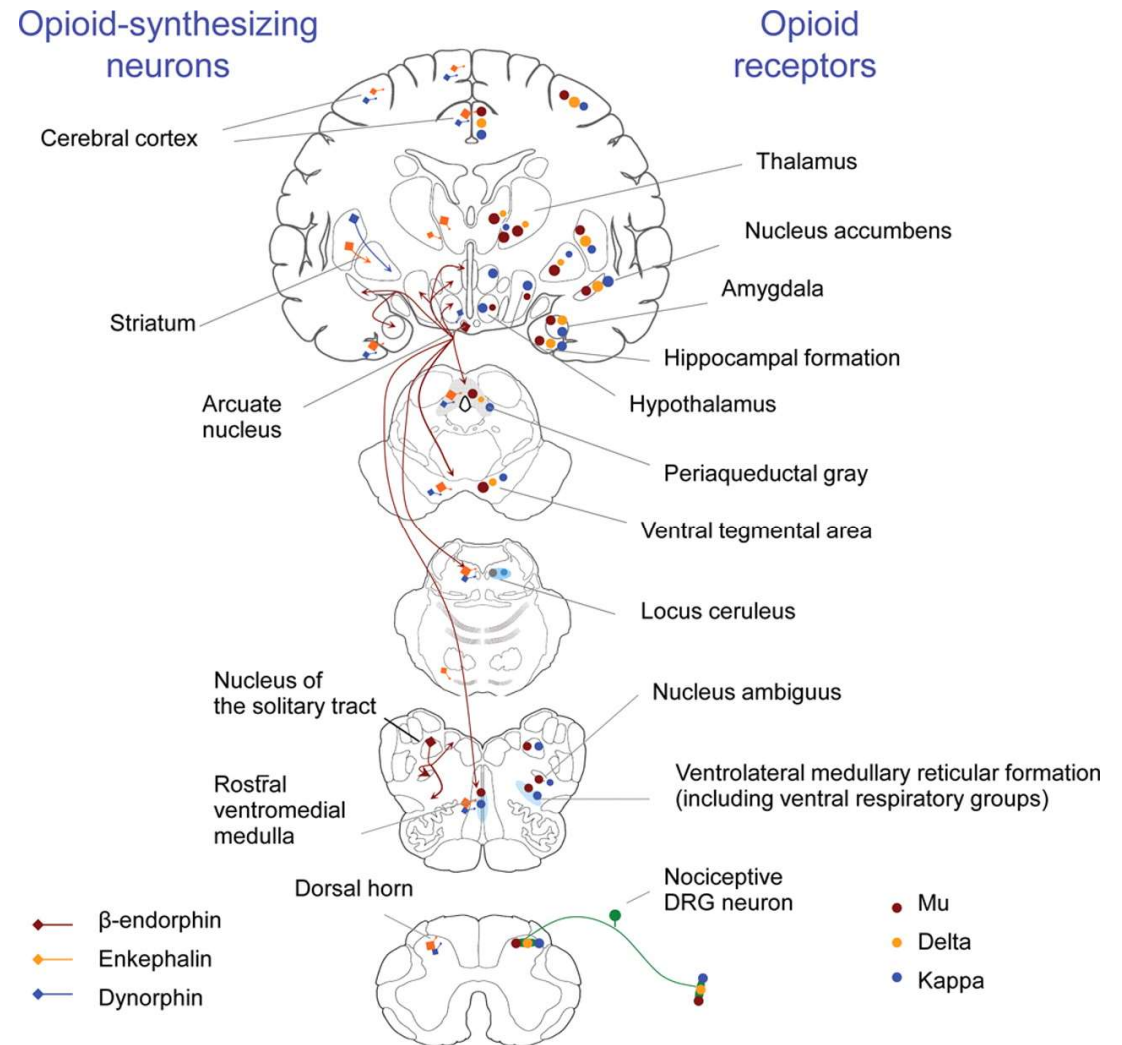


Endogenous opioid system

# What is „endogenous opioid system“?

- System of endogenous substances with affinity for opioid receptors
- CNS (brain stem, thalamus, hypothalamus, limbic system, spinal cord) outside the CNS (peripheral sensory nerve fibers, non-myelinated C and myelinated A $\delta$  fibers, immune system cells)
- Homeostatic and other functions
- Pain



# Endogenous opioid peptides

## Precursor peptides

- POMC
- Preproenkephalin
- Preprodynorphin

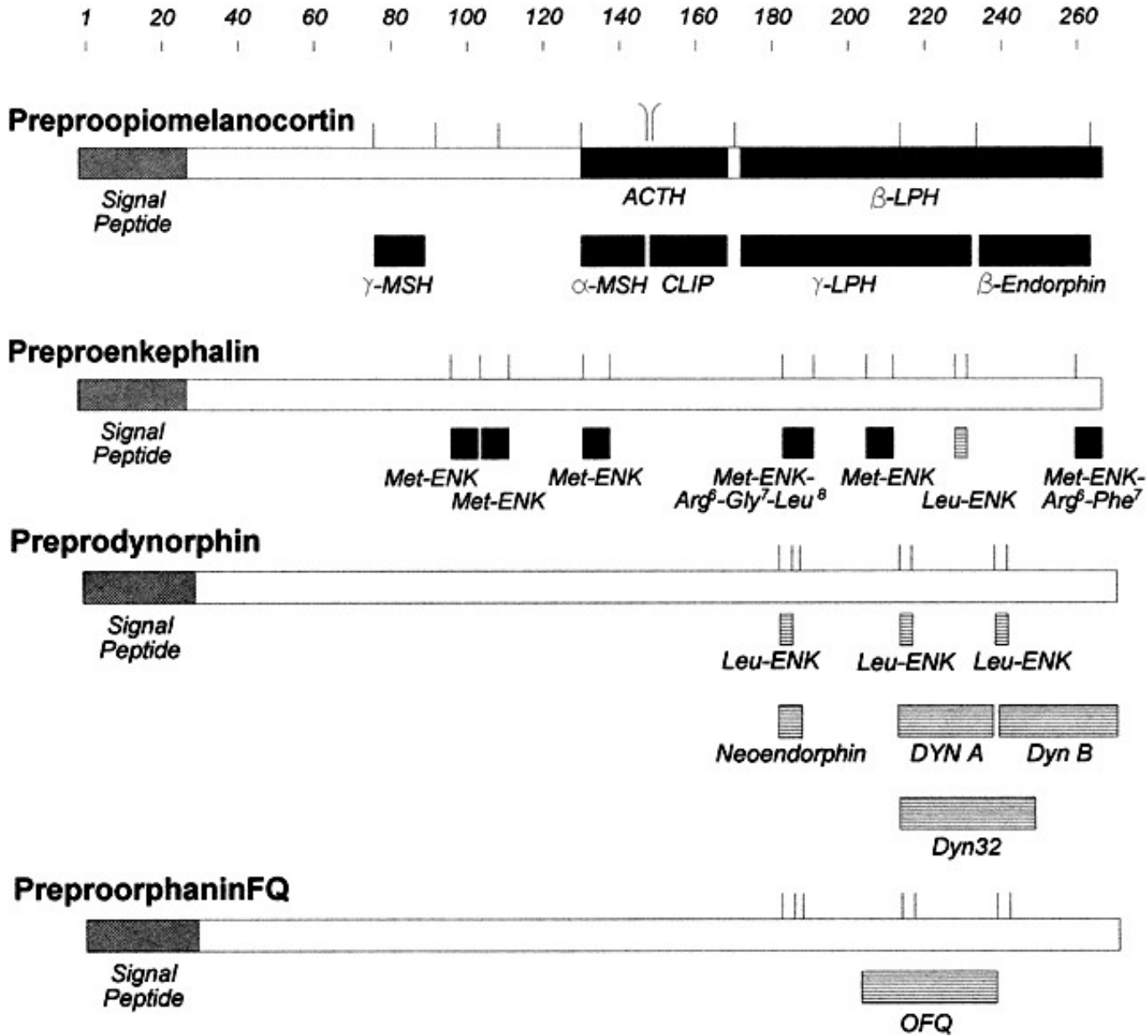


## Endogenous opioid peptides

- Endorphins
- Enkephalins
- Dynorphins
- Endomorphins

# Opioid motif

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



# Opioid receptors

- DOR –  $\delta$  opioid receptor

- KOR –  $\kappa$  opioid receptor

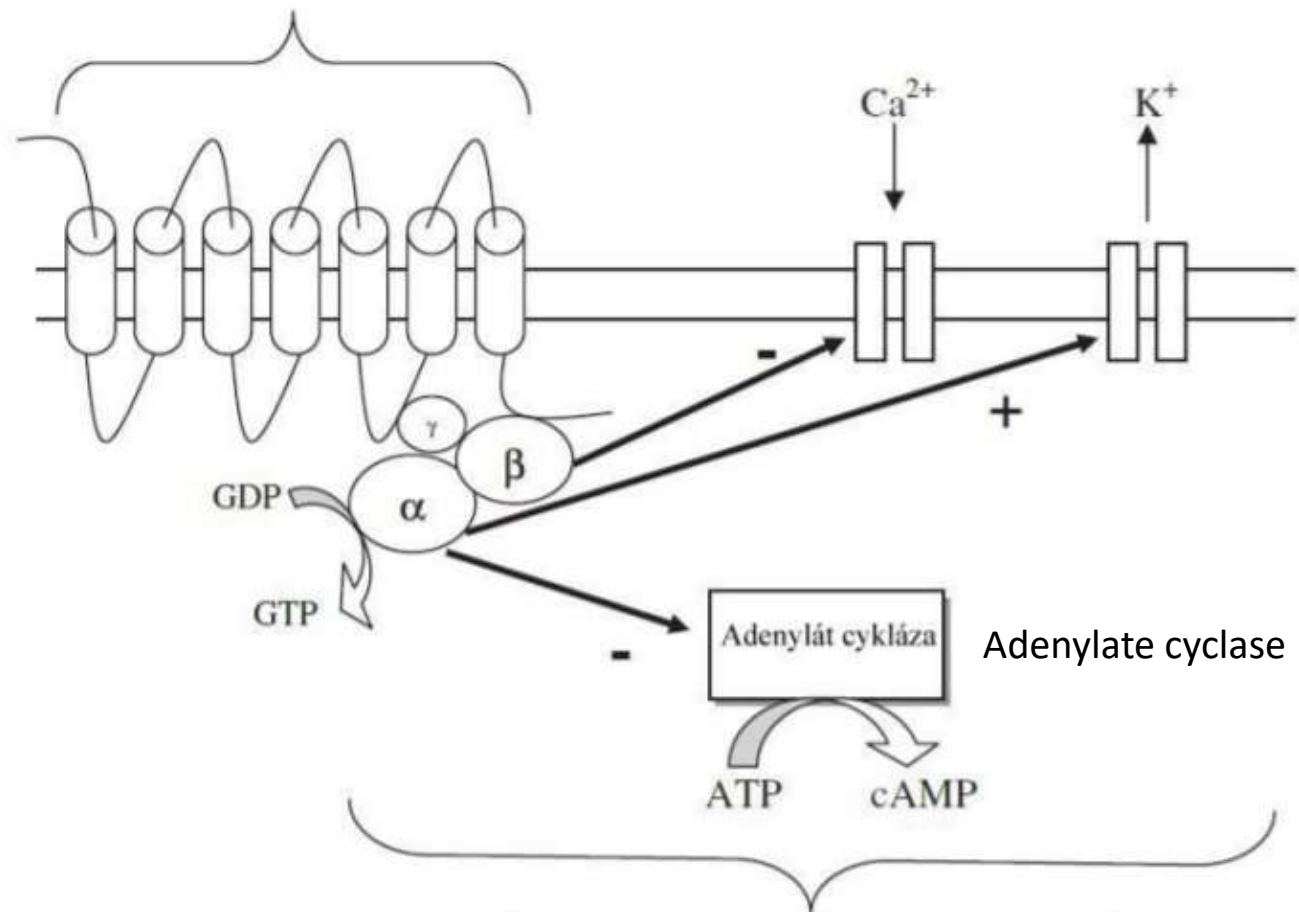
-MOR –  $\mu$  opioid receptor

-NOR – N/OFQ opioid receptor

Receptor	CNS Location	Response on activation
$\mu$	Brain (laminae III and IV of the cortex, thalamus, periaqueductal gray), spinal cord (substantia gelatinosa)	$\mu_1$ -supraspinal analgesia, physical dependence; $\mu_2$ -Respiratory depression, miosis, euphoria, reduced gastrointestinal motility, physical dependence
$\kappa$	Brain (hypothalamus, periaqueductal gray, claustrum), spinal cord (substantia gelatinosa)	Spinal analgesia, sedation, miosis, inhibition of antidiuretic hormone release
$\delta$	Brain (pontine nucleus, amygdala, olfactory bulbs, deep cortex)	Analgesia, euphoria, physical dependence

CNS-Central nervous system

Transmembrane protein coupled with G protein



Inhibition of neurotransmitter release

Anatomical Location	Receptor mRNA Detected	Receptor Protein Subtype(s) Detected	Inferred Function	References
<b>Central Regions<sup>3</sup></b>				
Caudate nucleus	μ, δ, κ		μ: Pain perception, sensorimotor integration	2
Cerebellum	μ, δ, κ		δ: Motor and cognitive functioning	2
Cerebral cortex	μ, δ, κ		κ: Feeding, pain perception, neuroendocrine function	2
Nucleus accumbens	μ, δ, κ		μ, δ, κ: Stress-related activation of endogenous opioid systems	2
Putamen	μ, δ, κ			2
Spinal cord	μ, δ, κ			2
Substantia nigra	μ, δ, κ			2
<b>Peripheral Regions</b>				
Adrenal gland	μ, δ, κ		Paracrine or autocrine role in adrenal function	2
Bone		μ	Endogenous opioid function in skeletal ontology	3
Cartilage	μ	μ		3
Dorsal root ganglion	μ, δ, κ		Analgesia	2
Enteric neurons		μ, δ, κ	μ, δ: Inhibition of adenylate cyclase and nerve terminal Ca <sup>2+</sup> channels, activation of K <sup>+</sup> channels, inhibition of submucosal secretomotor neurons κ: Inhibition of Ca <sup>2+</sup> channels, inhibition of neurotransmitter release μ, δ, κ: Inhibition of acetylcholine release from enteric interneurons and purine/nitric oxide release from inhibitory motoneurons	4
Heart	δ, κ	μ, δ, κ	Myocardial performance; regulation of sympathetic and parasympathetic control of the heart	2,5
Kidney	δ, κ			2
Liver	κ			2
Lung	δ, κ			2
Pancreas	μ, δ, κ		Modulation of visceral pain	2
Periosteum		μ	Endogenous opioid function in skeletal ontology	3
Skeletal Muscle	δ, κ			2
Spleen	κ		Possible involvement in immune function	2
Synovium	μ, δ, κ	μ, δ, κ	μ, δ: Modulation of nociception, endogenous analgesia κ: Possible role in inflammation	3
Tendon		δ		3
Thymus	δ, κ		Possible involvement in immune function	2

# Endorphins

$\mu / \delta$

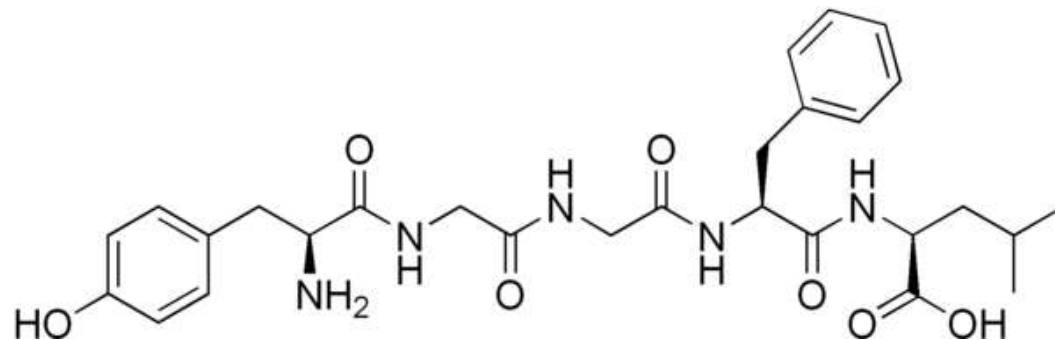
- Alpha, beta, gamma and delta
- Pituitary / hypothalamus and other sites
- Strenuous exercise / physical activity, pain, orgasm
- Analgesia and Feelings of Wellbeing
- Mobilizing the immune system?
- Creating emotional ties
- Food intake
- Same effect in pain but different in stress



# Enkephalins

$\mu / \delta$

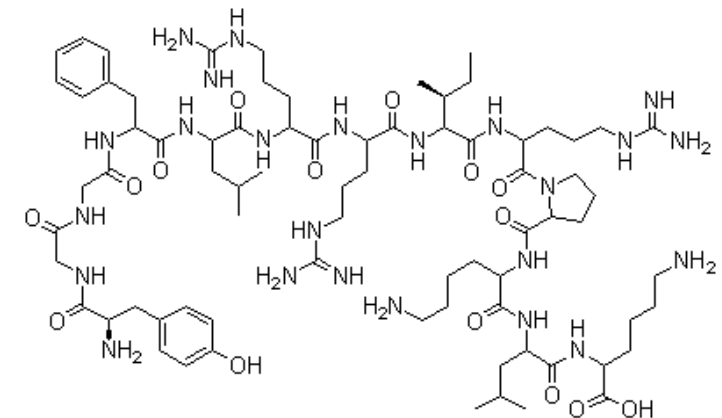
- Met- / Leu-
- CNS sites related to pain perception, behavior, motor control, and neuroendocrine functions
- T cells, macrophages, mast cells
- Excitement, physical exertion, sexual activity, fear



# Dynorphins

$\mu / \kappa$

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

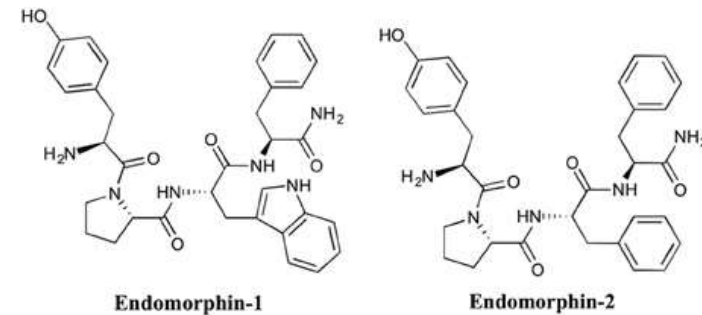


H-Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys-OH

# Endomorphins

$\mu$

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



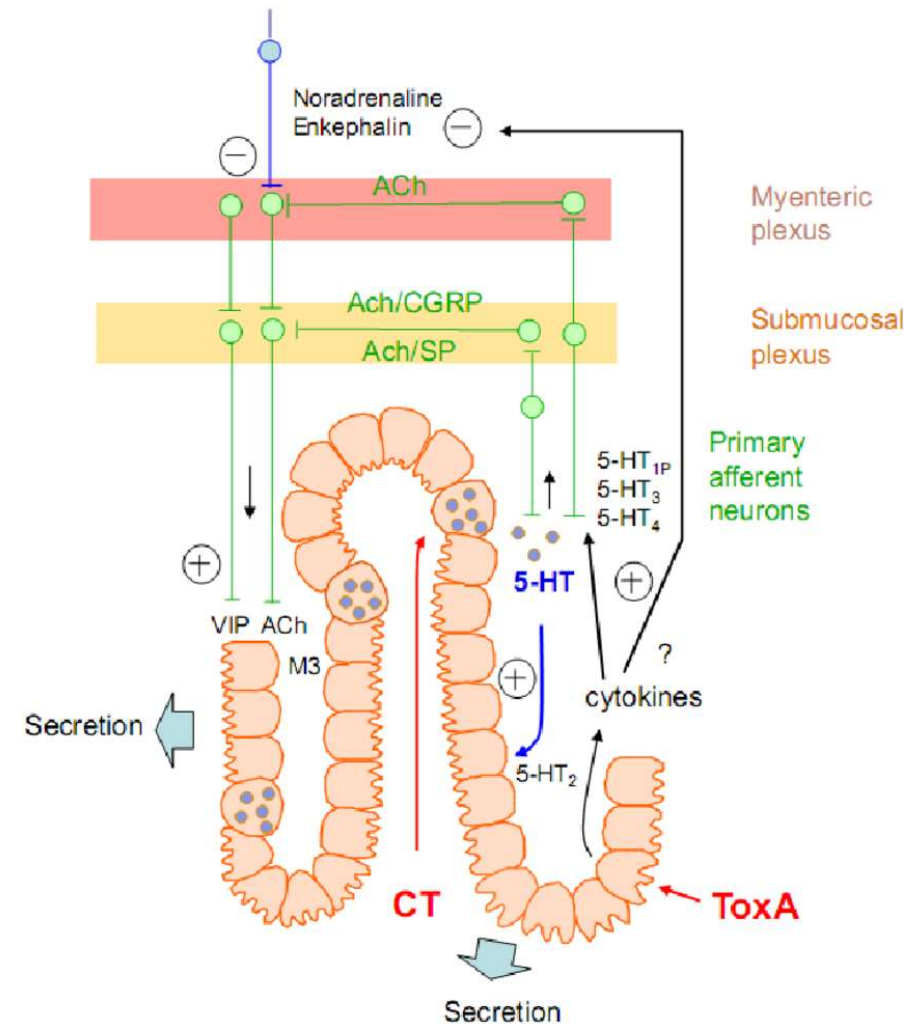
# Nociceptin/orphanin FQ

**NOP**

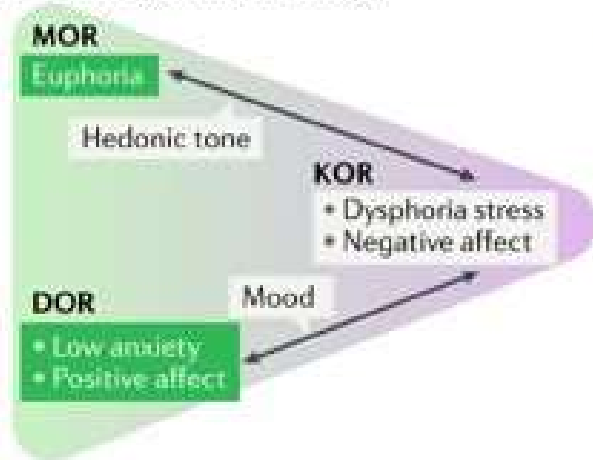
- Hippocampus, cortex, spinal cord
- It triggers hyperalgesia and allodynia by reversing opioid-induced analgesia
- Behavior, drug addiction
- Cardiovascular - hypotension / bradycardia

# Physiological functions of EOS

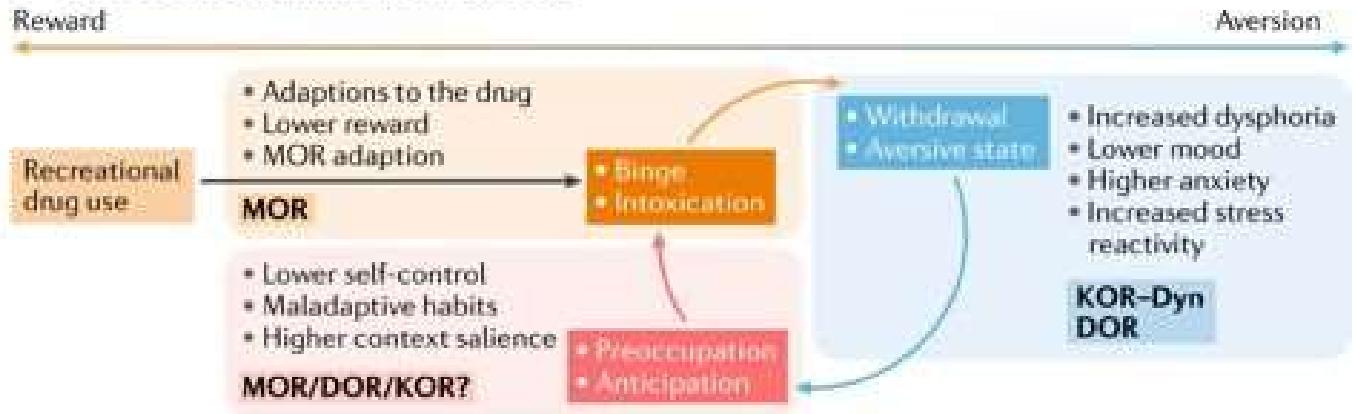
- Stress -  $\beta$ -endorphin binding and ACTH = connection of both systems
- (+) food intake, effect on food's palatability
- (-) / (+) concentration-dependent fluid intake
- GIT - inhibition of neurotransmitter release - constipation / reduction of motility
- Renal function (-) - diuresis inhibition ( $\mu$ ), (-) - water resorption ( $\kappa$ )
- Memory
- Emotion, mood (+) to euphoric effect
- Sexual behavior - rather (-), (-) socio-sexual interactions BUT increase sexual arousal and motivation
- Delivery?



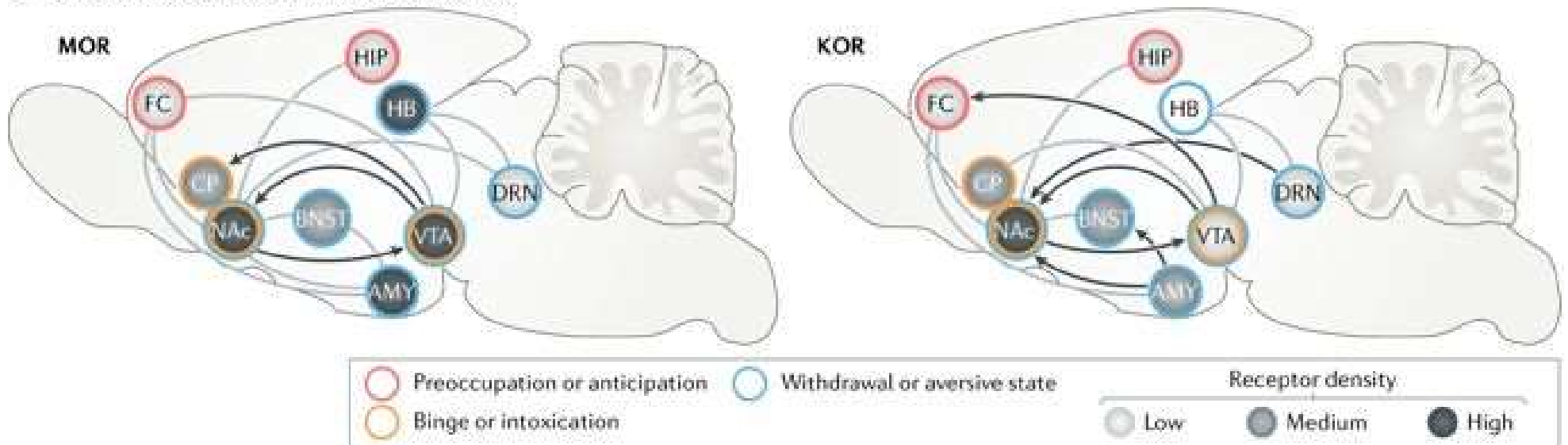
### a Opioid system physiology



### b Opioid receptors in the disease process



### c Opioid receptor function in addiction circuits



# Physiological functions of EOS

## - Respiration

- Suppression of respiratory neuron activity - bradypnea?
- Respiratory stress, protective function in hypoxia and hypercapnia

## - Cardiovascular function

- In general, inhibitory
- Reduces PF and BP BUT Depends on the Situation!

## - Immune function

- Dual effect depending on many factors
- Maybe protection against cancer?

## Endogenous opioids

