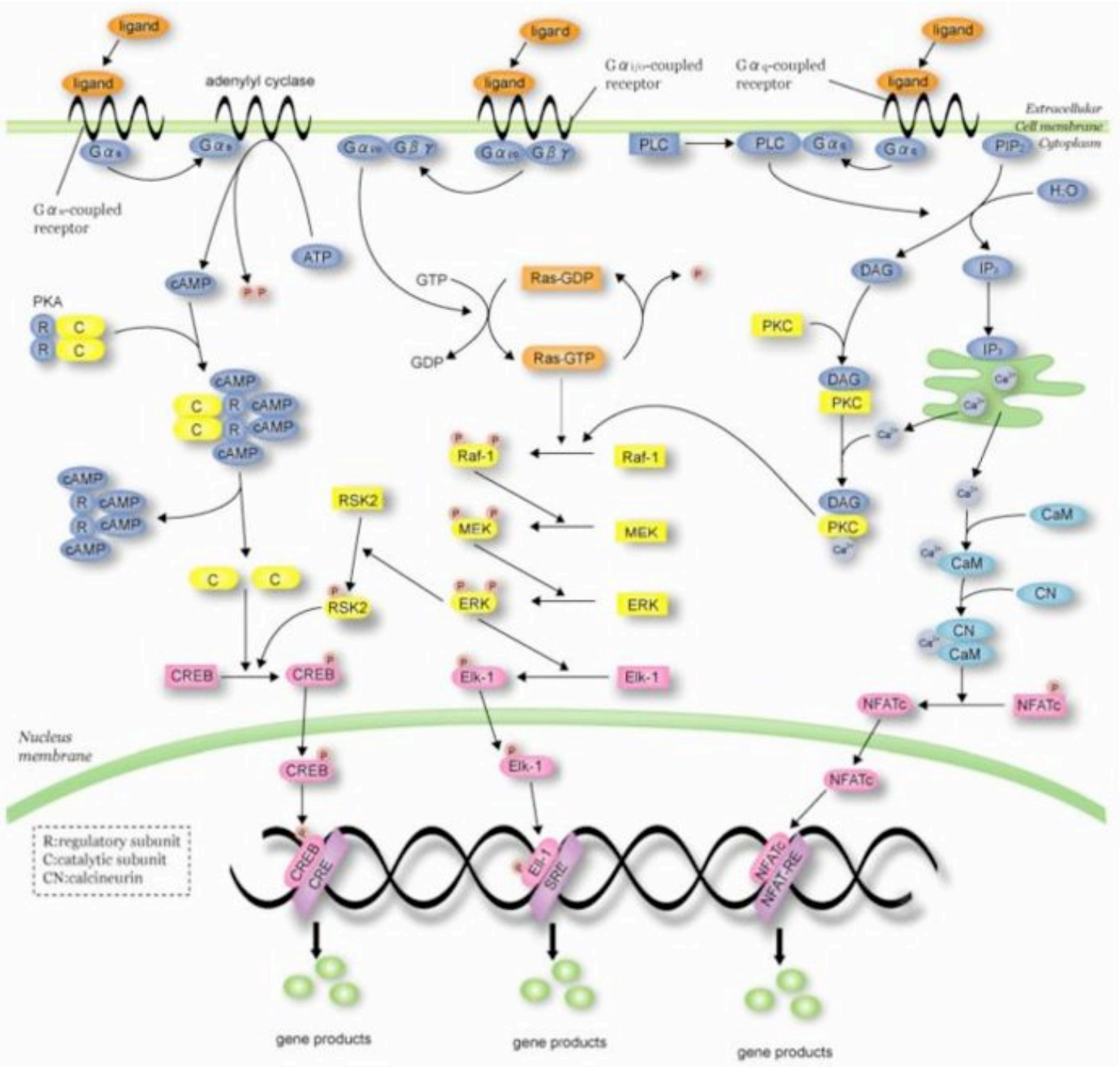

G-Beta Gamma Signaling
GPCR Ligands
GPCR
EGFR
Ca2+
CaCn
K+
GIRK
GRB2
SOS
SHC
PROHB-EGF
Gα
GTP
GDP
Gβ
Gγ
G-Alpha Signaling
ACII
ACI
PAK1
Btk
c-Src
Ras
PI3Kβ
PIX-α
Dynamin2
PLCγ
PLCβ
cAMP
PIP3
PIP2
CDC42
Raf
IP3
PKA
Caveolin
CDC42 Pathway
PDK1
DAG
MEK1/2
Endocytosis
Akt
IP3 Signaling
PKA Signaling
ERK1/2
Akt Signaling
PKC
Cell Proliferation
Cell Survival

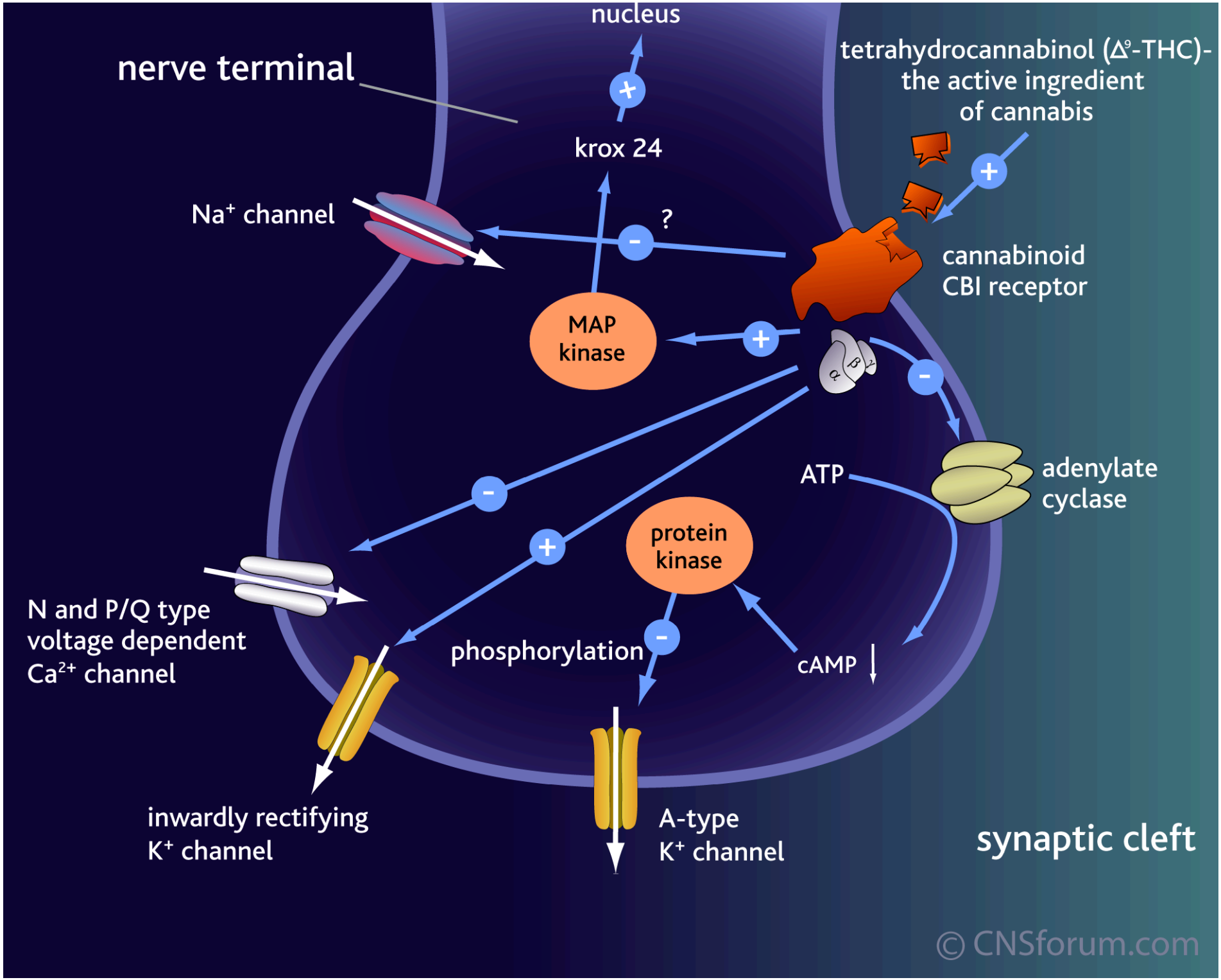


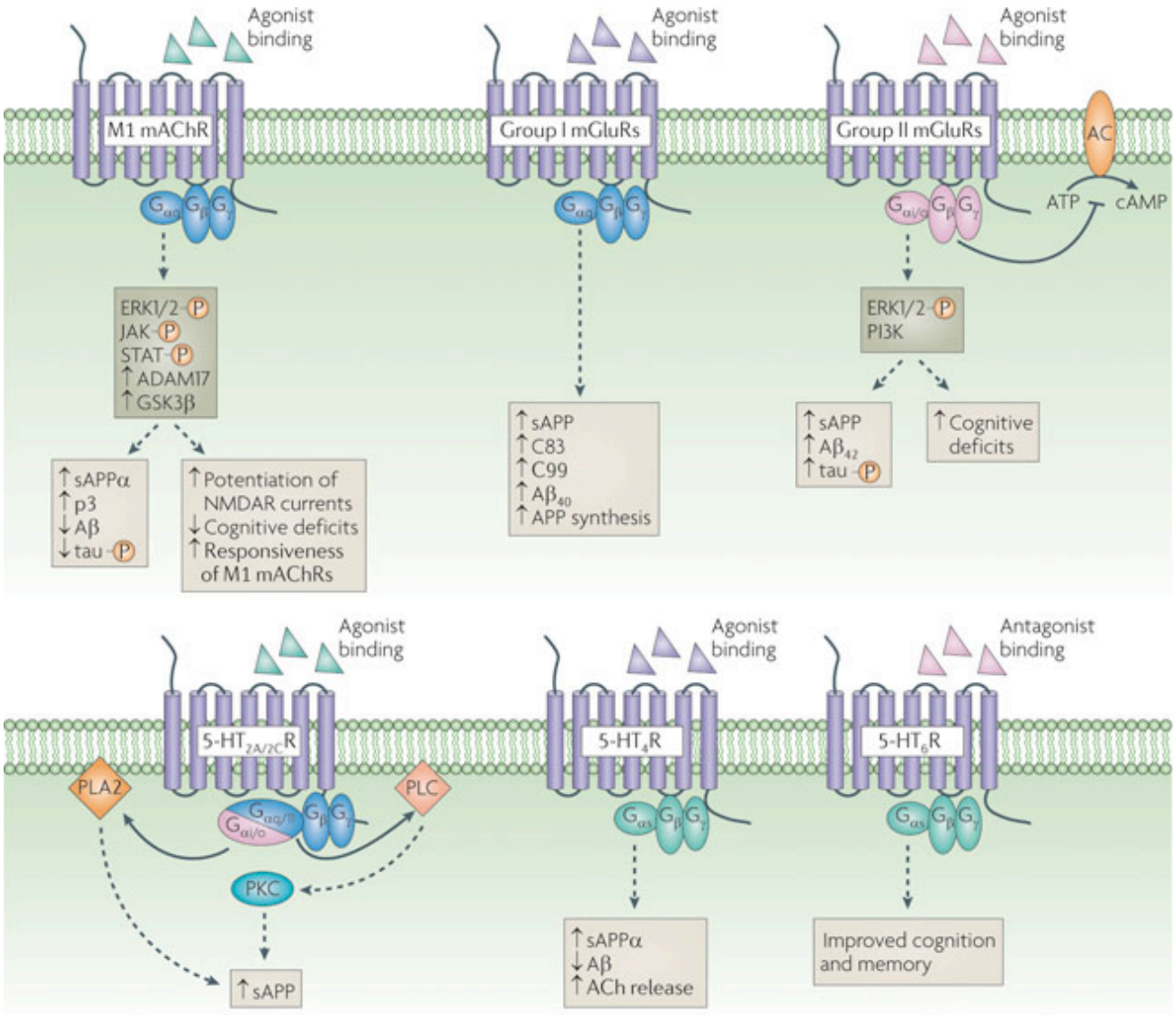
B

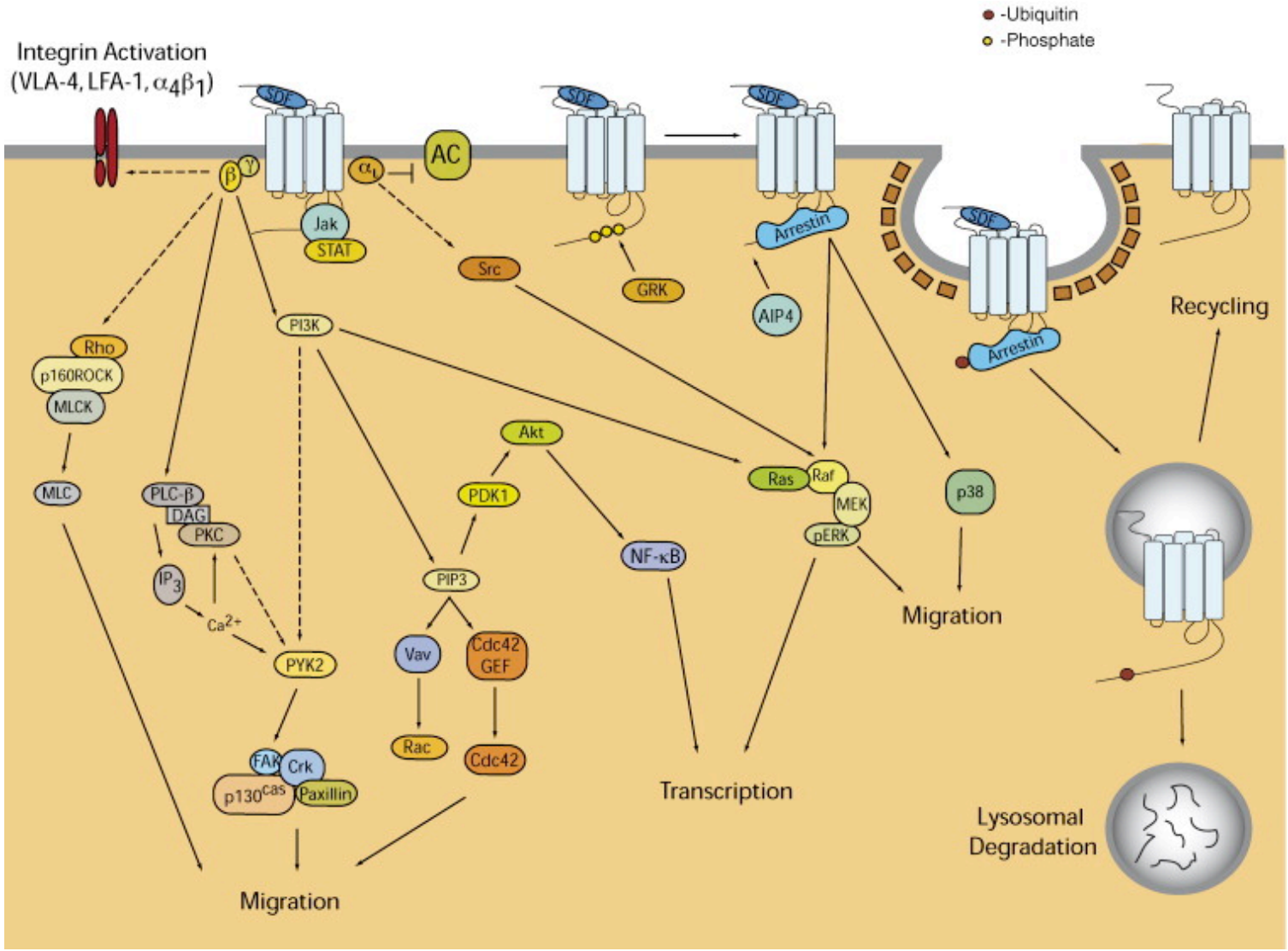
Flow Chart for MAPK 1,2 Activation in 5HT1AR and 5HT2AR Signaling Transduction

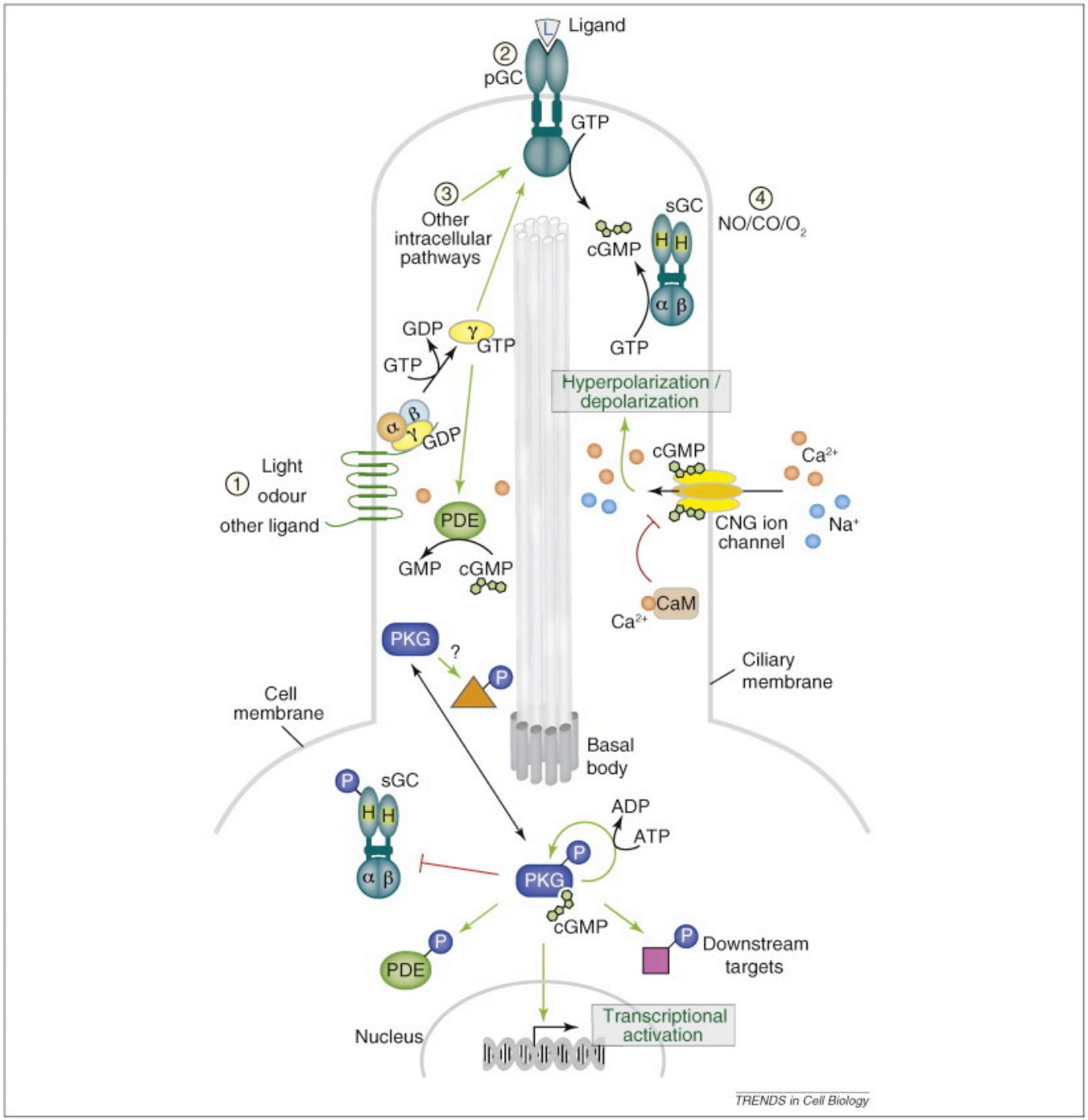


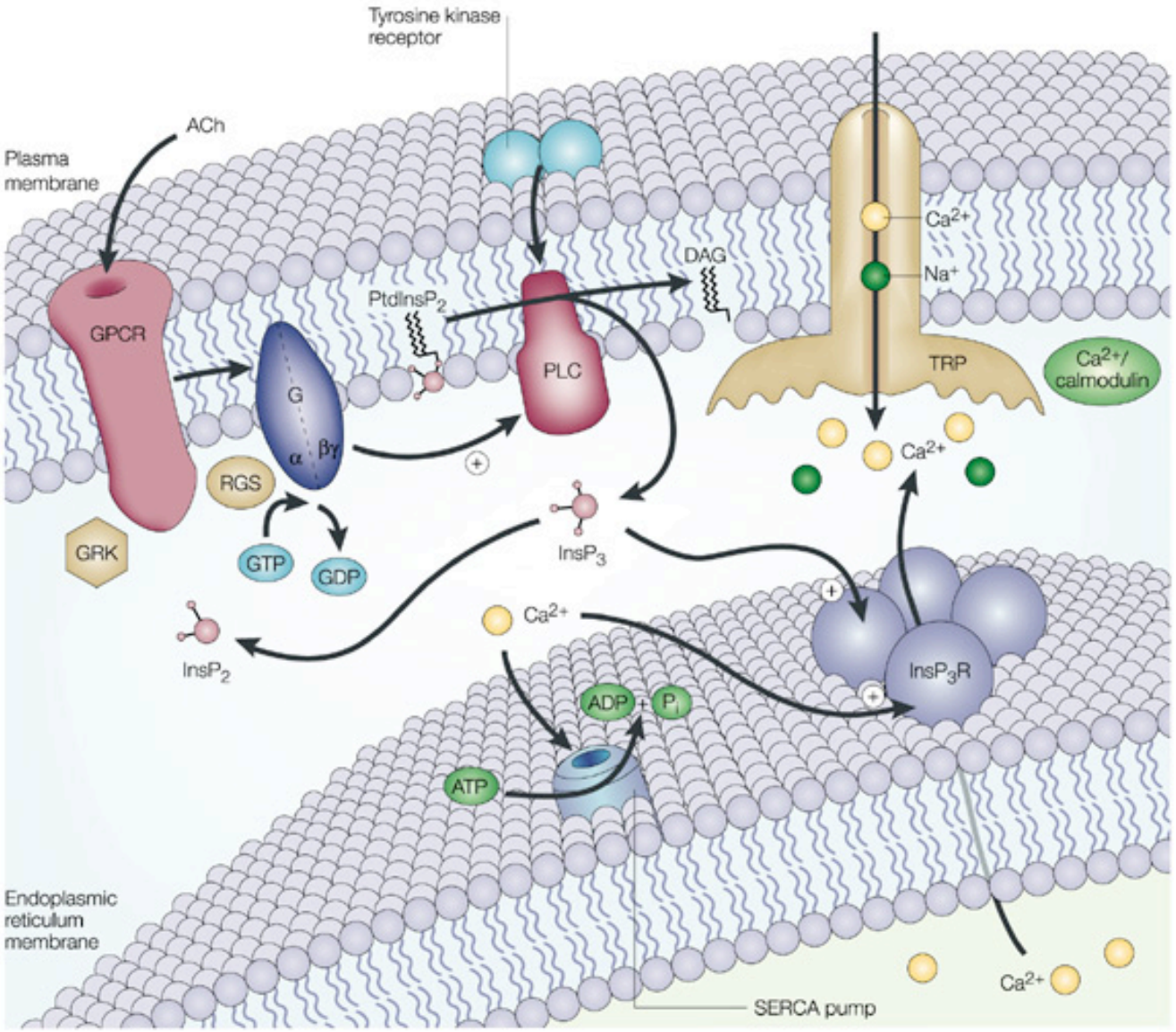

ligand
adenylyl cyclase
Gαs-coupled receptor
Gαi/o-coupled receptor
Gαq-coupled receptor
Extracellular
Cell membrane
Cytoplasm
Gαs
Gαi/o
Gβγ
Gαq
PLC
PIP2
H2O
ATP
cAMP
PKA
R
C
GTP
GDP
Ras-GDP
Ras-GTP
DAG
IP3
PKC
Ca2+
CaM
CN
Raf-1
MEK
ERK
RSK2
Elk-1
CREB
NFATc
Nucleus membrane
CRE
SRE
NFAT-RE
gene products
R:regulatory subunit
C:catalytic subunit
CN:calcineurin


nucleus
nerve terminal
tetrahydrocannabinol (Δ⁹-THC)-
the active ingredient
of cannabis
krox 24
Na⁺ channel
?
cannabinoid
CBI receptor
MAP
kinase
α
β
γ
ATP
adenylate
cyclase
protein
kinase
N and P/Q type
voltage dependent
Ca²⁺ channel
phosphorylation
cAMP
inwardly rectifying
K⁺ channel
A-type
K⁺ channel
synaptic cleft
© CNSforum.com

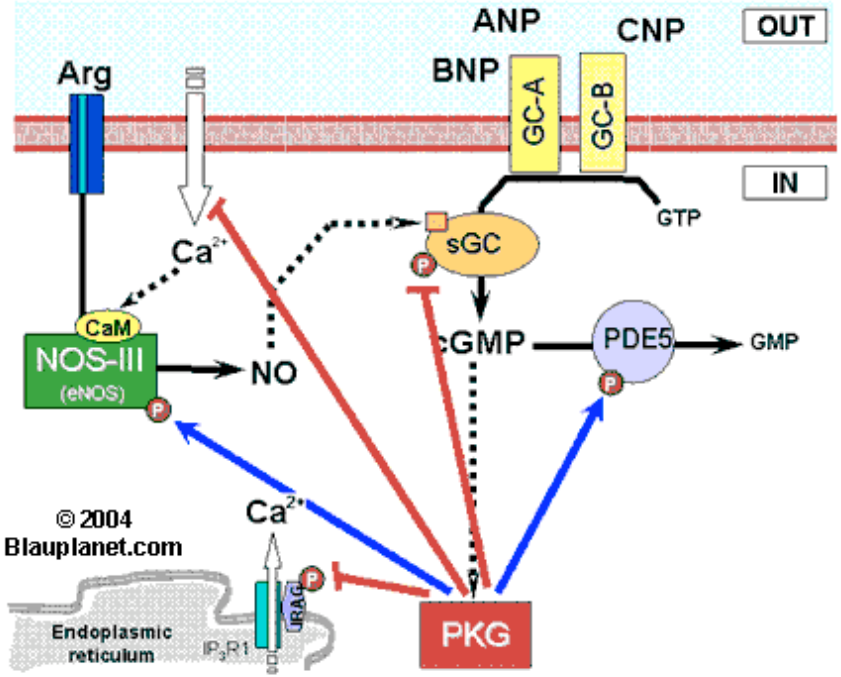

Agonist binding
M1 mAChR
ERK1/2 P
JAK P
STAT P
↑ADAM17
↑GSK3β
↑sAPPα
↑p3
↓Aβ
↓tau P
↑Potentiation of NMDAR currents
↓Cognitive deficits
↑Responsiveness of M1 mAChRs
Agonist binding
Group I mGluRs
↑sAPP
↑C83
↑C99
↑Aβ40
↑APP synthesis
Agonist binding
Group II mGluRs
AC
ATP
cAMP
ERK1/2 P
PI3K
↑sAPP
↑Aβ42
↑tau P
↑Cognitive deficits
Agonist binding
5-HT2A/2CR
PLA2
PLC
PKC
↑sAPP
Agonist binding
5-HT4R
↑sAPPα
↓Aβ
↑ACh release
Antagonist binding
5-HT6R
Improved cognition and memory


-Ubiquitin
-Phosphate
Integrin Activation
(VLA-4, LFA-1, $\alpha_4\beta_1$)
SDF
AC
α_i
β
γ
Jak
STAT
Src
GRK
Arrestin
AIP4
Recycling
Rho
p160ROCK
MLCK
MLC
PI3K
PLC-β
DAG
PKC
IP_3
Ca^{2+}
PYK2
FAK
Crk
$p130^{cas}$
Paxillin
Migration
Akt
PDK1
PIP3
Vav
Cdc42 GEF
Rac
Cdc42
NF-κB
Transcription
Ras
Raf
MEK
pERK
p38
Migration
Lysosomal Degradation

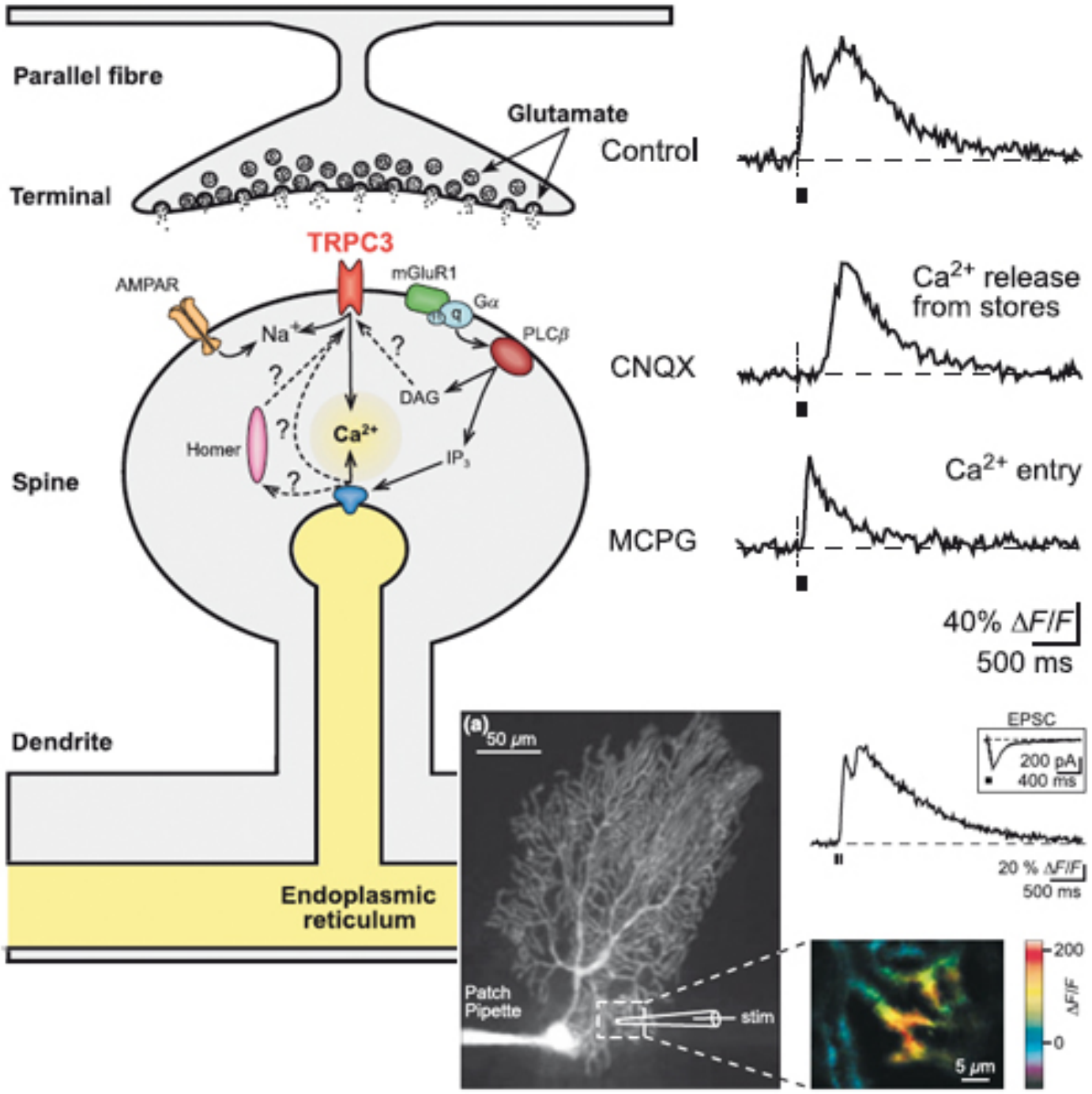

Ligand
② pGC
GTP
③ Other intracellular pathways
sGC
④ NO/CO/O2
cGMP
GTP
GDP
GTP
GTP
Hyperpolarization / depolarization
① Light odour other ligand
PDE
GMP
cGMP
cGMP
Ca2+
CNG ion channel
Na+
CaM
Ca2+
PKG
?
P
Cell membrane
Ciliary membrane
Basal body
sGC
ADP
ATP
PKG
cGMP
PDE
Downstream targets
Nucleus
Transcriptional activation
TRENDS in Cell Biology


Tyrosine kinase receptor
ACh
Plasma membrane
GPCR
G
α
βγ
PtdInsP2
PLC
DAG
Ca2+
Na+
TRP
Ca2+/ calmodulin
Ca2+
RGS
GRK
GTP
GDP
InsP3
InsP2
Ca2+
InsP3R
ADP
Pi
ATP
Endoplasmic reticulum membrane
SERCA pump
Ca2+

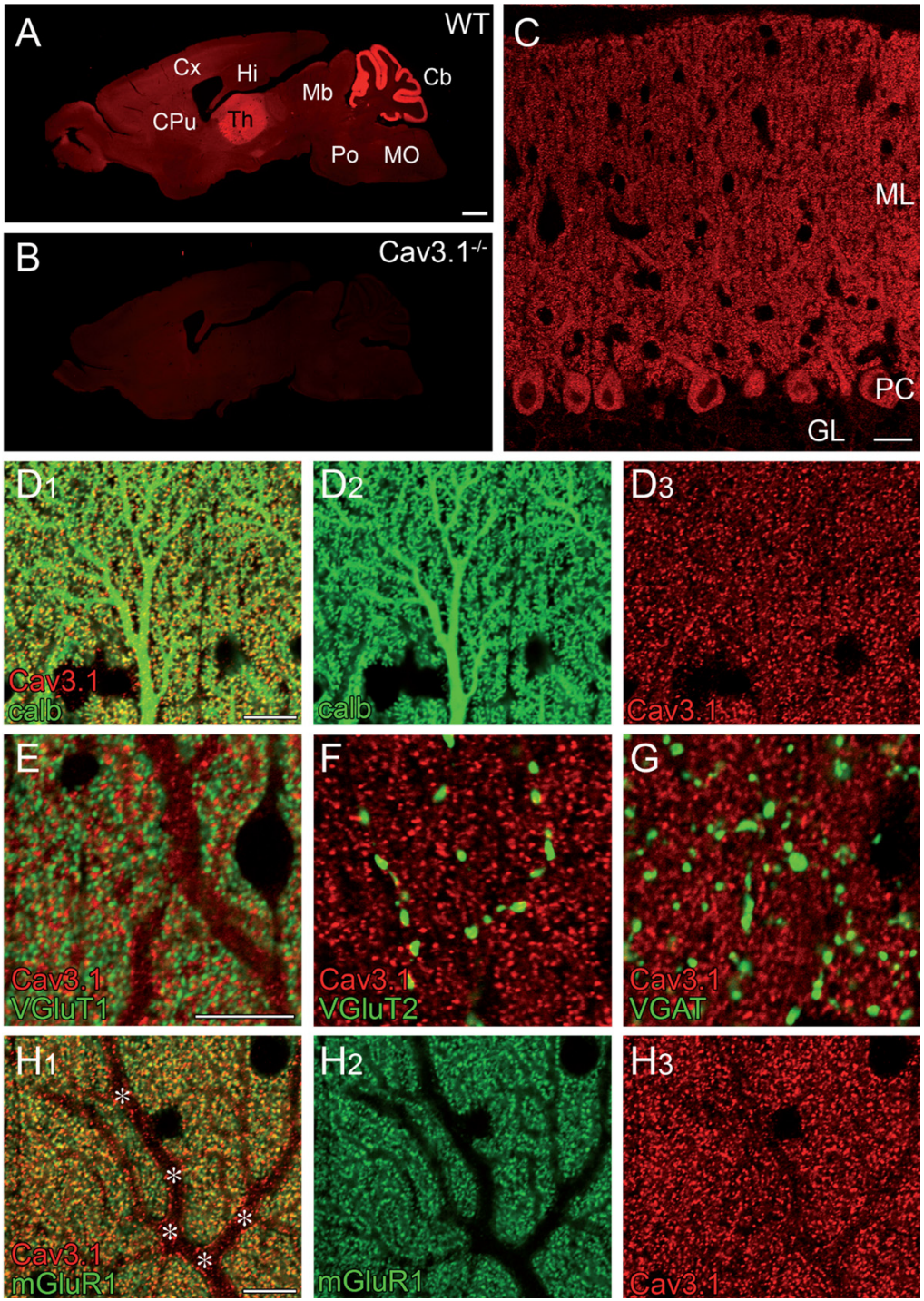
- The G_{α} subunit will eventually hydrolyze the attached GTP to GDP by its inherent enzymatic activity, allowing it to re-associate with $G_{\beta\gamma}$ and starting a new cycle. A group of proteins calledRegulator of G protein signalling (RGSs), act as GTPase-activating proteins (GAPs), specific for G_{α} subunits. These proteins act to accelerate hydrolysis of GTP to GDP and terminate the transduced signal. In some cases, the effector itself may possess intrinsic GAP activity, which helps deactivate the pathway. This is true in the case of phospholipase C beta, which possesses GAP activity within its C-terminal region. This is an alternate form of regulation for the G_{α} subunit.



- ***<u>Fig. 1. Hypothetical center role of protein kinase G in pathway regulation.</u> Blue linesrepresent stimulation of target activity (not an increase in target phosphorylation). Red linesrepresent decrease of target activity.***
- ***Abbreviations:***
  ANP, atrial natriuretic peptide; Arg, L-arginine; BNP, brain natriuretic peptide; CaM, calmodulin;cGMP, cyclic GMP; CNP, natriuretic peptide C; GC-A (GC-B), particulate guanylyl cyclase type A (or type B), the guanylyl cyclase stimulated by natriuretic petides (ANP and BNP bind to GC-A, while CNP binds to GC-B); Gi, protein Gi; IRAG, Inositol-3-phosphate receptor associated cyclic GMP kinase substrate; NOS, nitric oxide synthase (I, neuronal NOS or nNOS; II, inducible NOS or iNOS; III, eNOS or endothelial NOS);P, represent a phosphorylated aminoacid that results from cyclic GMP-dependent protein kinase activity; PDE5, cyclic nucleotide phosphodiesterase type 5 (it degrades cGMP; this isoenzyme is considered specific for cGMP, however other types of PDE are also able to degrade cGMP); PKG, cyclic GMP-dependent protein kinase; sGC, soluble guanylyl cyclase (guanylyl cyclase stimulated by NO and CO).


Parallel fibre
Glutamate
Terminal
TRPC3
AMPAR
mGluR1
Gα
q
PLCβ
Na+
?
DAG
Homer
Ca2+
IP3
Spine
Dendrite
Endoplasmic reticulum
Control
Ca2+ release from stores
CNQX
Ca2+ entry
MCPG
40% ΔF/F
500 ms
(a)
50 μm
Patch Pipette
stim
EPSC
200 pA
400 ms
20 % ΔF/F
500 ms
5 μm
200
ΔF/F
0

- Acta Physiol (Oxf). 2008 Oct 28. [Epub ahead of print]
- **Mechanisms of metabotropic glutamate receptor-mediated synaptic signaling in cerebellar Purkinje cells.**
- Hartmann J, Konnerth A.
- **Source**
- Institute of Neuroscience and Center for Integrated Protein Science, Technical University Munich, Germany.
- **Abstract**
- The metabotropic glutamate receptors type 1 (mGluR1s) are required for a normal function of the mammalian cerebellum. These G-protein coupled receptors are abundantly expressed in the principle cerebellar cells, namely the Purkinje neurons. Under physiological conditions, mGluR1s are activated during repetitive activity of both afferent glutamatergic synaptic inputs provided by the climbing and parallel fibers, respectively. Unlike the common ionotropic glutamate receptors that underlie rapid synaptic excitation, mGluR1s produce a complex postsynaptic response consisting of a Ca(2+) release signal from intracellular stores and a slow excitatory postsynaptic potential. While it is well established that the mGluR1-dependent Ca(2+) release signal from intracellular stores involves the activation of inositol-trisphosphate (IP(3)) receptors, the mechanisms underlying the slow synaptic excitation remained unclear. Here we will review recent evidence indicating an essential role of C type transient receptor potential (TRPC) cation channels, especially that of the subunit TRPC3, for the generation of the mGluR1-dependent synaptic current. For the signaling pathways underlying both, Ca(2+) release from intracellular stores and the slow synaptic potential, we present current knowledge about the activators, downstream effectors and possible roles for mGluR1-dependent signaling in Purkinje neurons.



Cav3.1 slow type are thought to set pacemaker rhythm. Parallel fiber stimulation activates mGluR1-potentiated T-type Ca++ transients

Functional Coupling between mGluR1 and Cav3.1 T-Type Calcium Channels Contributes to Parallel Fiber-Induced Fast Calcium Signaling within Purkinje Cell Dendritic Spines

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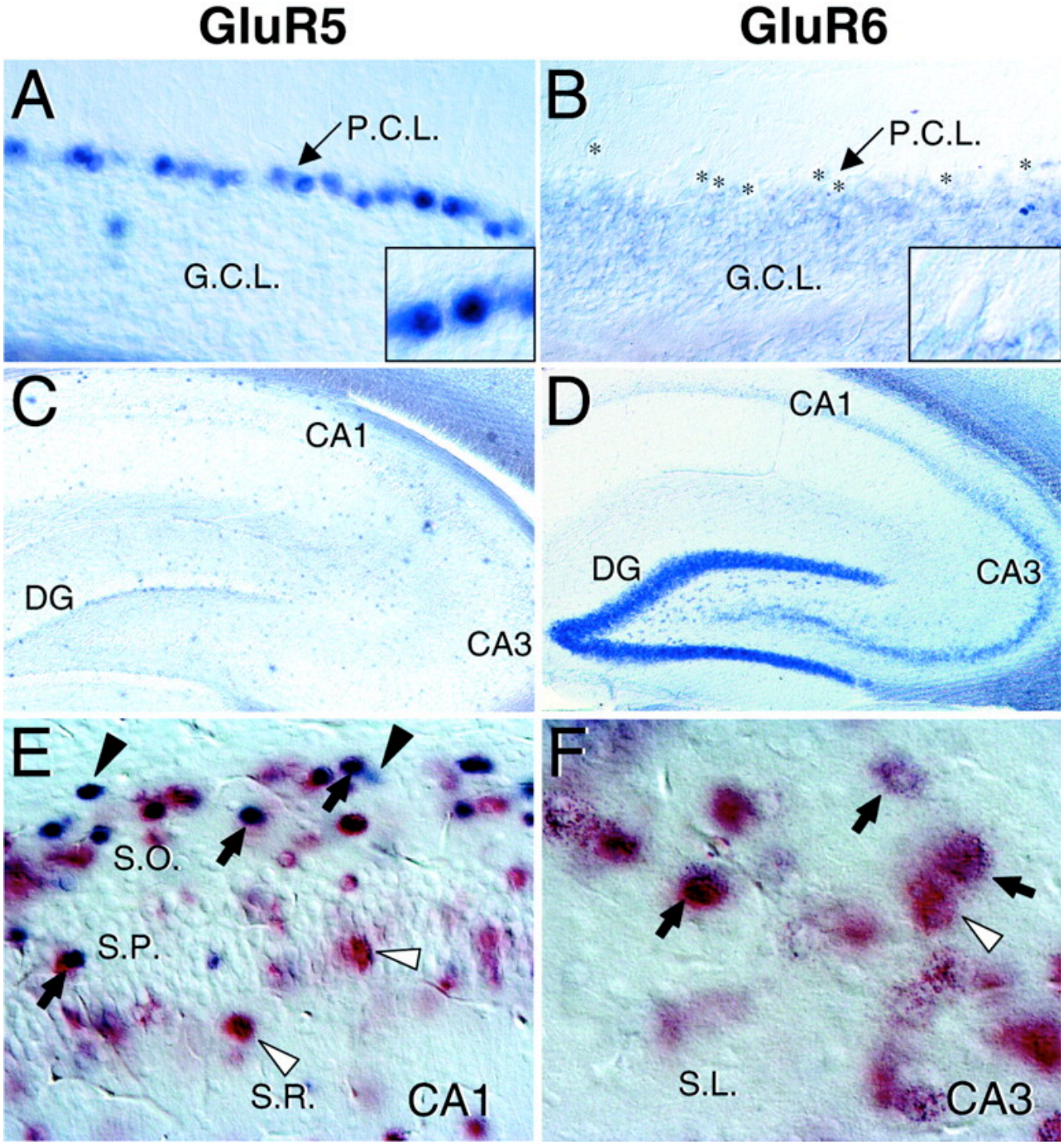
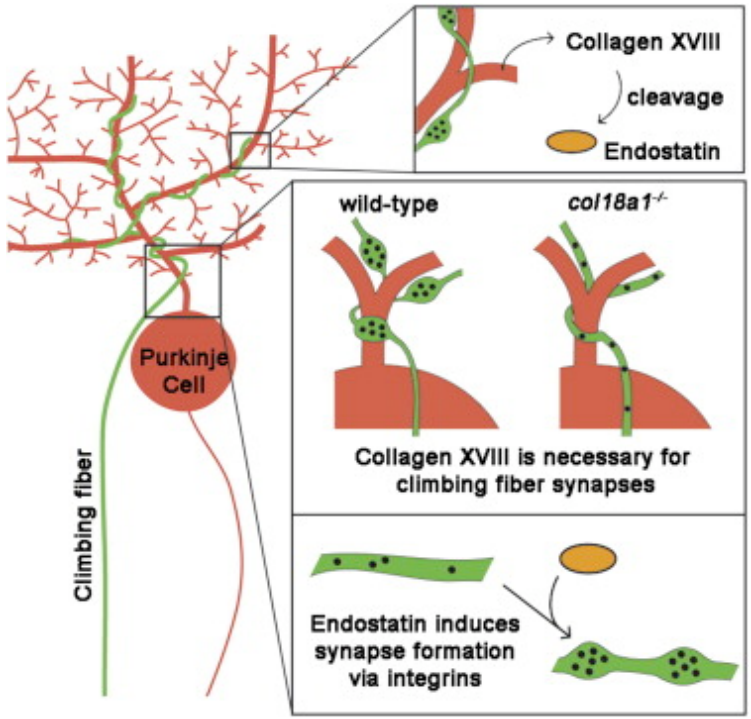
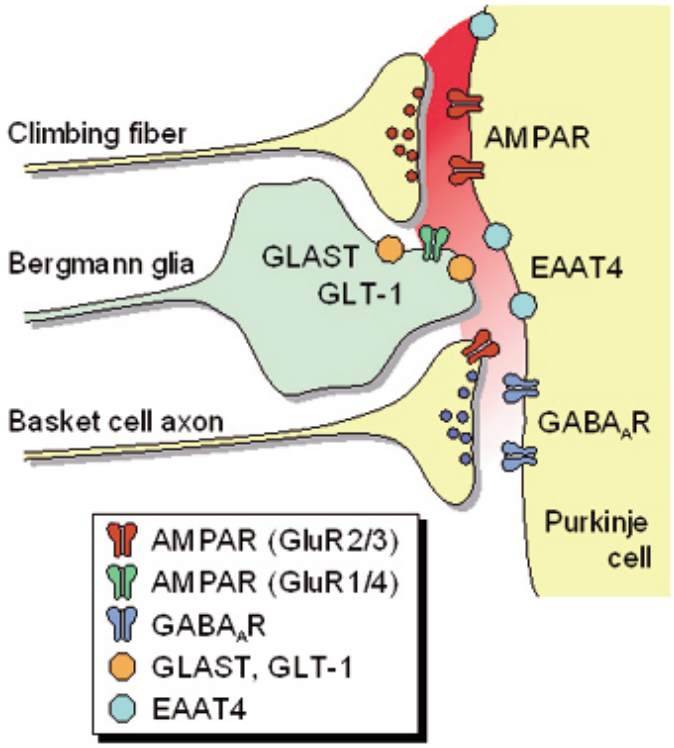

GluR5
GluR6
A
P.C.L.
G.C.L.
B
P.C.L.
G.C.L.
C
CA1
DG
CA3
D
CA1
DG
CA3
E
S.O.
S.P.
S.R.
CA1
F
S.L.
CA3

- **Fig. 3.**Expression pattern of GluR5 and GluR6 mRNA. In the cerebellum (*A*), GluR5 is expressed in the Purkinje cell layer (P.C.L.) and in Golgi cells of the granule cell layer (G.C.L.), whereas GluR6 is abundantly expressed by the granule cells (*B*). The asterisks indicate unlabeled Purkinje cell bodies. *Insets* show a magnification of the Purkinje cell layer. In the hippocampus, GluR5 is mainly expressed by interneurons (*C*), and GluR6 is predominantly expressed in the principal cells (*D*). Double in situ hybridization with glutamic acid decarboxylase (GAD) and either GluR5 (*E*) or GluR6 (*F*) probes is shown. The expression of GAD is labeled red (white arrowheads). The expression of GluR5 or GluR6 is labeled blue (black arrowheads). Coexpression appears as a brown precipitate (black arrows). *E* and *F*correspond to a close view of the CA1 and CA3 regions, respectively. S.O., stratum oriens; S.P., stratum pyramidale; S.R., stratum radiatum; S.L., stratum lucidum. [*C*–*F* from Paternain et al. (122).]

- Most abundant at synapse with climbing fiber.


Collagen XVIII
cleavage
Endostatin
wild-type
col18a1-/-
Purkinje Cell
Climbing fiber
Collagen XVIII is necessary for climbing fiber synapses
Endostatin induces synapse formation via integrins

Array analyses of Ccl32/2; Npc12/2 mice compared with agematched and background-matched Npc12/2 cerebella showed slight decreases in expression of cerebellar Purkinje neuronspecific genes: Calb1/D28K, Pcp2, Stk17b/Drak2, Fgf7 and Gpr63 (Fig. 3A). Decreased expression of these genes is likely due to reduced numbers of surviving Purkinje neurons (48). Stk17b, for example, is produced only in Purkinje neurons of the cerebellum and serves as useful indicator of cell number (Fig. 3C). The expression of Tyrosine hydroxylase (Th) can also be used to assess the condition of Purkinje neurons in the cerebellum in NPC disease since Th is ectopically expressed in cerebellar Purkinje neurons as a consequence of the disease (49). Th levels on average were higher in Ccl32/2; Npc12/2 cerebella than in Npc12/2 mice (Fig. 3A and J). Based in part on the reduction, though slight, of Purkinje neuron-specific genes and mainly on the increase in Th, we conclude that the loss of Ccl3 is deleterious to neurons in Npc12/2 mice.


Climbing fiber
AMPAR
Bergmann glia
GLAST
GLT-1
EAAT4
Basket cell axon
GABA$_A$R
Purkinje cell
AMPAR (GluR2/3)
AMPAR (GluR1/4)
GABA$_A$R
GLAST, GLT-1
EAAT4

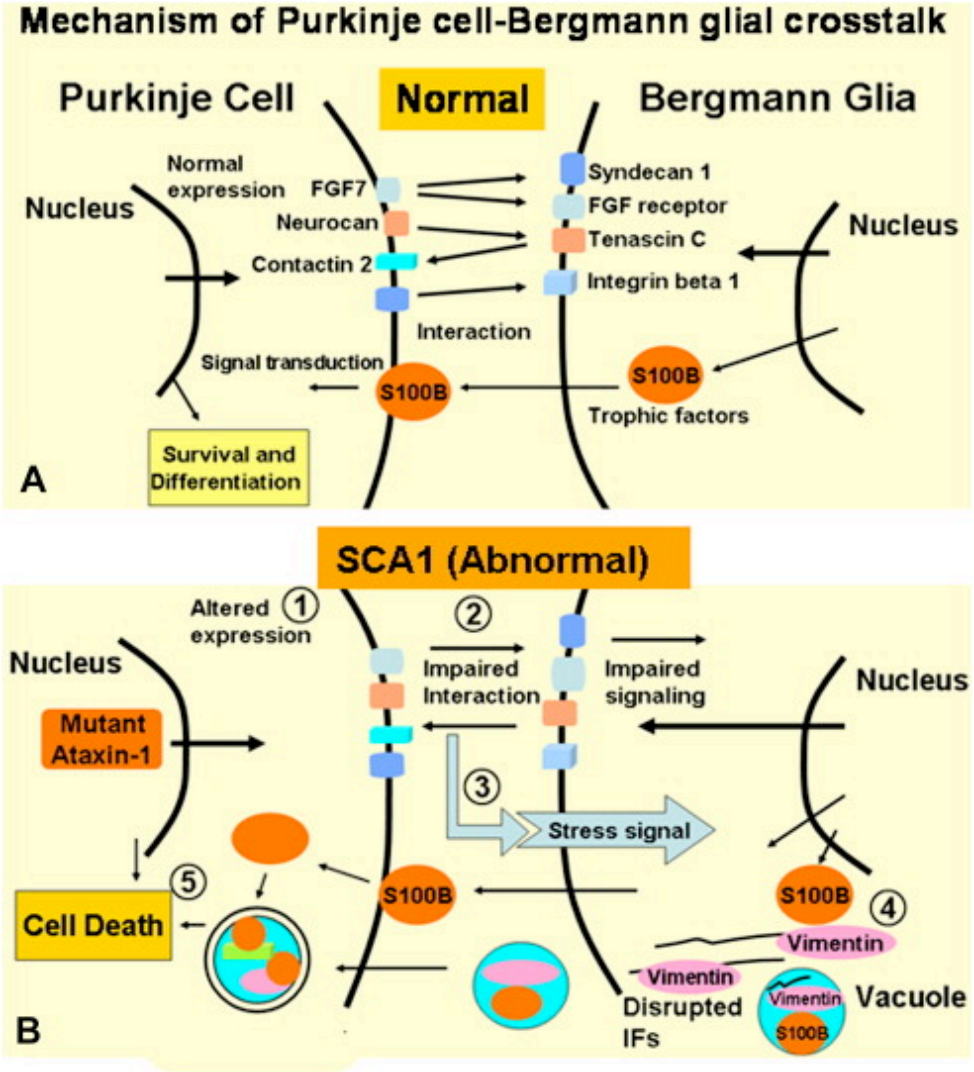
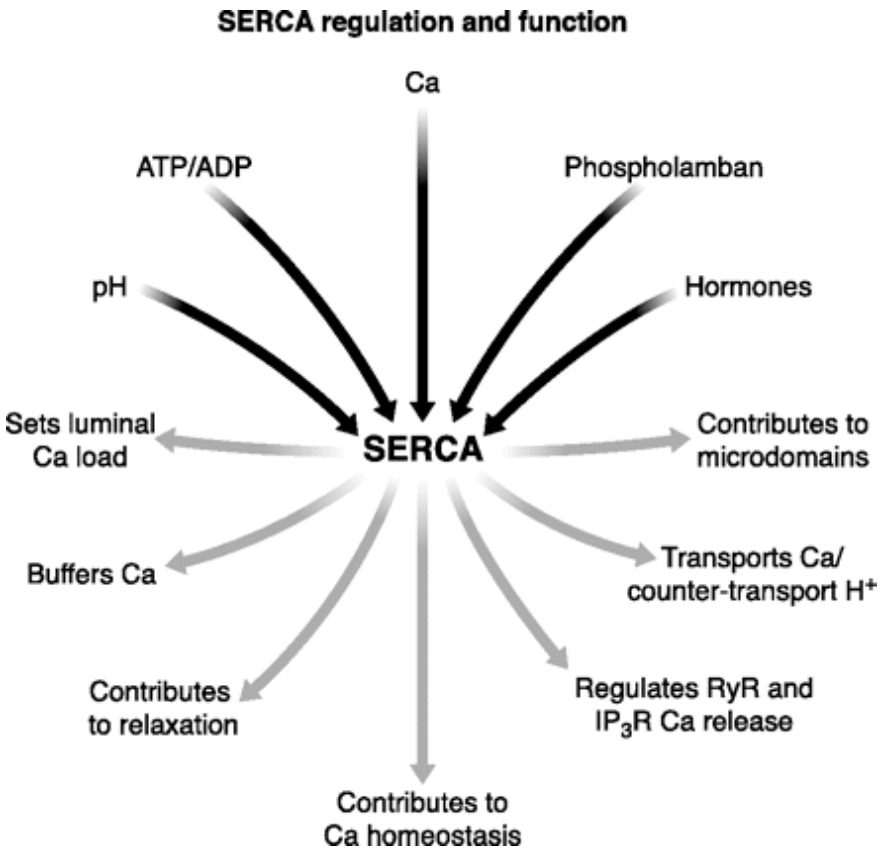


Figure 1. (A) Schematic diagram showing hypothetical mechanism of normal and impaired Purkinje cell (PC)–Bergmann glia (BG) crosstalk. In SCA1 (B), impaired PC–BG interaction results in cytoplasmic vacuole formation in PCs (steps 1–5). Mutant ataxin-1 (transcriptional repressor) early in development causes alterations in the expression of signaling and cell adhesion molecules like FGF7, neurocan and contactin 2. The neighboring BG respond by similar modulations, which produce a stress signal and glia react by releasing high levels of S100B protein. At higher concentrations, S100B either disrupts IFs or causes vimentin to aggregate, and to form vacuoles in PCs. This model was developed based on the preliminary results and gene expression data of 2 week old wildtype and SCA1 mice. FGF7, fibroblast growth factor 7; IF, intermediate filaments.


SERCA regulation and function
Ca
ATP/ADP
Phospholamban
pH
Hormones
Sets luminal
Ca load
SERCA
Contributes to
microdomains
Buffers Ca
Transports Ca/
counter-transport H+
Contributes
to relaxation
Regulates RyR and
IP3R Ca release
Contributes to
Ca homeostasis