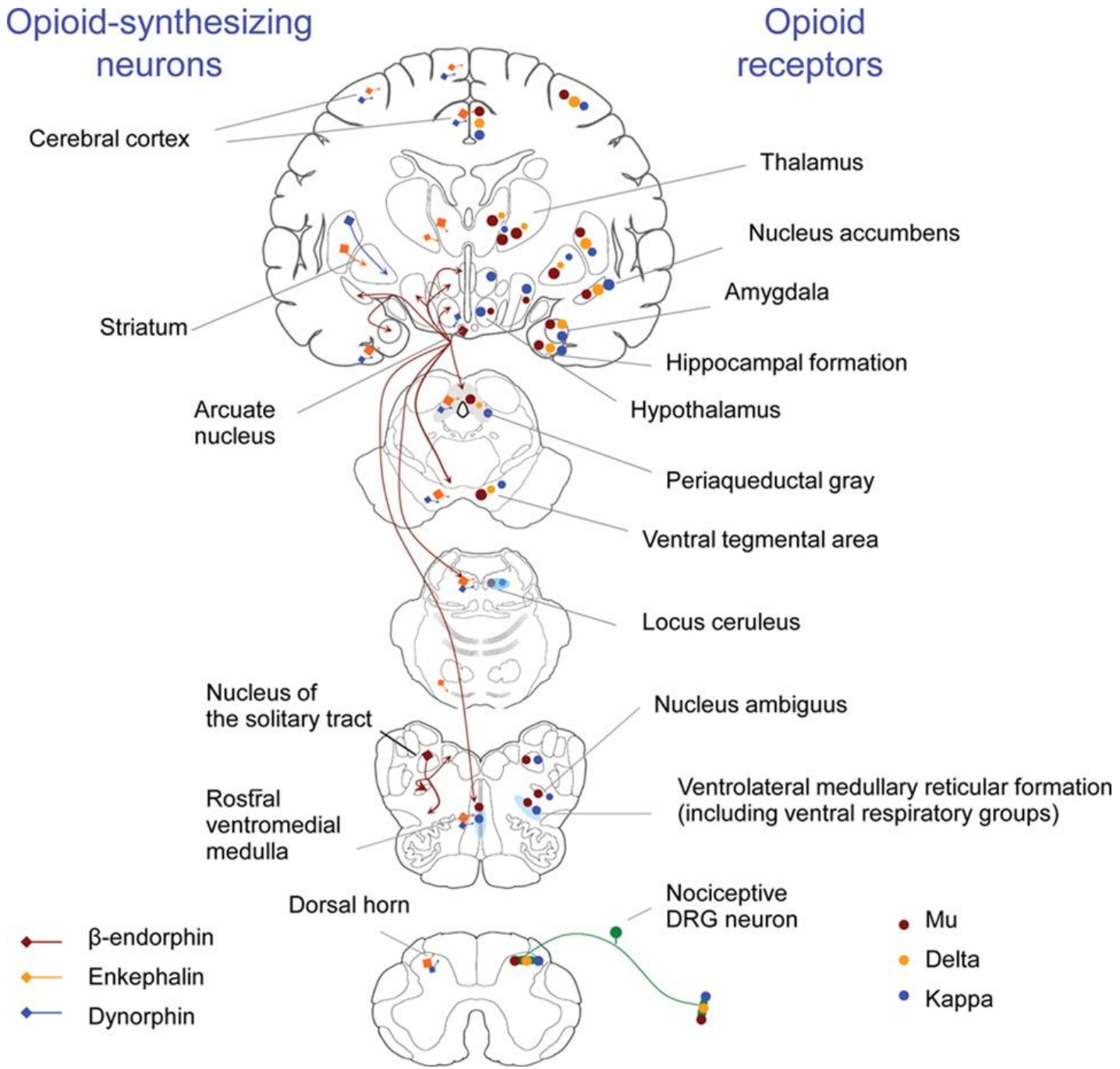
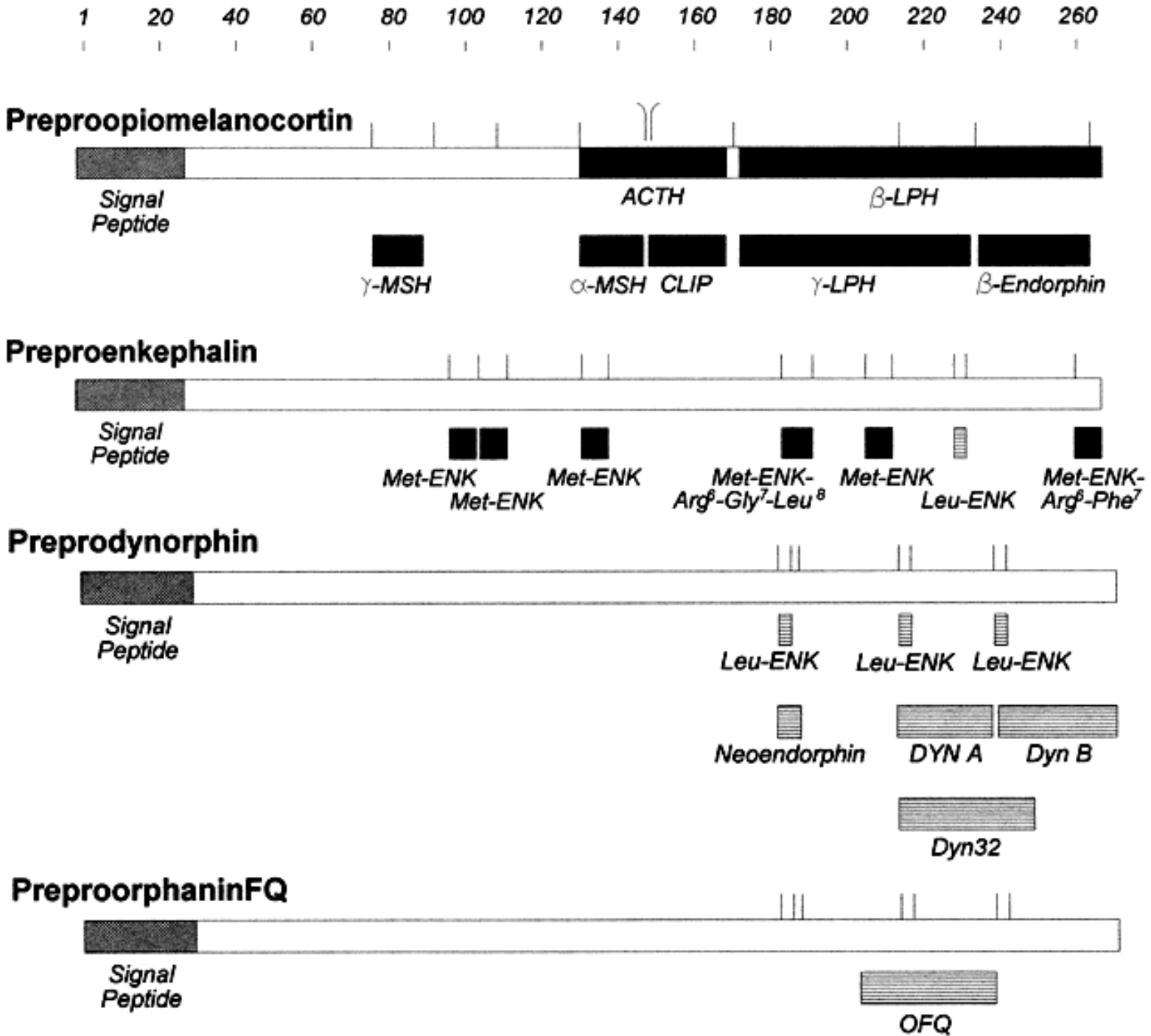
Endogenous opioid system


Opioid-synthesizing neurons
Opioid receptors
Cerebral cortex
Thalamus
Nucleus accumbens
Striatum
Amygdala
Hippocampal formation
Arcuate nucleus
Hypothalamus
Periaqueductal gray
Ventral tegmental area
Locus ceruleus
Nucleus of the solitary tract
Nucleus ambiguus
Rostral ventromedial medulla
Ventrolateral medullary reticular formation (including ventral respiratory groups)
Dorsal horn
Nociceptive DRG neuron
β-endorphin
Enkephalin
Dynorphin
Mu
Delta
Kappa

Opioid motif

Tyr-Gly-Gly-Phe-(Met/Leu)



- DOR – δ opioid receptor

- KOR – κ opioid receptor

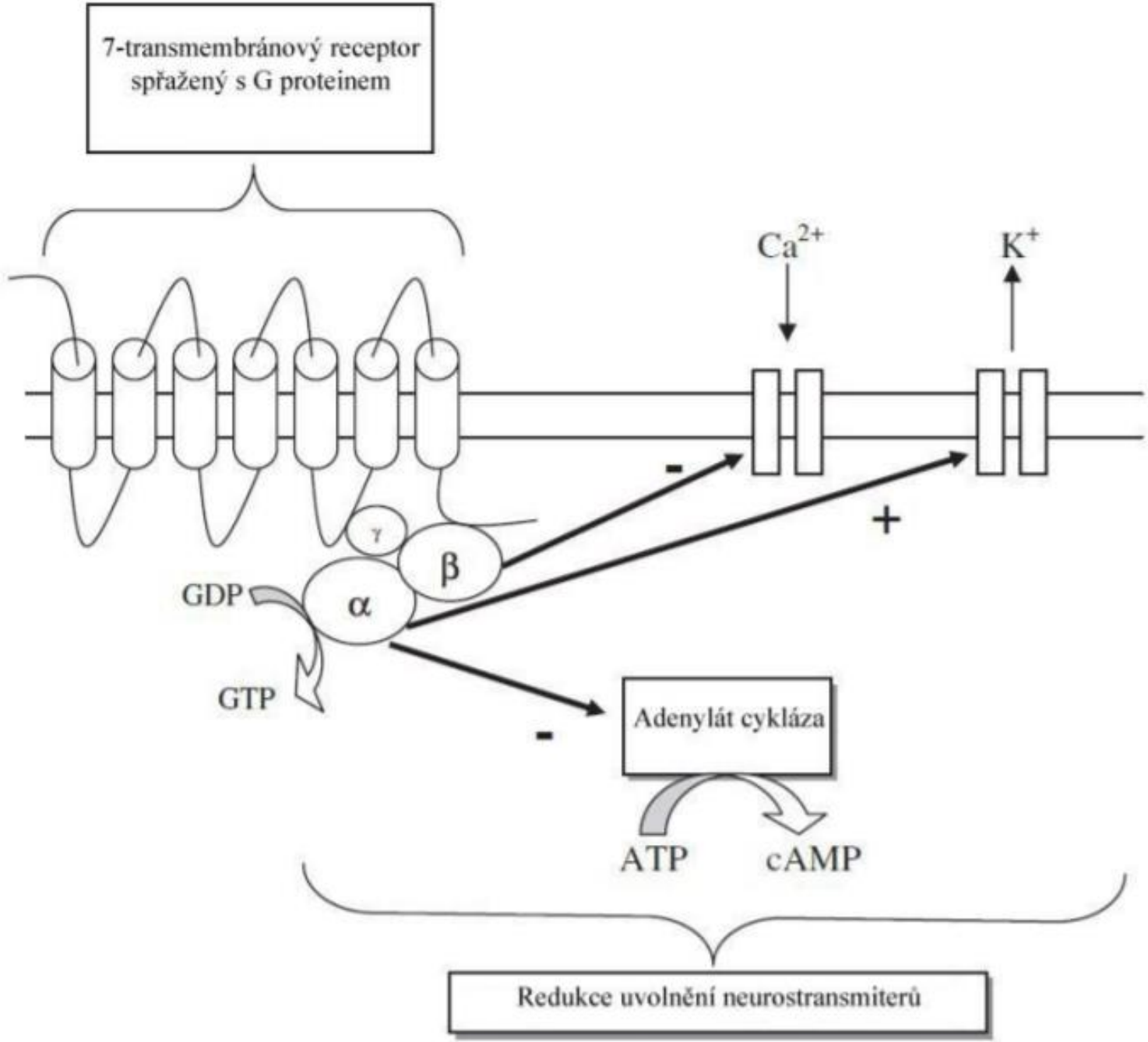
-MOR – μ opioid receptor

-NOR – N/OFQ opioid receptor

Table 1: Opioid receptors location and responses mediated by them

Receptor	CNS Location	Response on activation
μ	Brain (laminae III and IV of the cortex, thalamus, periqueductal gray), spinal cord (substantia gelatinosa)	μ_1-supraspinal analgesia, physical dependence; μ_2-Respiratory depression, miosis, euphoria, reduced gastrointestinal motility, physical dependence
κ	Brain (hypothalamus, peri-aqueductal gray, claustrum), spinal cord (substantia gelatinosa)	Spinal analgesia, sedation, miosis, inhibition of antidiuretic hormone release
δ	Brain (pontine nucleus, amygdala, olfactory bulbs, deep cortex)	Analgesia, euphoria, physical dependence

CNS-Central nervous system


7-transmembránový receptor spřažený s G proteinem
Ca2+
K+
-
+
γ
β
α
GDP
GTP
-
Adenylát cykláza
ATP
cAMP
Redukce uvolnění neurostransmiterů

Endorfins

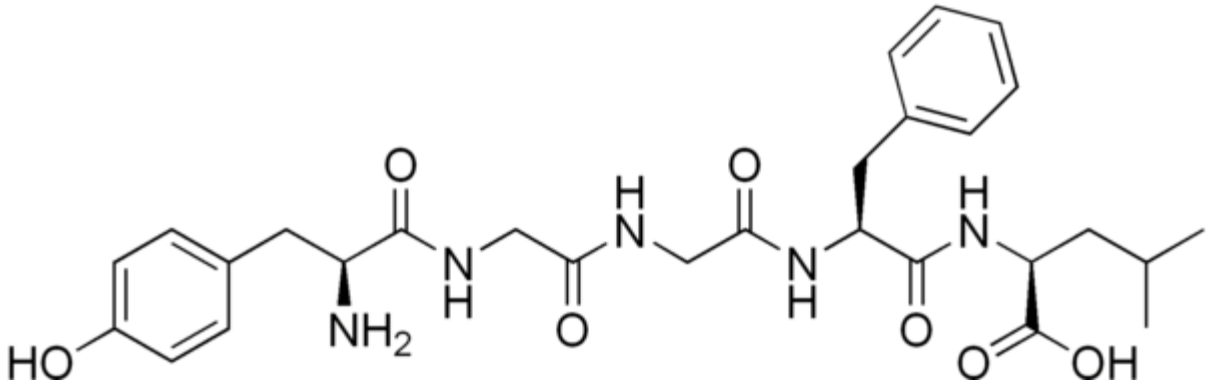
μ / δ

- Alpha, beta, gamma and delta
- hypophysis / hypothalamus and elsewhere
- Strenuous exercise / physical activity, pain, orgasm
- Analgesia and feelings of "well-being„
- Immune system mobilization?
- Creating emotional connections
- Food intake
- The same effect for pain but different for stress

Enkephalins

μ / δ

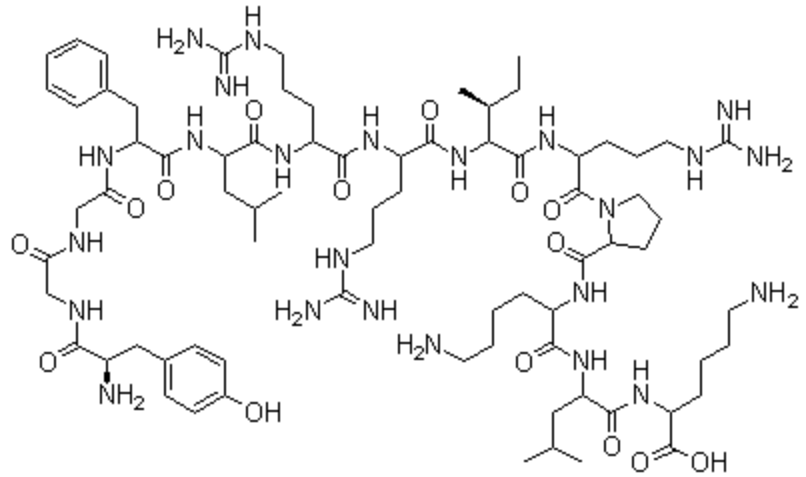
- Met-/Leu-
- CNS sites associated with pain perception, behavior, motor control, and neuroendocrine function
- T cells, macrophages, mast cells
- Excitement, physical activity, sexual activity, fear



Dynorphins

μ / κ

- A and B
- Periaqueductal gray matter, medulla oblongata
- Parts of the spinal cord involved in pain transmission
- Hypothalamus, hippocampus, mesencephalon
- Mechanical and thermal hyperalgesia

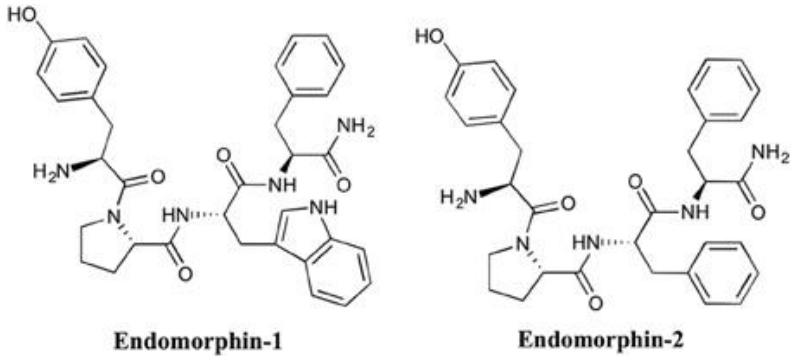


H-Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys-OH

Endomorphins

μ

- 1 and 2
- Heterogeneous distribution in the CNS
- Antinociceptive function
- NO-mediated vasodilation



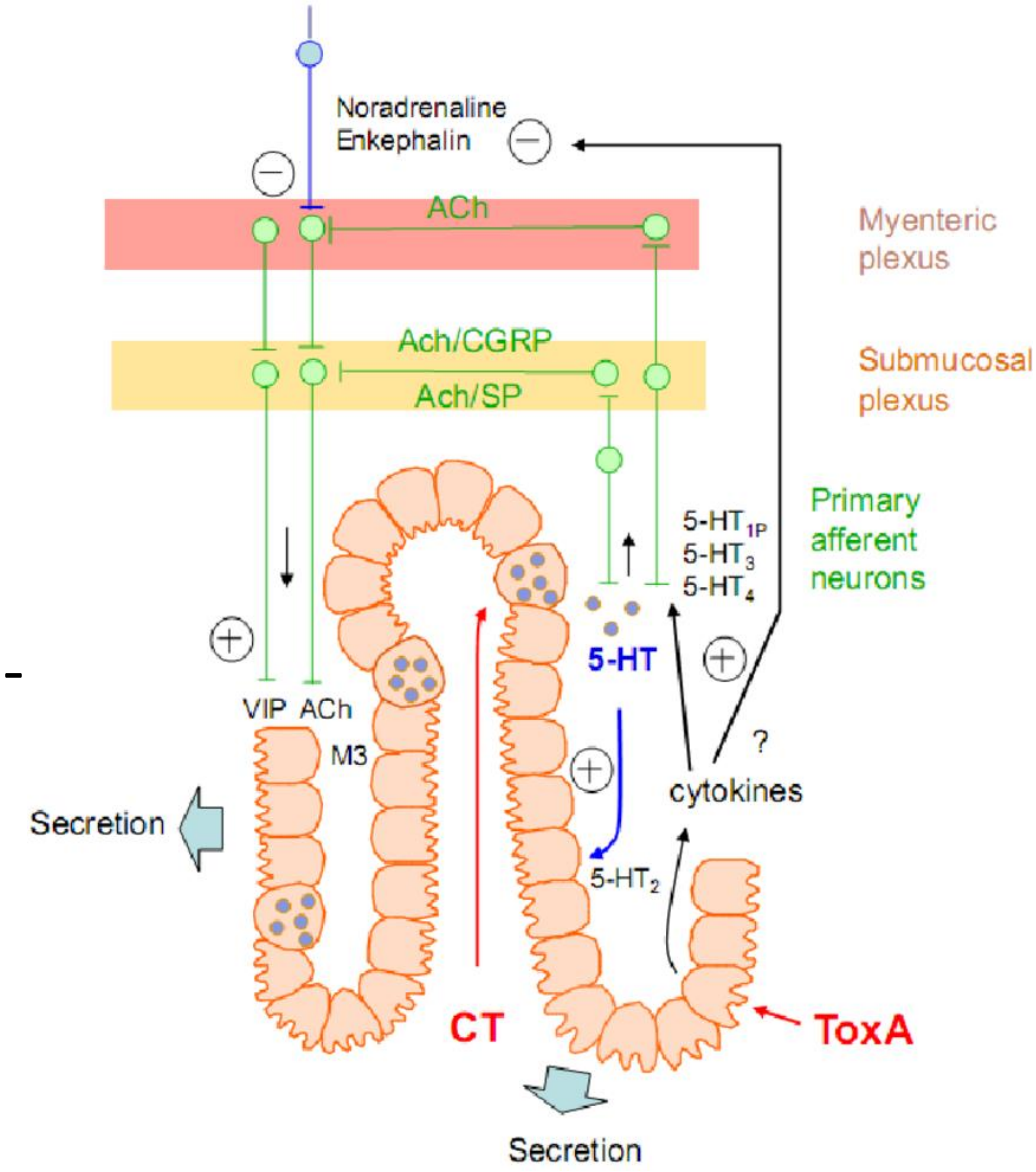
Nociceptin/orphanin FQ

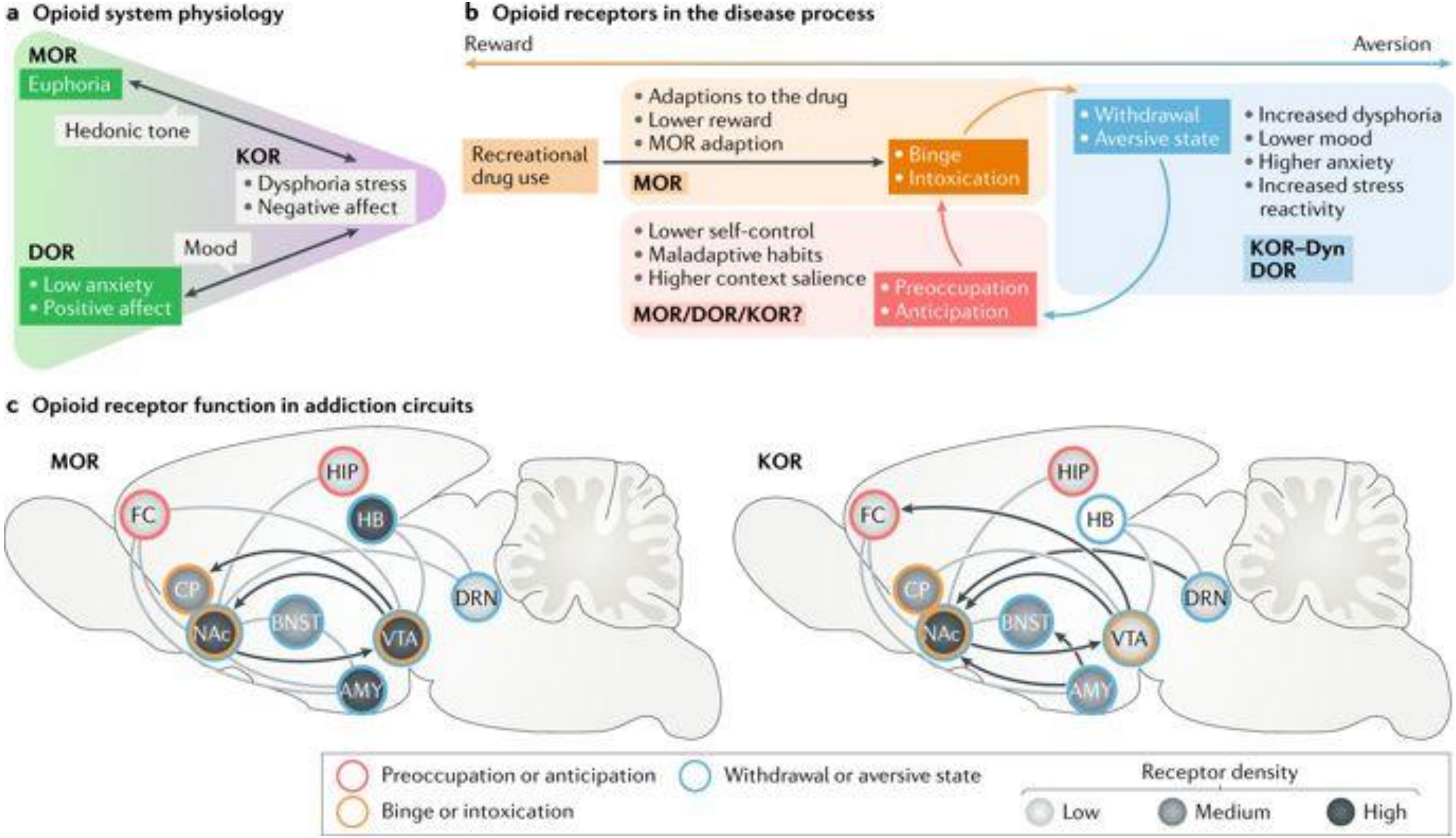
NOP

- Hippocampus, cerebral cortex, spinal cord
- It triggers hyperalgesia and allodynia by reversing opioid-induced analgesia
- Behavior, drug addiction
- Cardiovascular system - hypotension / bradycardia

Physiological functions

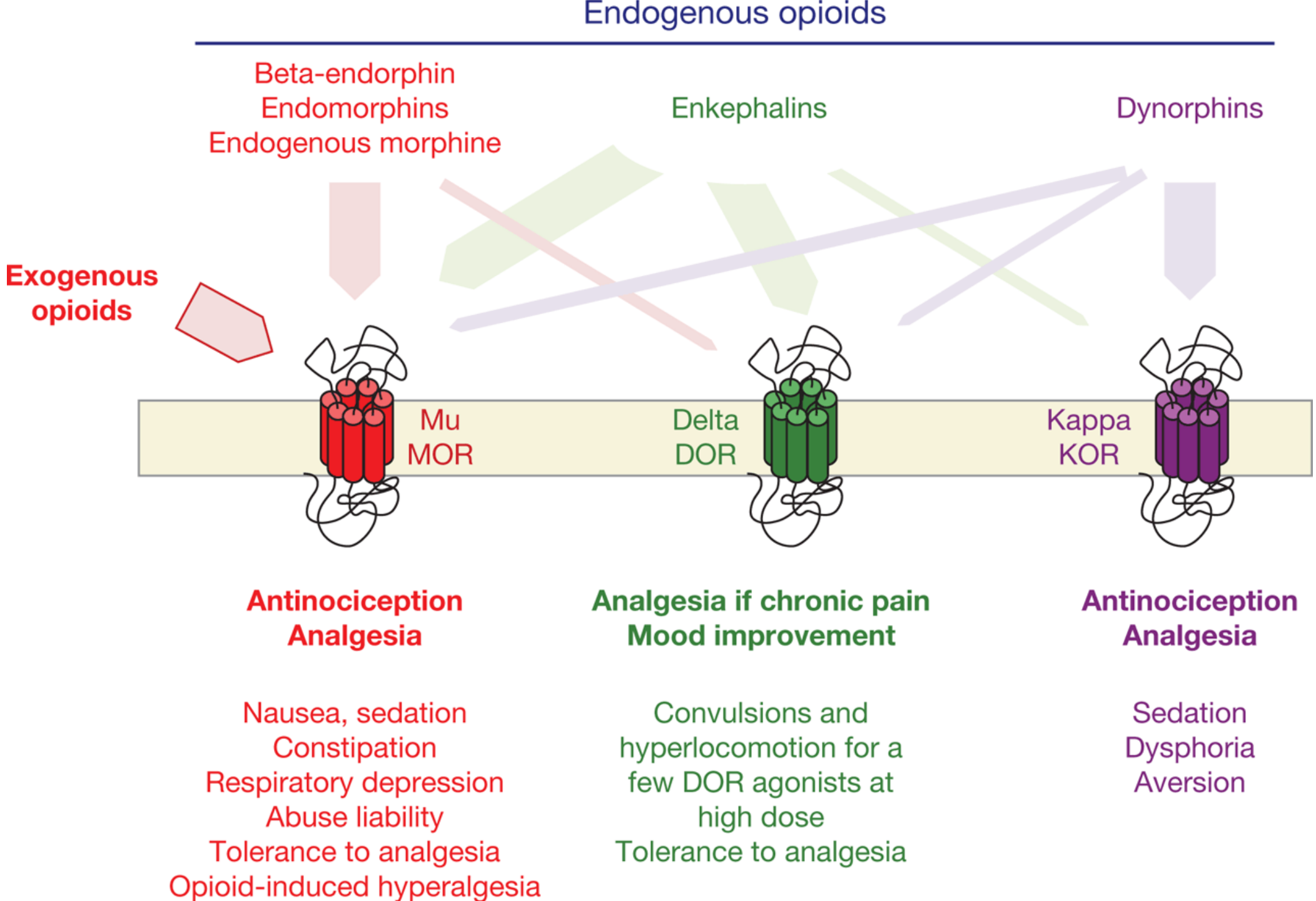
- Stress – connection between β-endorphin and ACTH
- (+) food intake, effect on food "palatability"
- (-)/(+) concentration-dependent fluid intake
- GIT – inhibition of neurotransmitter release - constipation / reduction of motility
- Renal functions (-) – inhibition of diuresis (μ), (-)-resorption of water(κ)
- memory
- Emotions, mood (+) euphoric effect
- Sexual behaviour – rather (-), (-) socio-sexual interactions BUT increase sexual arousal and motivation
- Parturition?

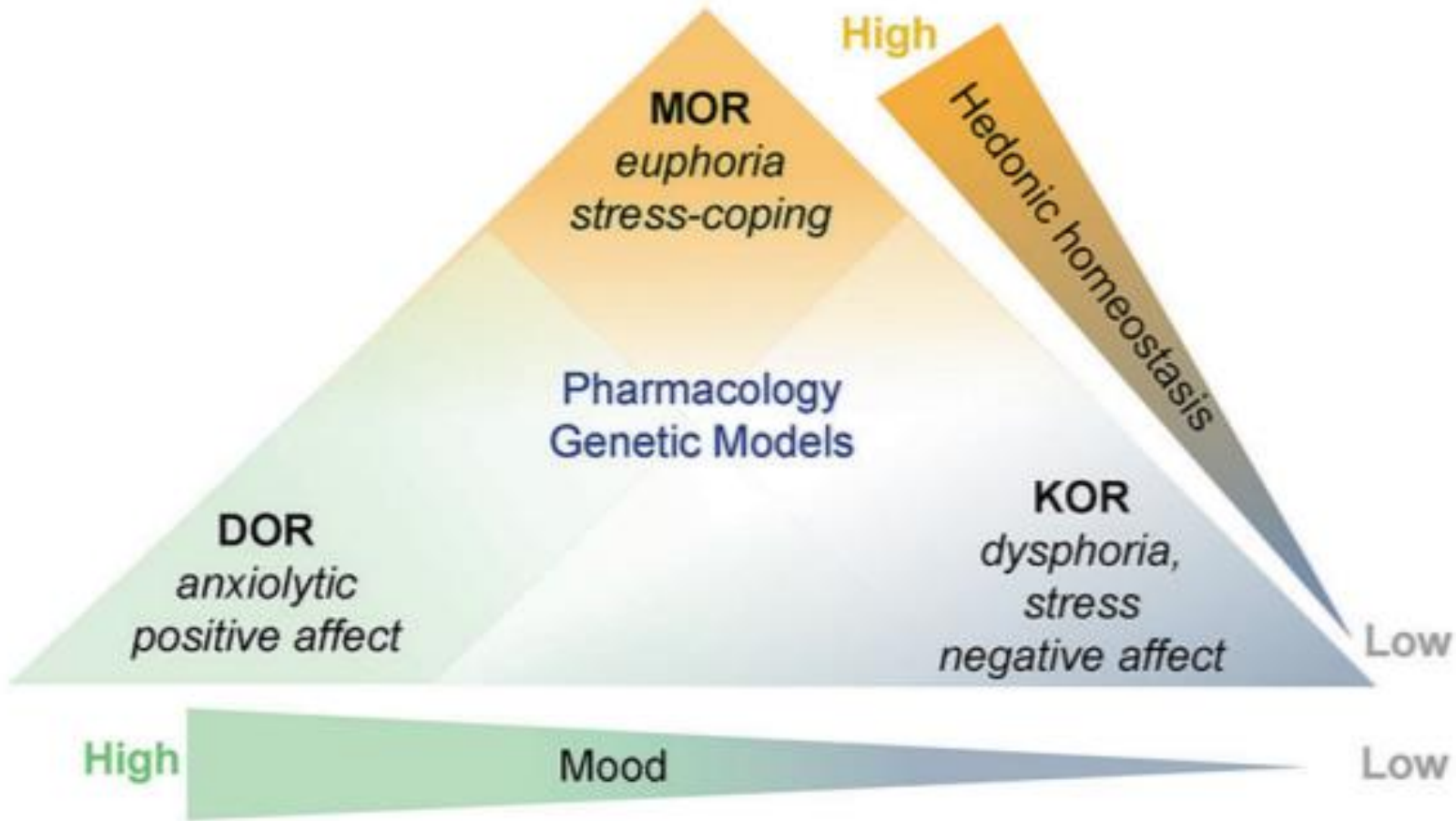


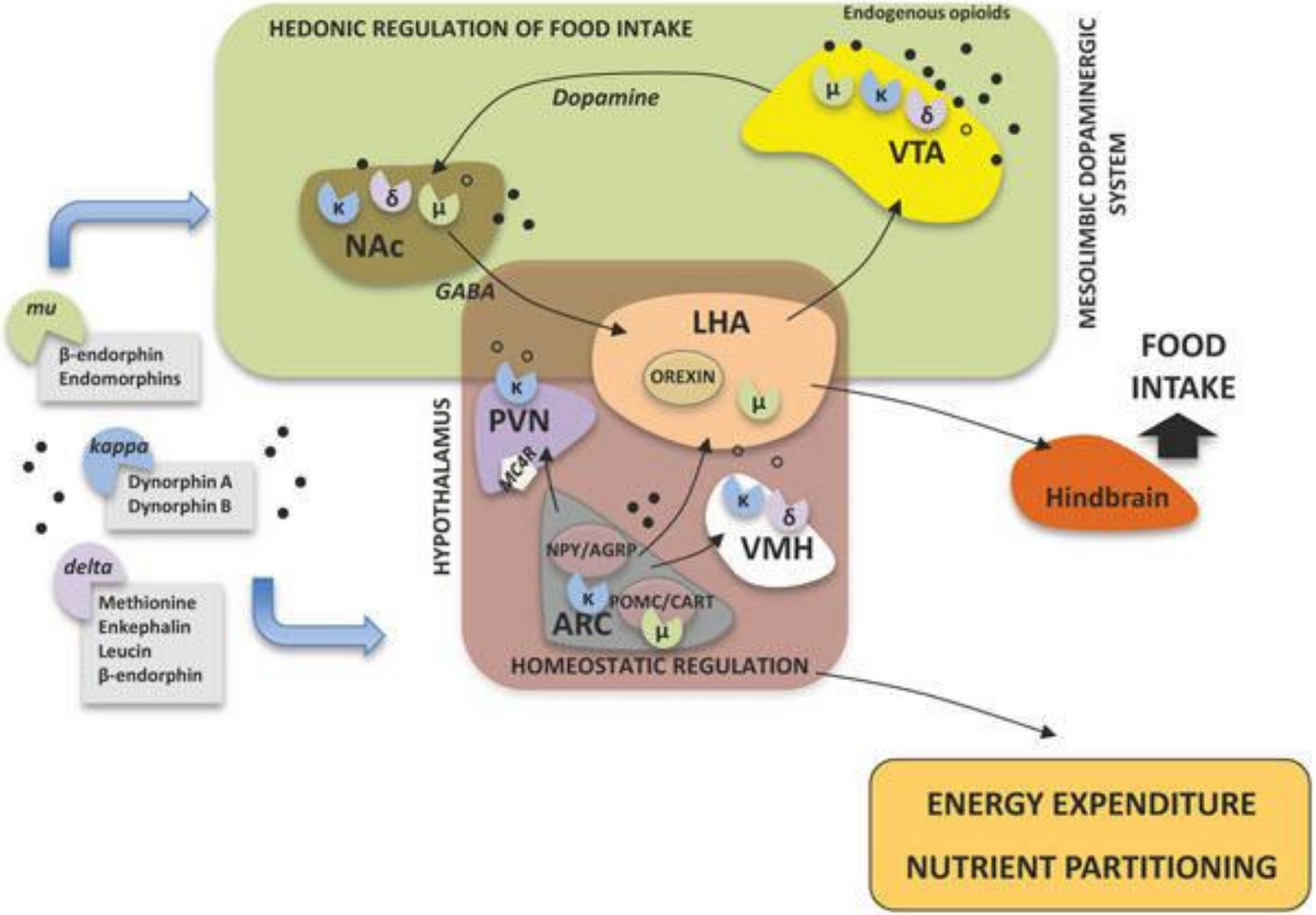

a Opioid system physiology
MOR
Euphoria
Hedonic tone
KOR
• Dysphoria stress
• Negative affect
Mood
DOR
• Low anxiety
• Positive affect
b Opioid receptors in the disease process
Reward
Aversion
Recreational drug use
• Adaptions to the drug
• Lower reward
• MOR adaption
MOR
• Binge
• Intoxication
• Withdrawal
• Aversive state
• Increased dysphoria
• Lower mood
• Higher anxiety
• Increased stress reactivity
KOR–Dyn
DOR
• Lower self-control
• Maladaptive habits
• Higher context salience
MOR/DOR/KOR?
• Preoccupation
• Anticipation
c Opioid receptor function in addiction circuits
MOR
HIP
FC
HB
CP
NAc
BNST
VTA
DRN
AMY
KOR
HIP
FC
HB
CP
NAc
BNST
VTA
DRN
AMY
Preoccupation or anticipation
Withdrawal or aversive state
Binge or intoxication
Receptor density
Low
Medium
High

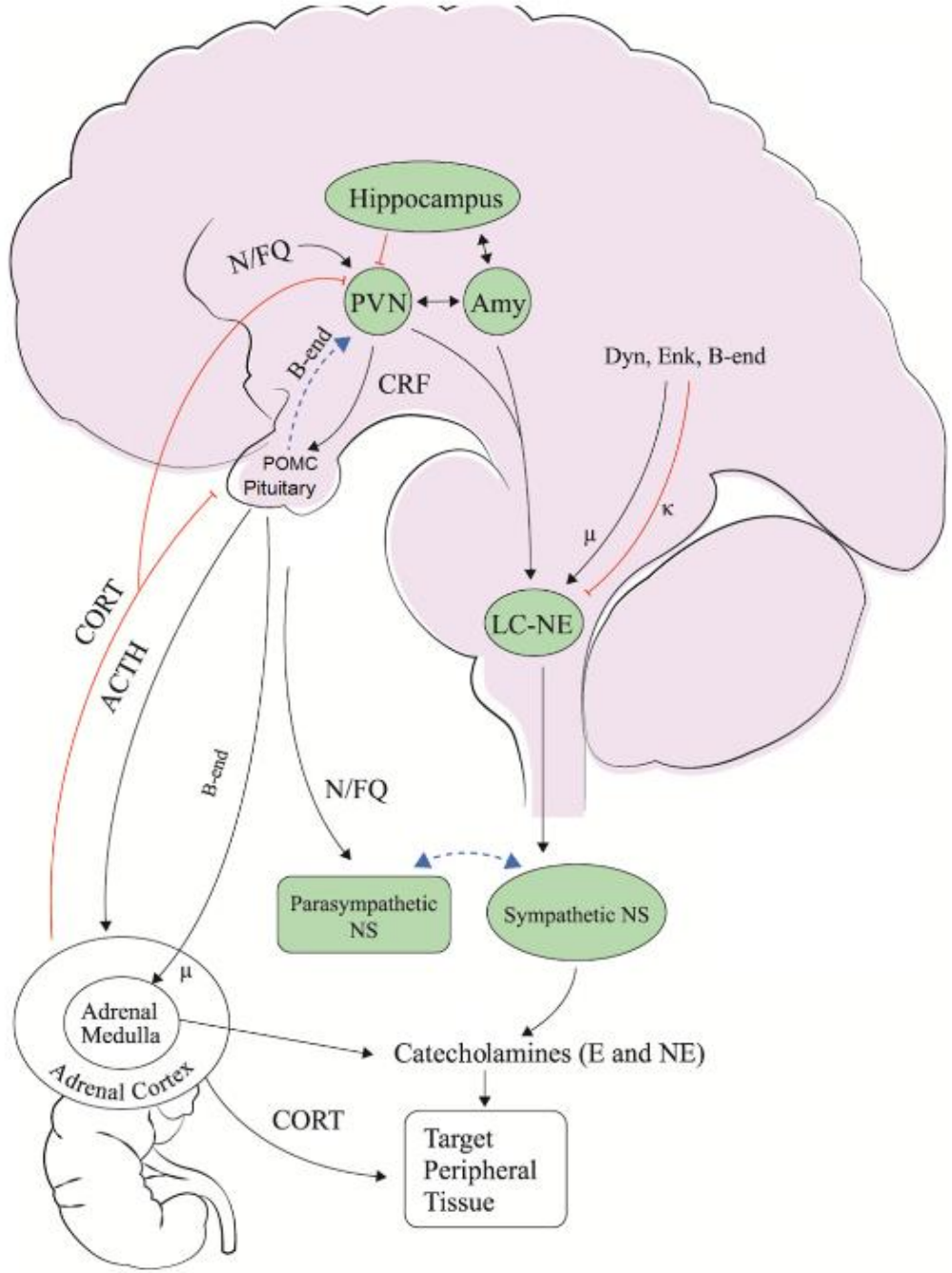
Physiological functions

- Respiration
  - Suppression of respiratory neuron activity - bradypnoea?
  - Respiration in stress conditions, protective functions in hypoxia and hypercapnia
- Cardiovascular functions
  - inhibitory
  - They reduce HF and BP BUT it depends on the situation!
- Immune functions
  - Dual effect depending on a number of factors
  - Possible protection against cancer?


Endogenous opioids
Beta-endorphin
Endomorphins
Endogenous morphine
Enkephalins
Dynorphins
Exogenous opioids
Mu
MOR
Delta
DOR
Kappa
KOR
Antinociception
Analgesia
Nausea, sedation
Constipation
Respiratory depression
Abuse liability
Tolerance to analgesia
Opioid-induced hyperalgesia
Analgesia if chronic pain
Mood improvement
Convulsions and
hyperlocomotion for a
few DOR agonists at
high dose
Tolerance to analgesia
Antinociception
Analgesia
Sedation
Dysphoria
Aversion


High
MOR
euphoria
stress-coping
Hedonic homeostasis
Pharmacology
Genetic Models
DOR
anxiolytic
positive affect
KOR
dysphoria,
stress
negative affect
Low
High
Mood
Low


HEDONIC REGULATION OF FOOD INTAKE
Endogenous opioids
Dopamine
VTA
NAc
GABA
MESOLIMBIC DOPAMINERGIC SYSTEM
mu
β-endorphin
Endomorphins
kappa
Dynorphin A
Dynorphin B
delta
Methionine
Enkephalin
Leucin
β-endorphin
LHA
OREXIN
PVN
MC4R
HYPOTHALAMUS
NPY/AGRP
VMH
ARC
POMC/CART
HOMEOSTATIC REGULATION
FOOD INTAKE
Hindbrain
ENERGY EXPENDITURE
NUTRIENT PARTITIONING


Hippocampus
N/FQ
PVN
Amy
B-end
CRF
Dyn, Enk, B-end
POMC
Pituitary
μ
κ
CORT
ACTH
LC-NE
B-end
N/FQ
Parasympathetic NS
Sympathetic NS
μ
Adrenal Medulla
Adrenal Cortex
Catecholamines (E and NE)
CORT
Target Peripheral Tissue

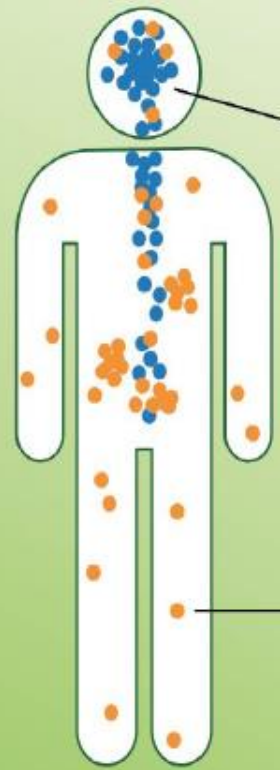
Endocannabinoid system

The Human Endocannabinoid System

MEDRELEAF
THE MEDICAL GRADE STANDARD™

The endocannabinoid system (ECS) consists of cannabinoid receptors, endocannabinoids and their metabolic enzymes. Two major cannabinoid receptors, CB1 and CB2, and two main endocannabinoids, anandamide (AEA) and 2-arachidonoyl-glycerol (2-AG), have been identified. Human endocannabinoids and plant cannabinoids, such as THC and CBD, bind to cannabinoid receptors with great specificity, much like a lock and key. Activation of the cannabinoid receptors inhibits the release of neurotransmitters. The ECS plays a key role in homeostasis and regulates many physiological processes such as inflammation and pain perception, immunity, neuropathy and metabolism.

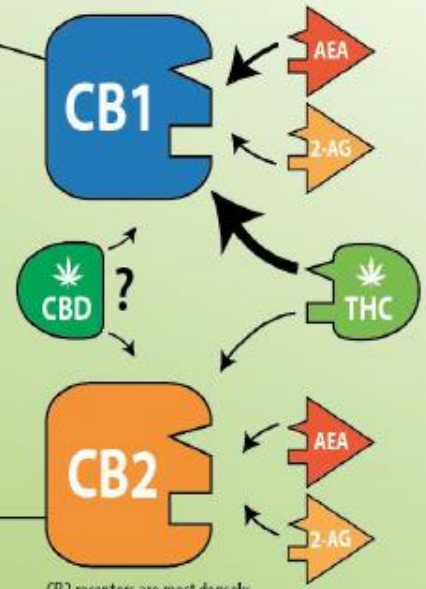
Cannabinoid receptors are widely distributed throughout the human body



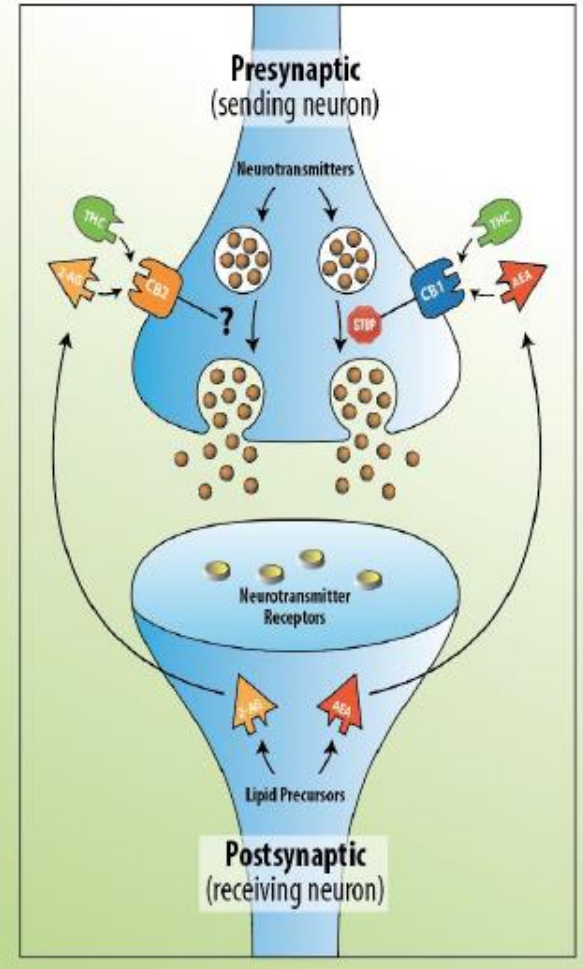
Receptors

CB1 receptors are mainly located in the brain and central nervous system but are also found in other tissues.

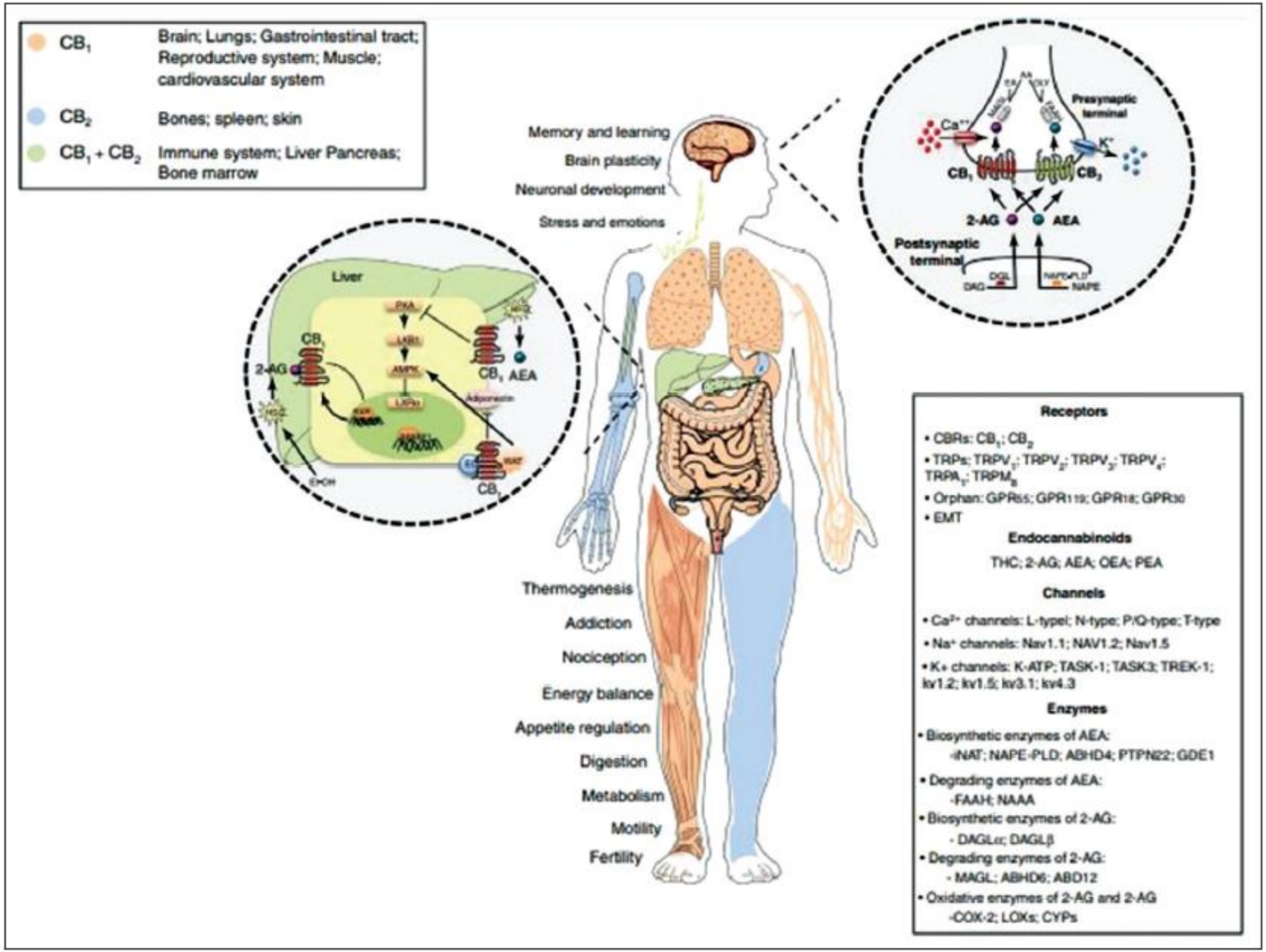
Ligands



CB2 receptors are most densely found in immunological tissues and modulate cell fate.



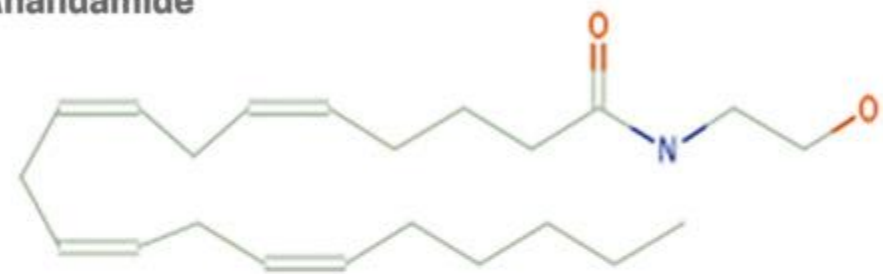
AEA binds to the CB1 receptor with greater affinity than CB2 whereas 2-AG binds both receptors with equal affinity. THC binds the CB1 receptor with greater affinity than the CB2 receptor and it has been suggested that binding effects of THC mimic AEA. CBD has low affinity for both receptors but interacts at low concentrations. It has been proposed that binding effects of CBD are mimetic to 2-AG.


CB1
Brain; Lungs; Gastrointestinal tract; Reproductive system; Muscle; cardiovascular system
CB2
Bones; spleen; skin
CB1 + CB2
Immune system; Liver Pancreas; Bone marrow
Memory and learning
Brain plasticity
Neuronal development
Stress and emotions
Liver
2-AG
CB1
CB1 AEA
CB1
Presynaptic terminal
Ca++
K+
CB1
CB2
2-AG
AEA
Postsynaptic terminal
DAG
DGL
NAPE-PLD
NAPE
Thermogenesis
Addiction
Nociception
Energy balance
Appetite regulation
Digestion
Metabolism
Motility
Fertility
Receptors
• CBRs: CB1; CB2
• TRPs: TRPV1; TRPV2; TRPV3; TRPV4; TRPA1; TRPM8
• Orphan: GPR55; GPR119; GPR18; GPR30
• EMT
Endocannabinoids
THC; 2-AG; AEA; OEA; PEA
Channels
• Ca2+ channels: L-type; N-type; P/Q-type; T-type
• Na+ channels: Nav1.1; NAV1.2; Nav1.5
• K+ channels: K-ATP; TASK-1; TASK3; TREK-1; kv1.2; kv1.5; kv3.1; kv4.3
Enzymes
• Biosynthetic enzymes of AEA:
-NAT; NAPE-PLD; ABHD4; PTPN22; GDE1
• Degrading enzymes of AEA:
-FAAH; NAAA
• Biosynthetic enzymes of 2-AG:
- DAGLα; DAGLβ
• Degrading enzymes of 2-AG:
- MAGL; ABHD6; ABD12
• Oxidative enzymes of 2-AG and 2-AG
-COX-2; LOXs; CYPs

ENDOCANNABINOIDS

cannabis-like cannabinoids manufactured internally by the body

Anandamide

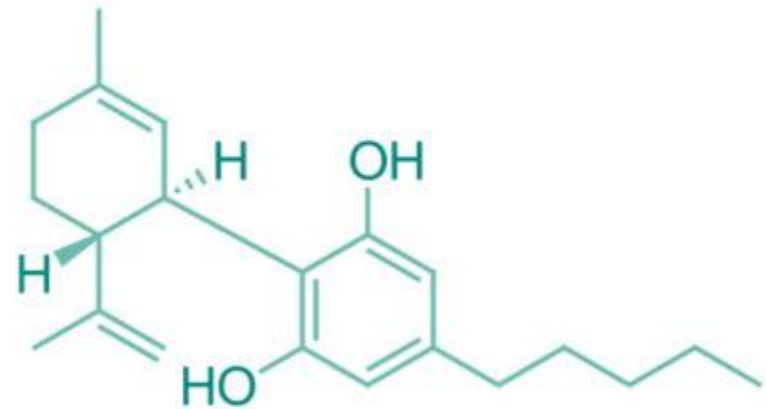


2-Arachidonoylglycerol (2-AG)

PHYTOCANNABINOIDS

cannabinoids found in cannabis plant and agricultural hemp

Cannabidiol (CBD)



CUREPHARMACEUTICAL.COM

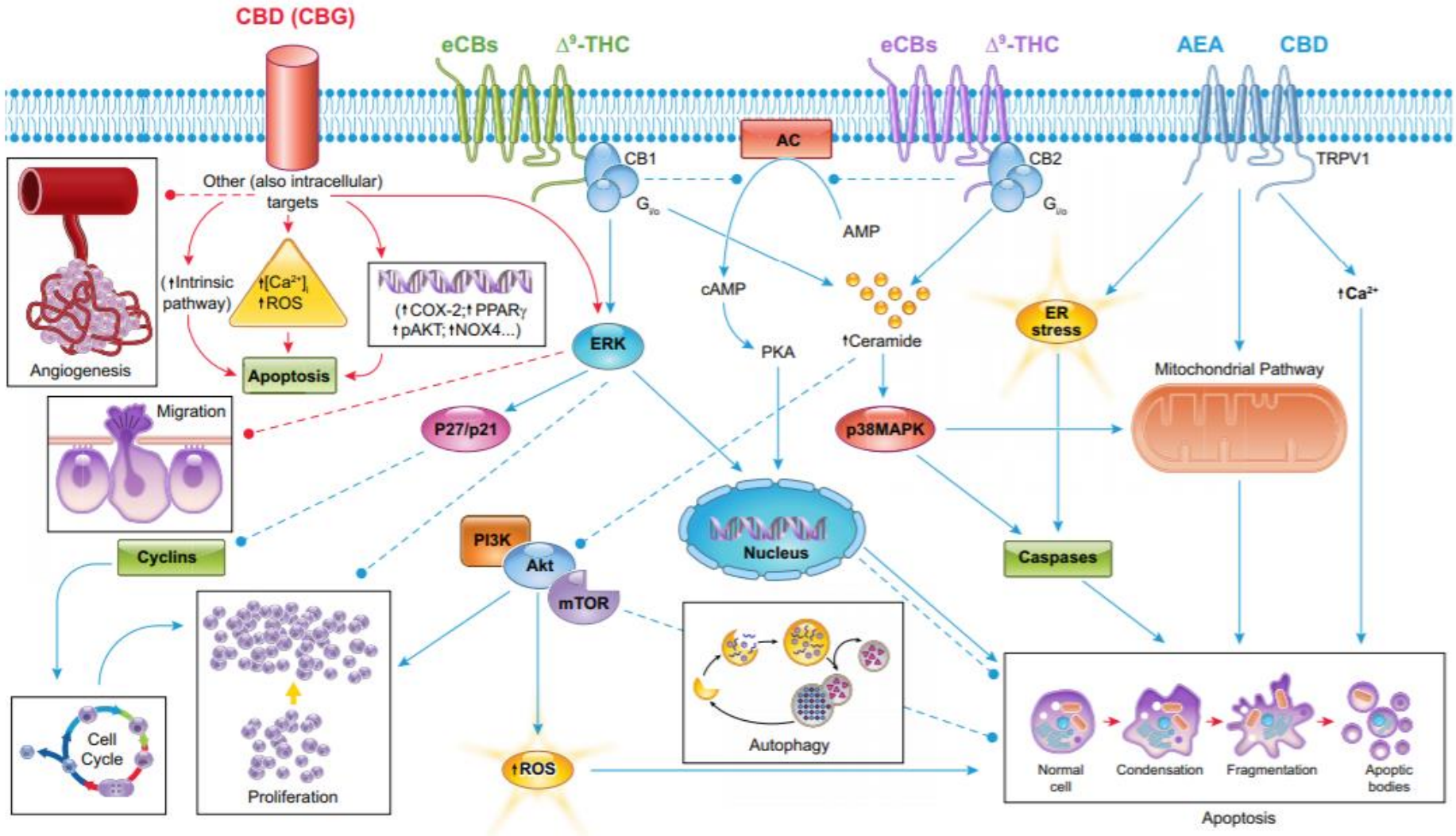


FIGURE 1. Schematic representation of the main signaling pathways through which (endo)cannabinoids impact proliferation, apoptosis, migration, and angiogenesis in cancer. Blue arrows indicate pathways initiated by cannabinoid/vanilloid receptor-mediated mechanisms, and red arrows indicate non-cannabinoid/vanilloid receptor-mediated mechanisms. Continuous lines indicate stimulation, and dotted lines indicate inhibition. AC, adenylyl cyclase; CBD, cannabidiol; CBG, cannabigerol; eCBs, endocannabinoids; ER, endoplasmic reticulum; Δ^9-THC, Δ^9-tetrahydrocannabinol; PKA, protein kinase A; AKT, protein kinase B; PI3K, phosphatidylinositol 3-kinase; ERK, extracellular regulated kinase; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; ROS, reactive oxygen species; p27/p21, cyclin-dependent kinase inhibitor proteins.

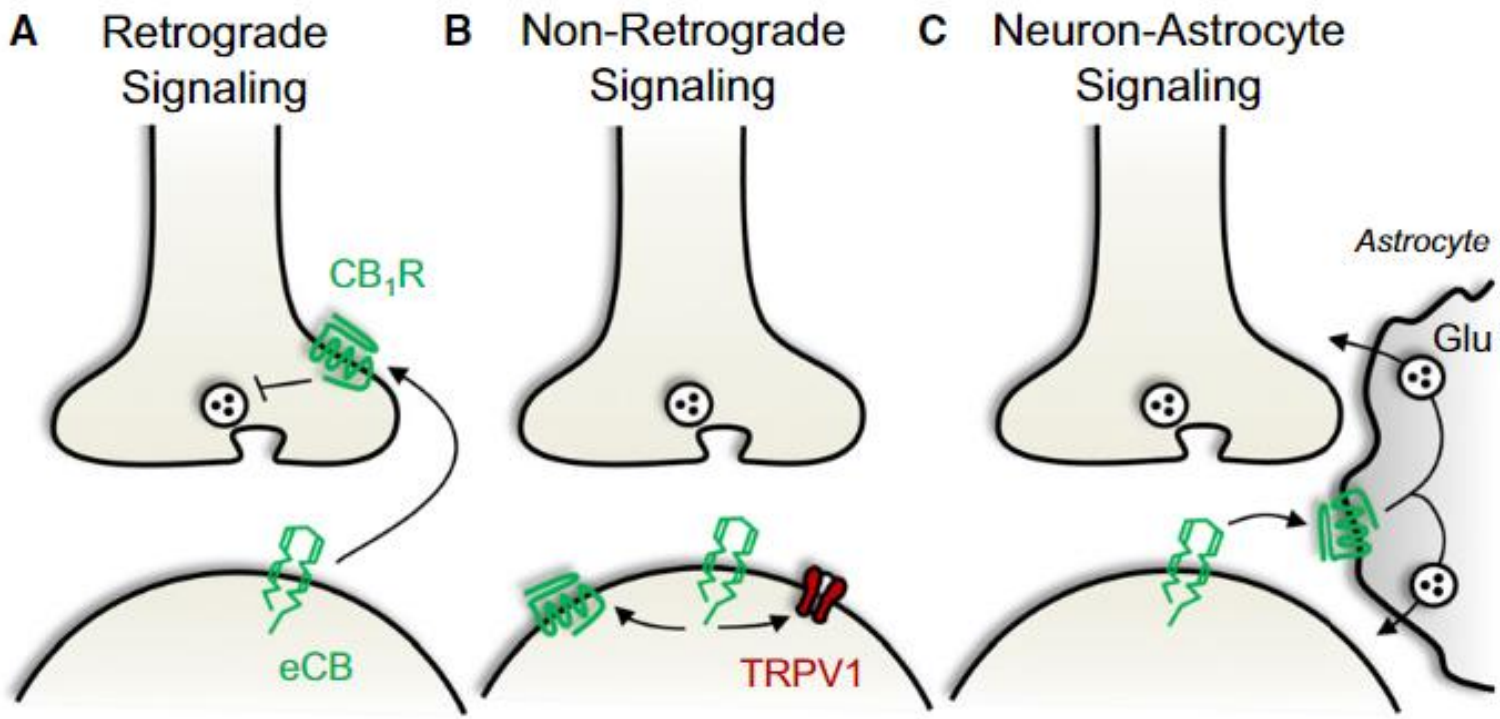


Figure 1. Endocannabinoid Signaling at the Synapse

(A) Retrograde endocannabinoid (eCB) signaling. eCBs are mobilized from postsynaptic neurons and target presynaptic cannabinoid type 1 receptors (CB_1Rs) to suppress neurotransmitter release.

(B) Nonretrograde eCB signaling. eCBs produced in postsynaptic neurons activate postsynaptic CB_1Rs or transient receptor potential vanilloid type 1 (TRPV1) channels.

(C) Neuron-astrocyte eCB signaling. eCBs released from postsynaptic neurons stimulate astrocytic CB_1Rs, thereby triggering gliotransmission. Glu, glutamate.

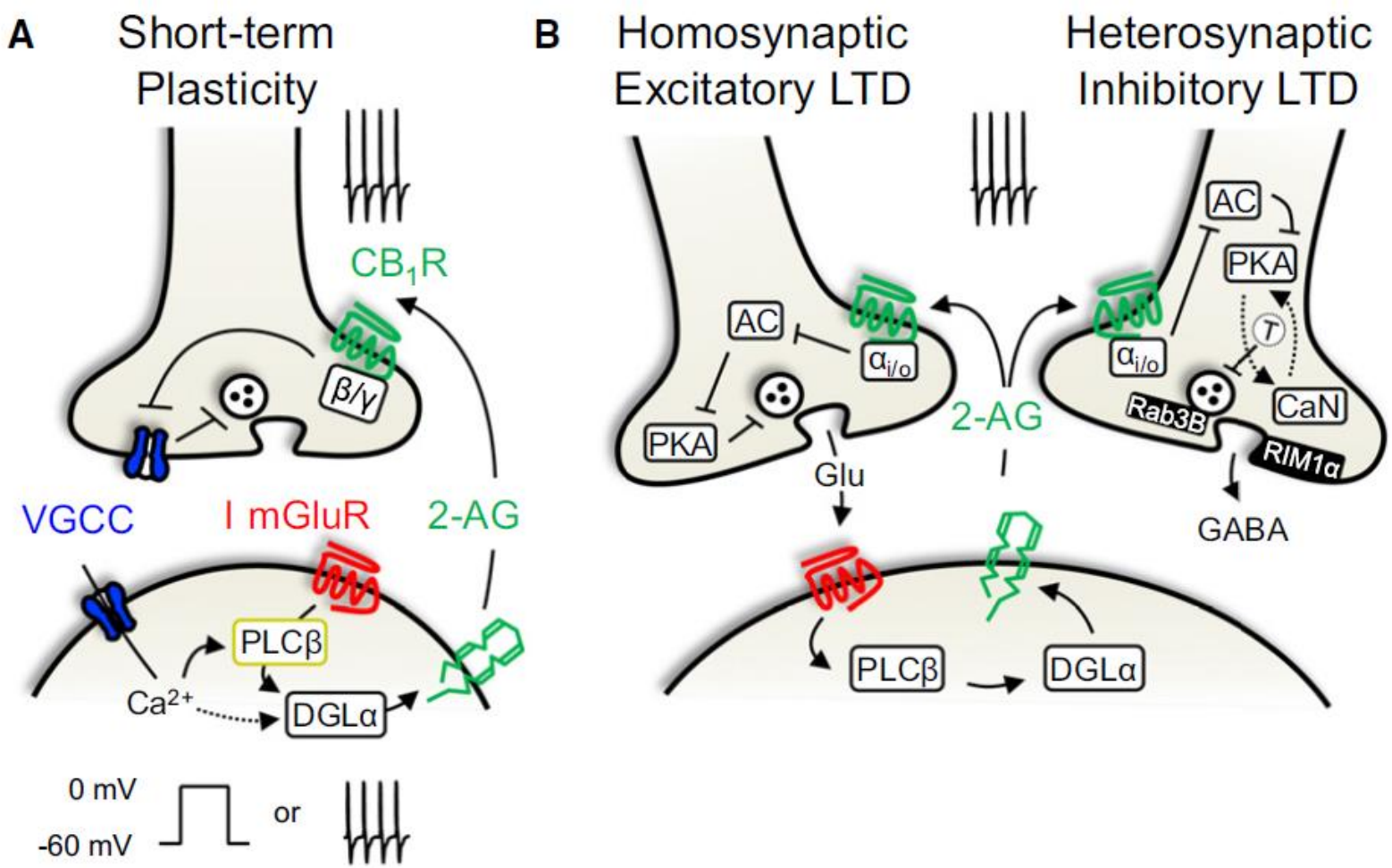


Figure 2. Molecular Mechanisms Underlying Endocannabinoid-Mediated Short- and Long-Term Synaptic Plasticity

(A) Short-term depression. Postsynaptic activity triggers Ca^{2+} influx via voltage-gated Ca^{2+} channels (VGCCs). Other Ca^{2+} sources, like NMDARs and internal stores, may contribute. Ca^{2+} promotes diacylglycerol lipase (DGLα)-mediated eCB production by an unknown mechanism. Presynaptic activity can also lead to eCB mobilization by activating postsynaptic group I metabotropic glutamate receptors (I mGluRs). Phospholipase-Cβ (PLCβ) can now act as a coincidence detector integrating pre- and postsynaptic activity. DGLα promotes 2-arachidonoylglycerol (2-AG) release, which retrogradely targets presynaptic CB_1Rs, and the βγ subunits probably couple to presynaptic VGCCs to reduce neurotransmitter release.

(B) eCB-mediated excitatory long-term depression (LTD) and inhibitory LTD (iLTD). Patterned presynaptic stimulation releases glutamate (Glu), which activates postsynaptic mGluRs coupled to PLCβ and DGLα. 2-AG homosynaptically targets CB_1Rs localized to excitatory terminals and heterosynaptically engages CB_1Rs at inhibitory terminals. A $G_{\alpha i/o}$-dependent reduction in adenylyl cyclase (AC) and protein kinase A (PKA) activity suppresses transmitter release. At inhibitory synapses, decreased PKA activity, in conjunction with activation of the Ca^{2+}-sensitive phosphatase calcineurin (CaN), shifts the phosphorylation status of an unidentified presynaptic target (T) required for iLTD. The active zone protein RIM1α and the vesicle-associated protein Rab3B are also necessary for iLTD. Induction of eCB-LTD may require presynaptic Ca^{2+} rise through VGCCs, NMDARs, or internal stores (not shown). Dashed lines indicate putative pathways.

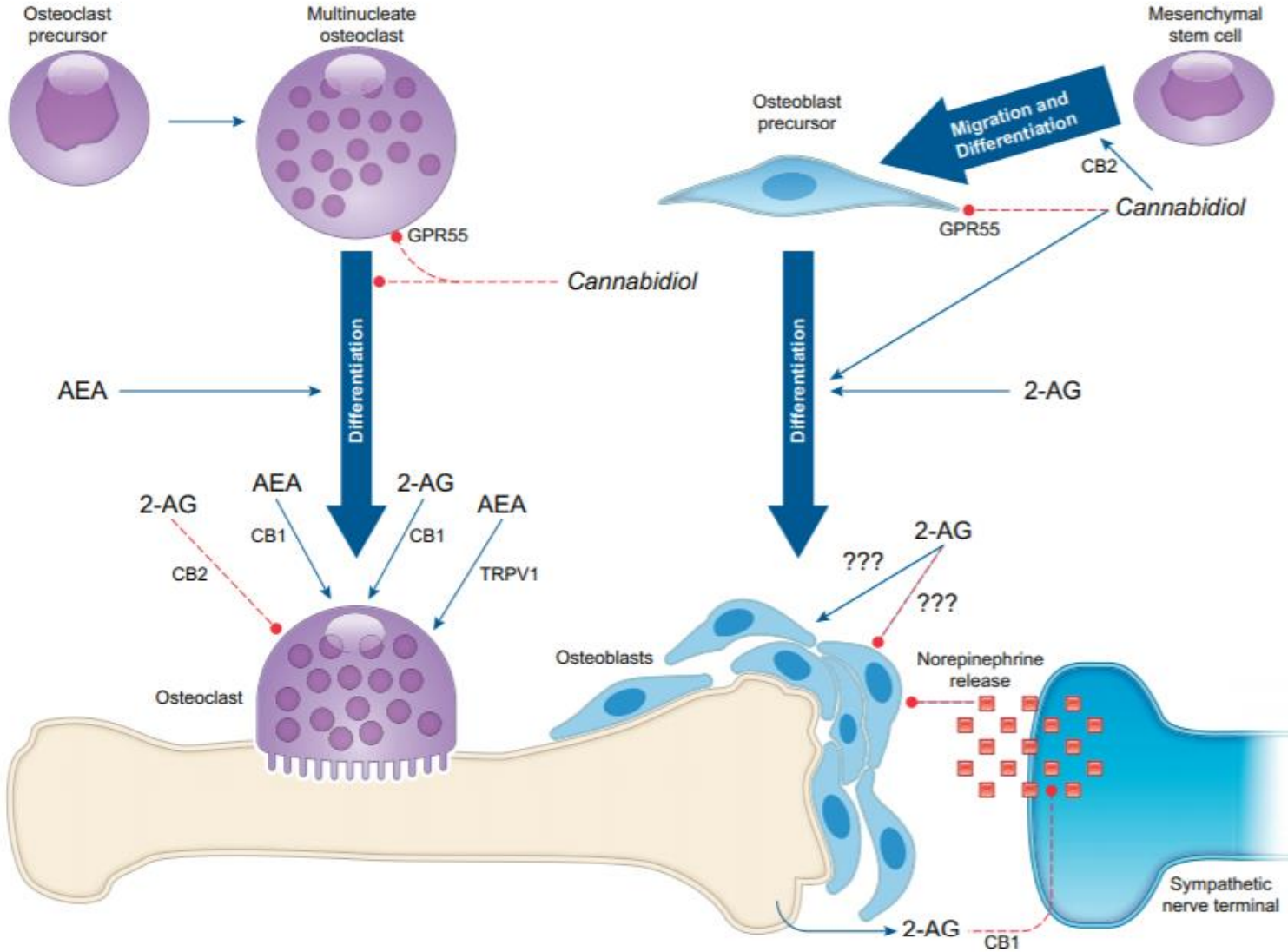


FIGURE 3. Endocannabinoid and phytocannabinoid modulation of bone formation and resorption. Blue arrows indicate stimulation, and red blunted arrows indicate inhibition. The molecular targets through which anandamide (AEA) and 2-arachidonoylglycerol (2-AG) seem to modulate osteoblast and osteoclast differentiation and activity are shown. Cannabidiol was suggested to inhibit osteoclast and stimulate osteoblast differentiation by blocking GPR55.

Cell-based model of coagulation

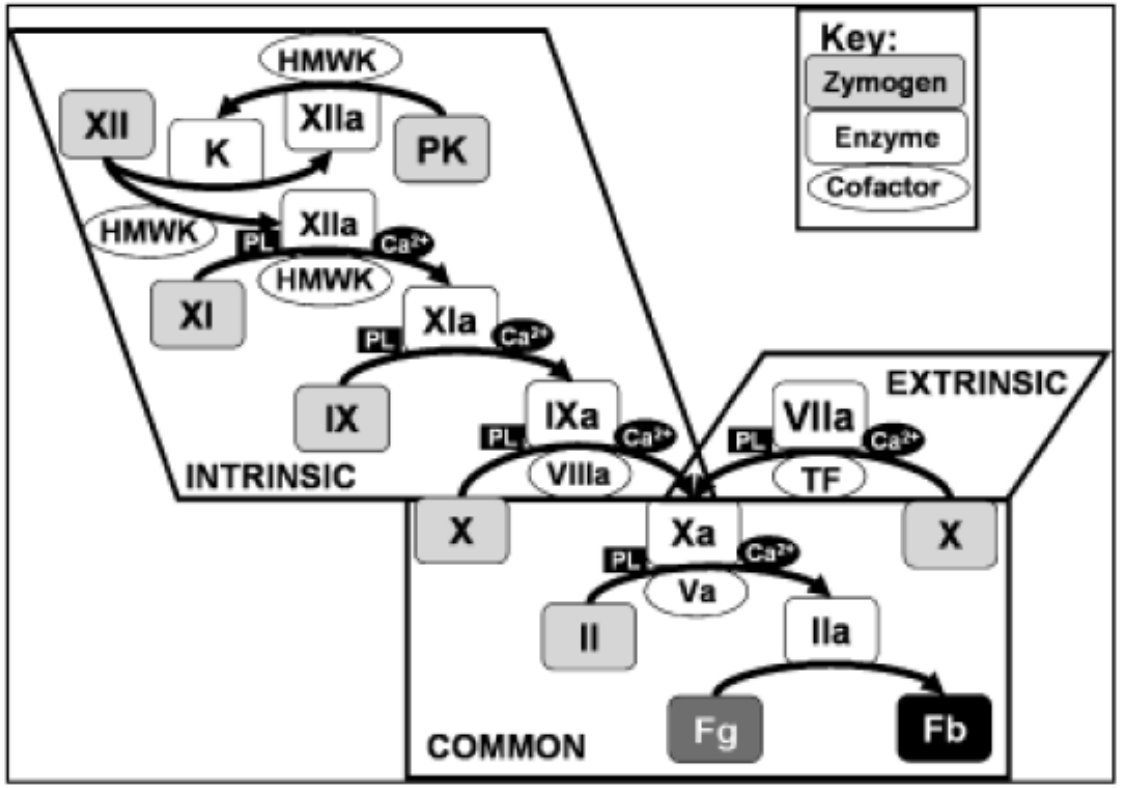
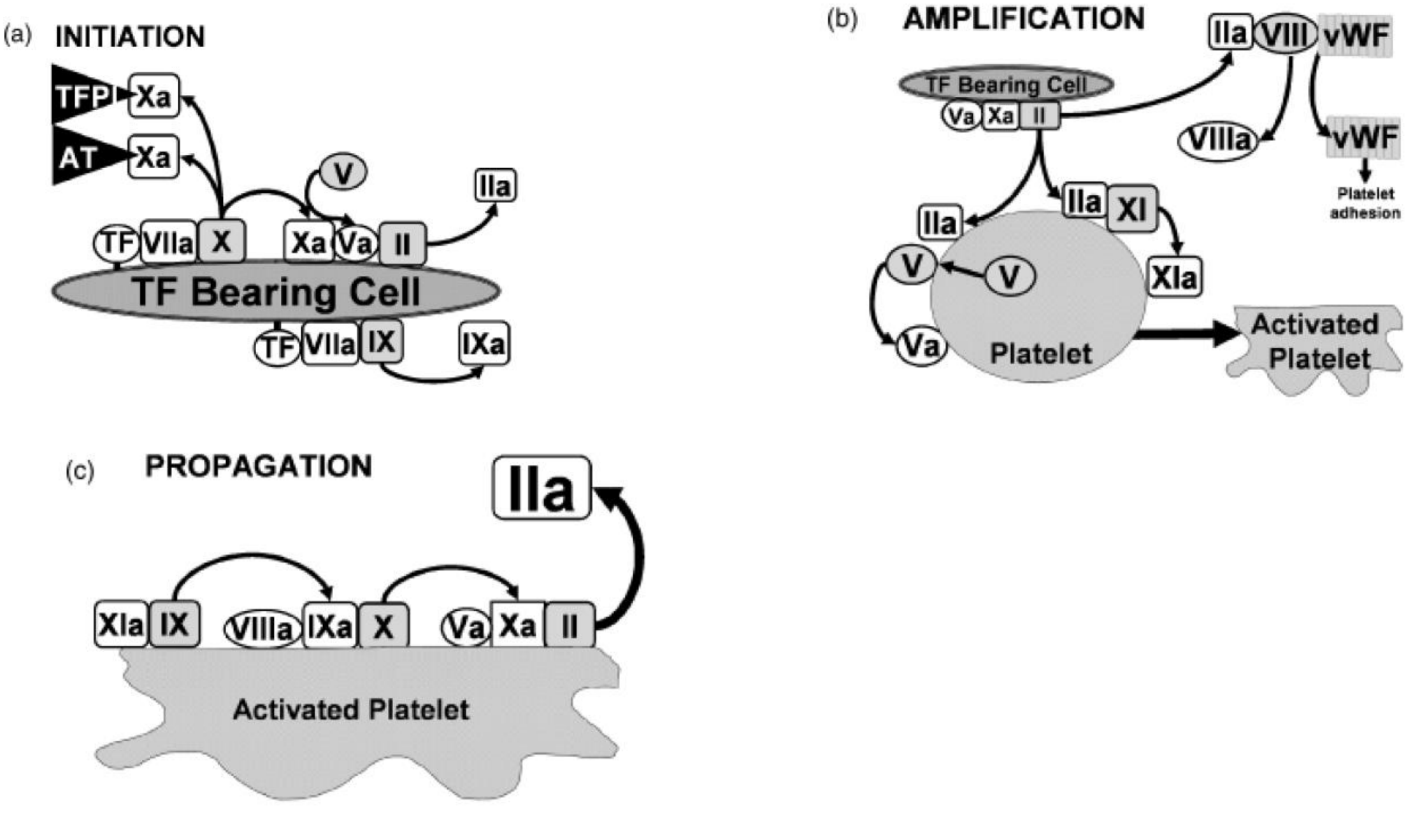


Figure 1: The cascade model of fibrin formation. This model divides the coagulation system into separate redundant pathways (extrinsic and intrinsic) either of which can result in generation of FXa. The common pathway results in generation of thrombin and subsequent cleavage of fibrinogen to fibrin. Many of the enzymes and enzymatic complexes require calcium (Ca^{2+}) and binding to active membrane surfaces (PL) for full activity. See Table 1 for abbreviations. For simplicity, feedback activation of procofactors to cofactors and the many inhibitors of the various enzymes have been omitted.


(a) INITIATION
TFP
Xa
AT
Xa
V
IIa
TF
VIIa
X
Xa
Va
II
TF Bearing Cell
TF
VIIa
IX
IXa
(b) AMPLIFICATION
IIa
VIII
vWF
TF Bearing Cell
Va
Xa
II
VIIIa
vWF
Platelet adhesion
IIa
IIa
XI
V
V
XIa
Va
Platelet
Activated Platelet
(c) PROPAGATION
IIa
XIa
IX
VIIIa
IXa
X
Va
Xa
II
Activated Platelet