Pain

Edna Mao

Group Meeting Literature Talk

October 18th, 2022

What is pain?

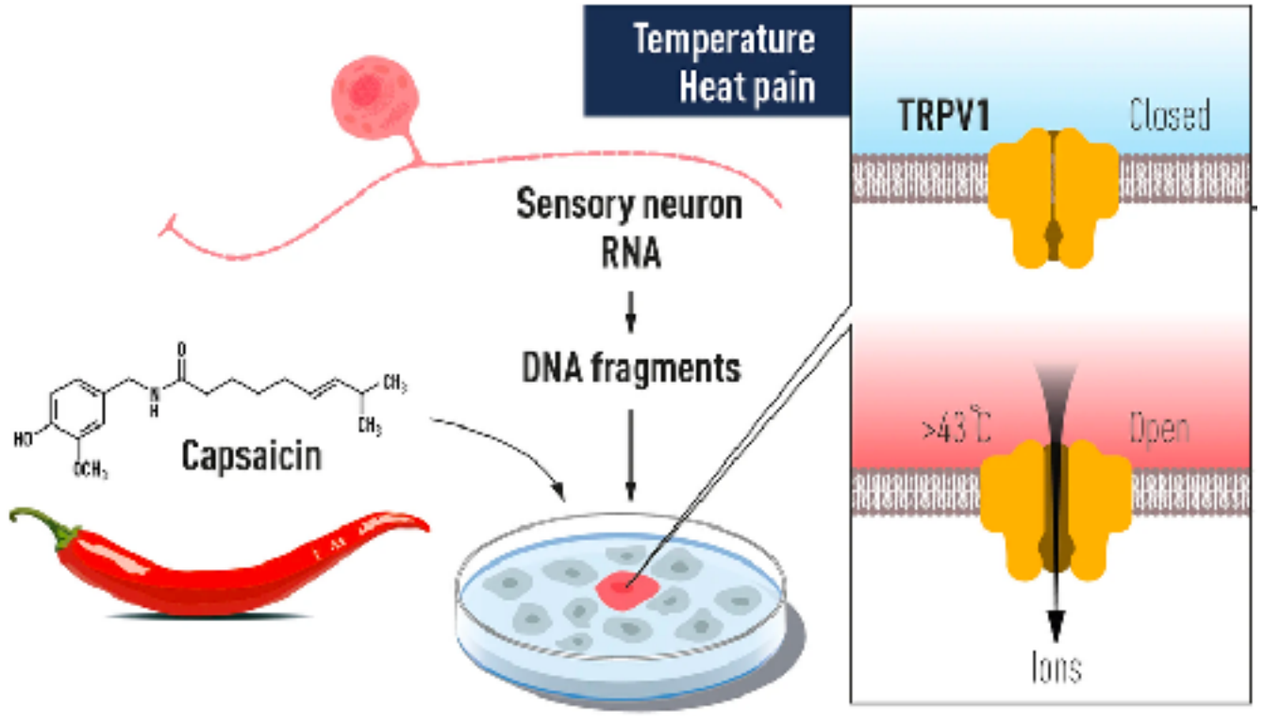
Nociceptive pain

Response to noxious stimuli

- Thermal
- Mechanical
- Chemical

First TRP channel identified in 1997

David Julius
University of California, San Francisco
Nobel Prize in Physiology or Medicine, 2021

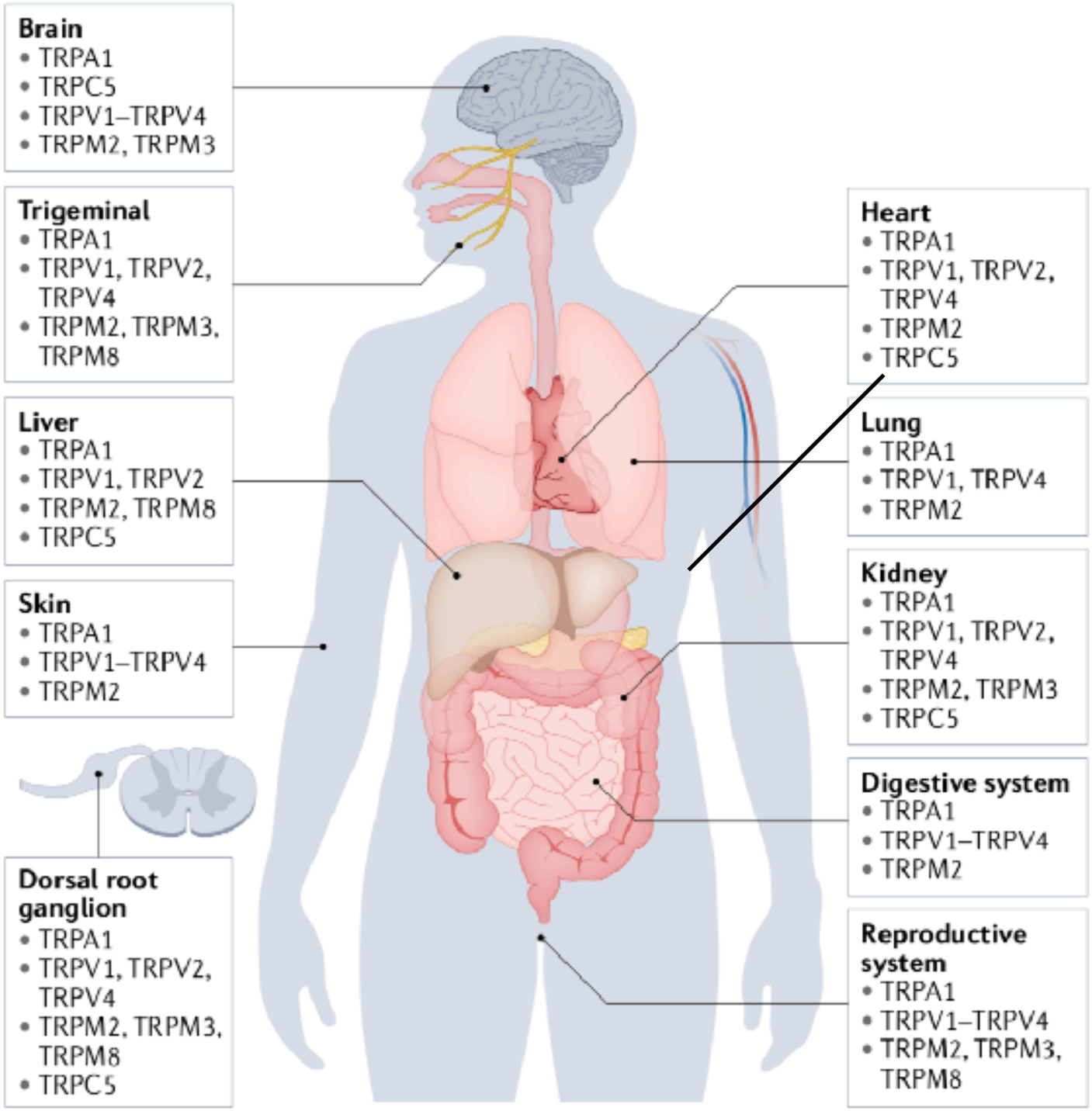


TRPV1
(Transient receptor potential vanillinoid 1)

Heat and chemical sensing

Caterina, M.J.; Schumacher, M.A.; Tominaga, M.; Rosen, T.A.; Levine J.D.; **Julius, D**. The capsaicin receptor: a heat-activated ion channel in the pain pathway. *Nature* **1997,** *389,* 816—824.

How do we feel pain?



Types of pain sensed:

- Mechanical
- Thermal
- Chemical
- Inflammatory
- Neuropathic

Detected temperature sensation:

- Warm
- Hot
- Cold

Rosenbaum, T.; Morales-Lázaro, S.L.; Islas, L.D. TRP channels: a journey towards a molecular understanding of pain. *Nat Rev Neurosci* **2022** *23*, 596–610.

What is pain?

Nociceptive pain

Response to noxious stimuli

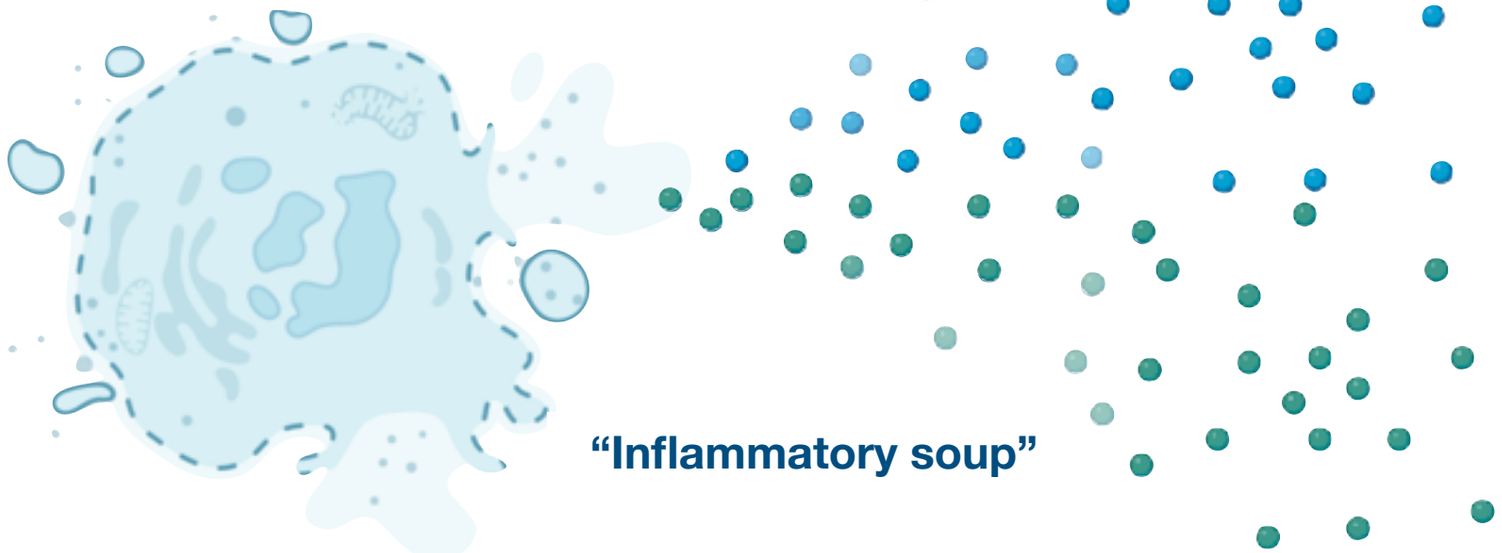
- Thermal
- Mechanical
- Chemical

Inflammatory pain

Caused by damage to body tissue

How do we feel pain?

Cell death



“Inflammatory soup”

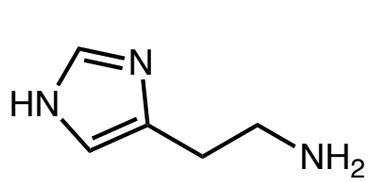
NGF
TNF-α
IL-1β

Cytokines

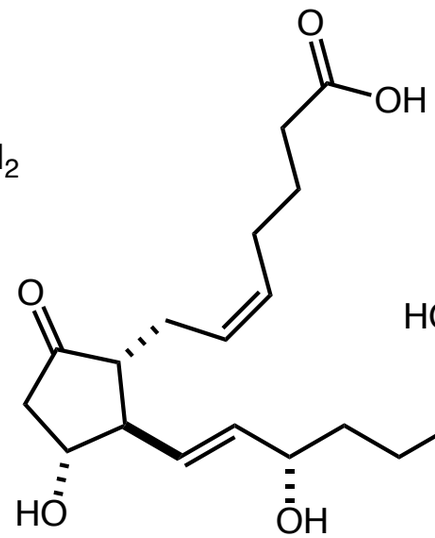
Substance P
CGRP
Bradykinin
Glutamate

Inflammatory peptides + neurotransmitters

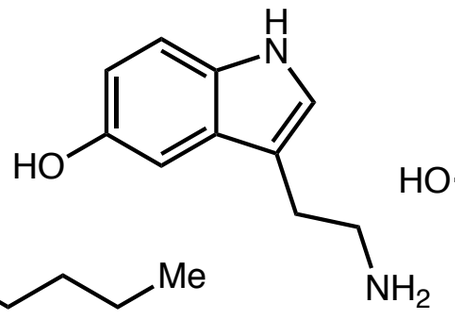
Histamine



Prostaglandins

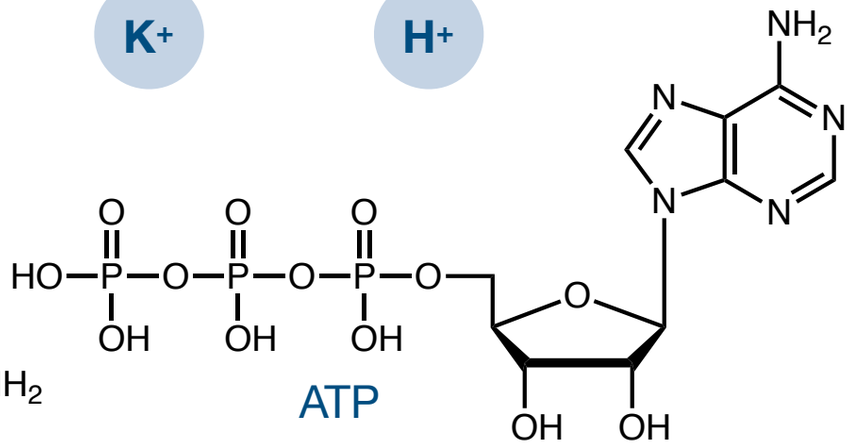


Serotonin

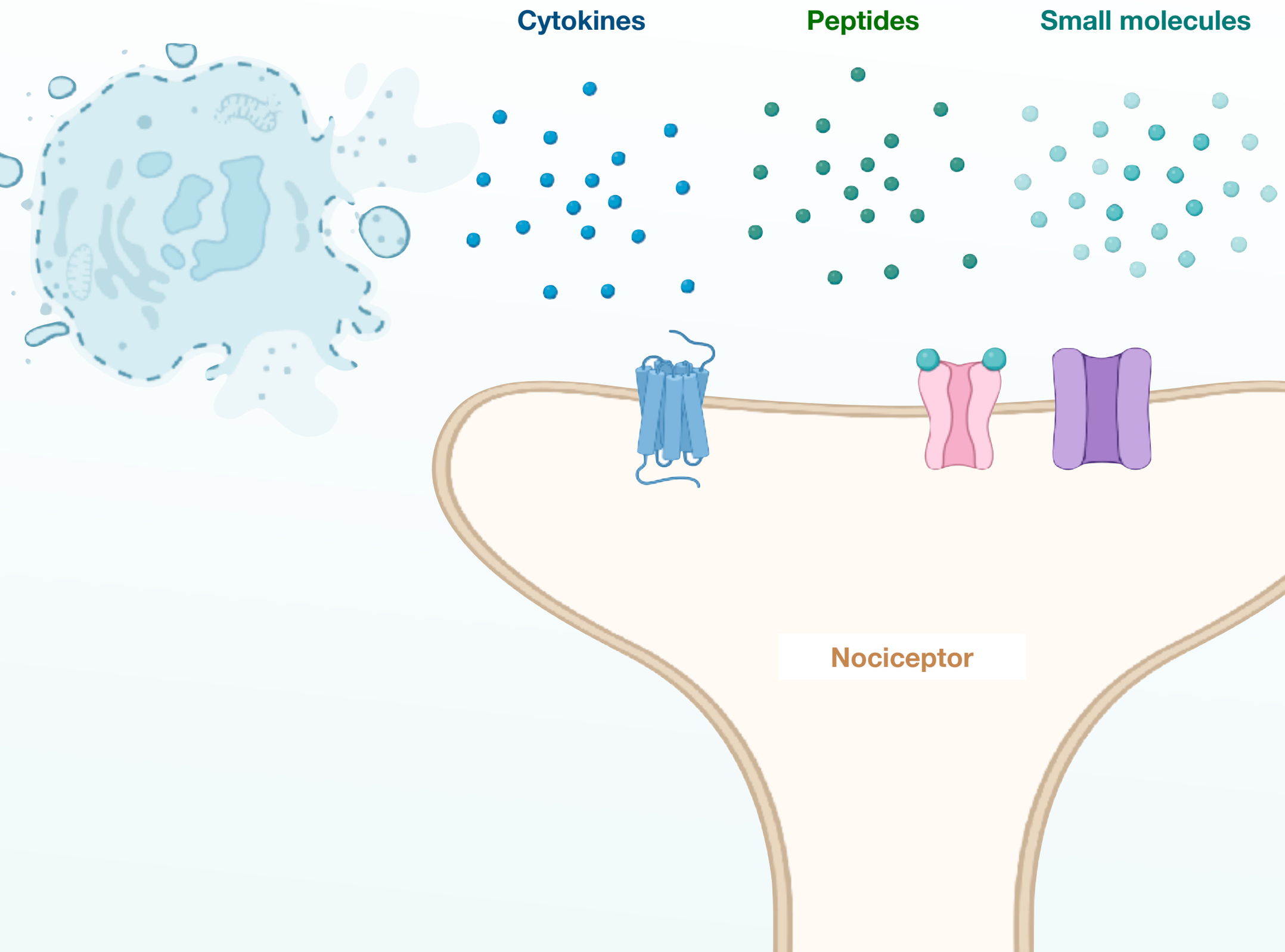


K^+ H^+

ATP



How do we feel pain?



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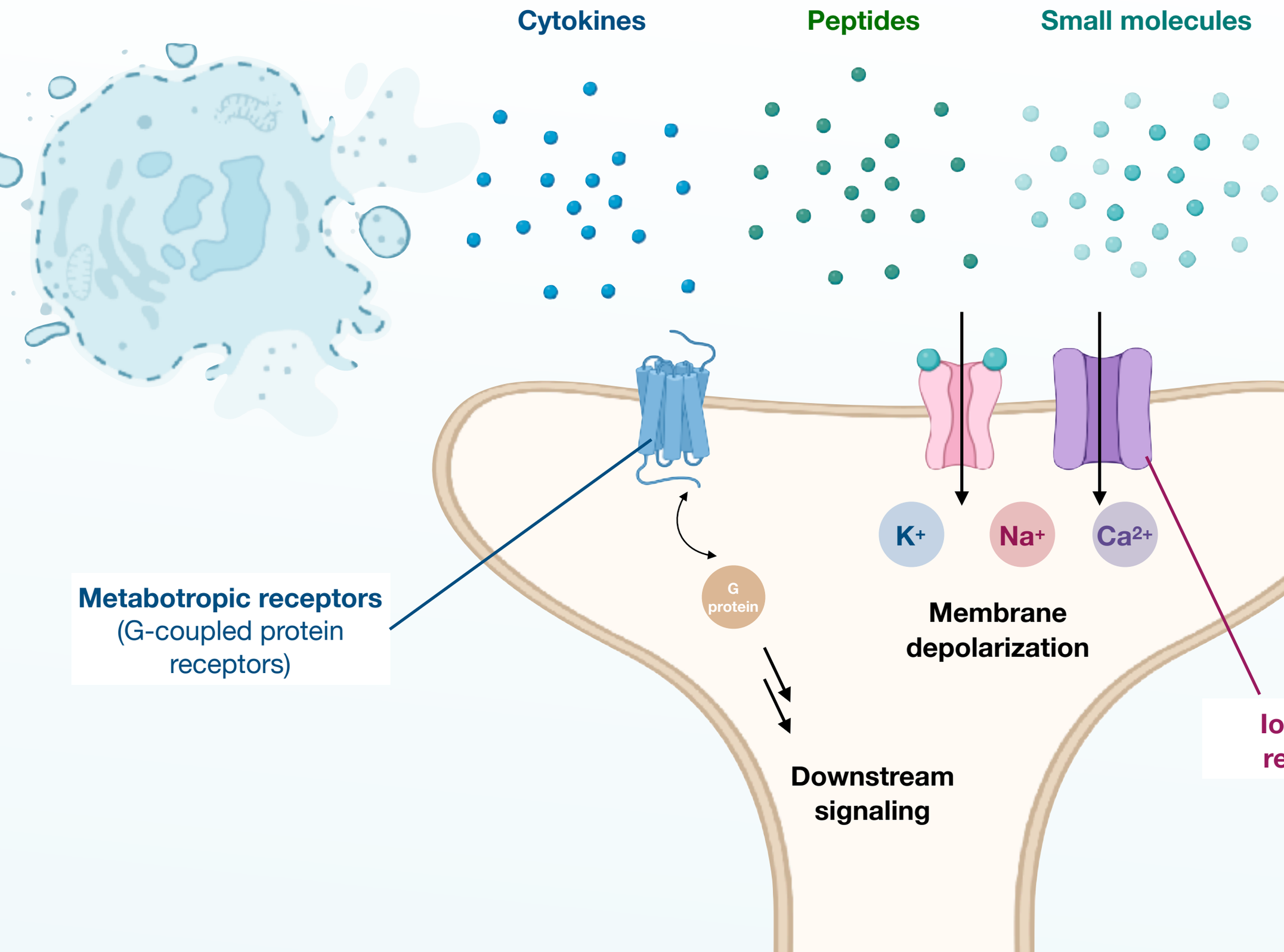
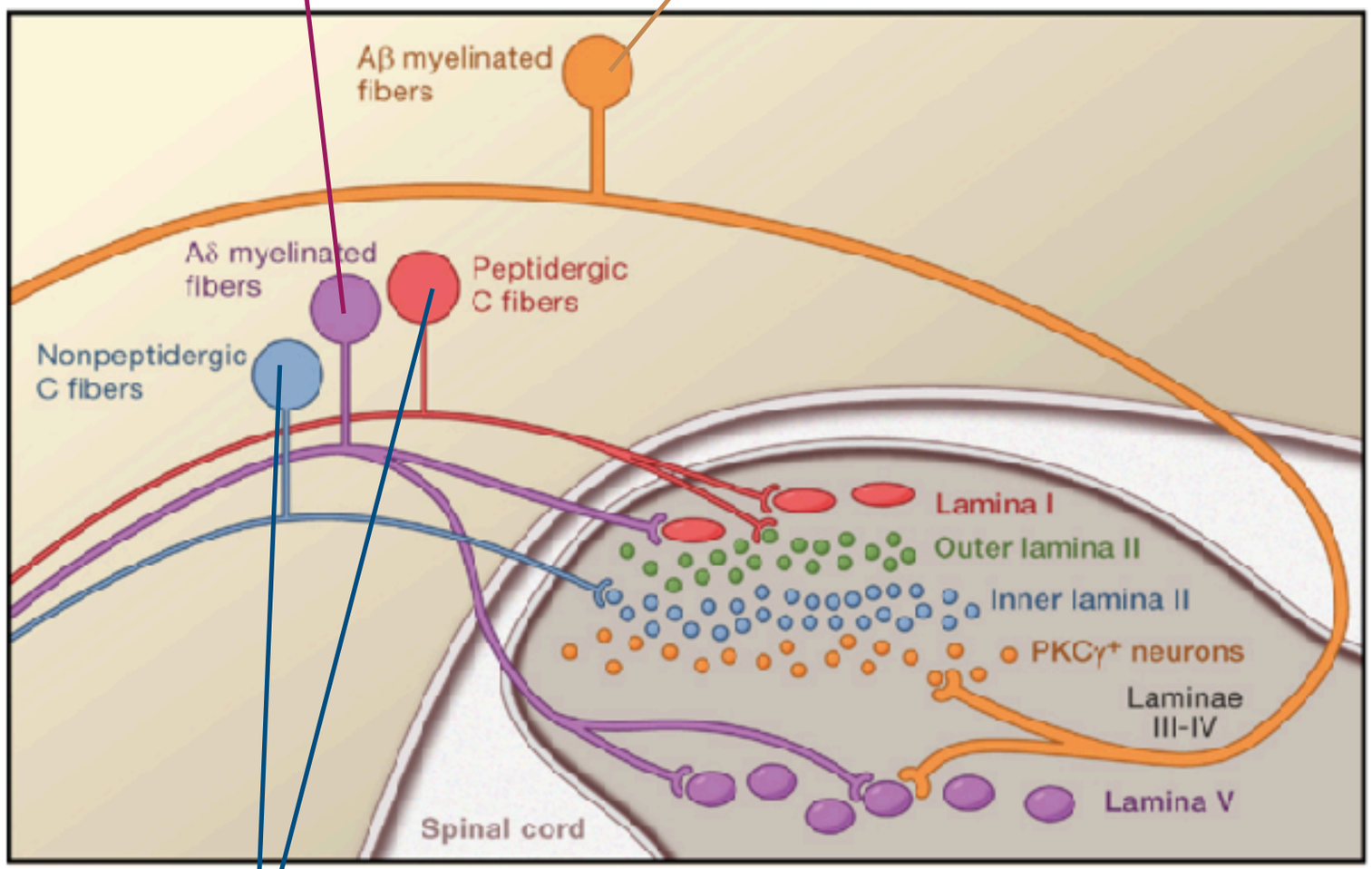


Classes of nociceptors

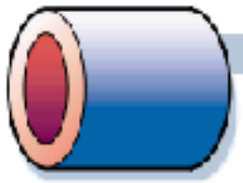
Acute, sharp pain

Touch and proprioception



Dull, throbbing pain

Primary afferent axons



Aα and Aβ fibres

Myelinated
Large diameter
Proprioception, light touch

Aδ Fibre

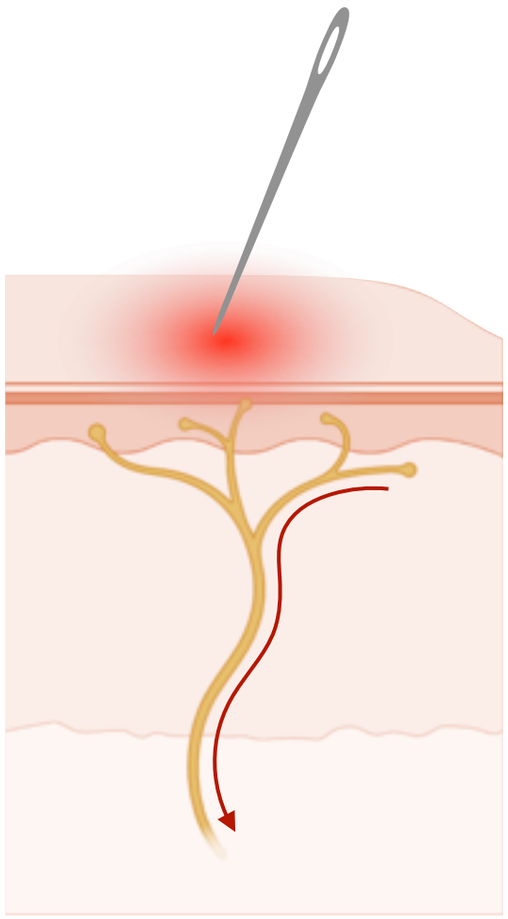
Lightly myelinated
Medium diameter
Nociception
(mechanical, thermal, chemical)

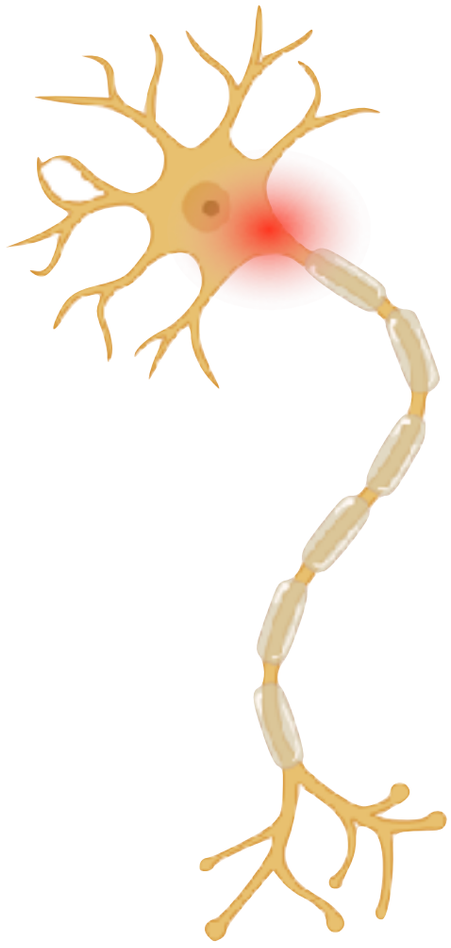
C fibre

Unmyelinated
Small diameter
Innocuous temperature, itch
Nociception
(mechanical, thermal, chemical)

How do we feel pain?

Nociceptive pain:
Stimuli causes pain signal



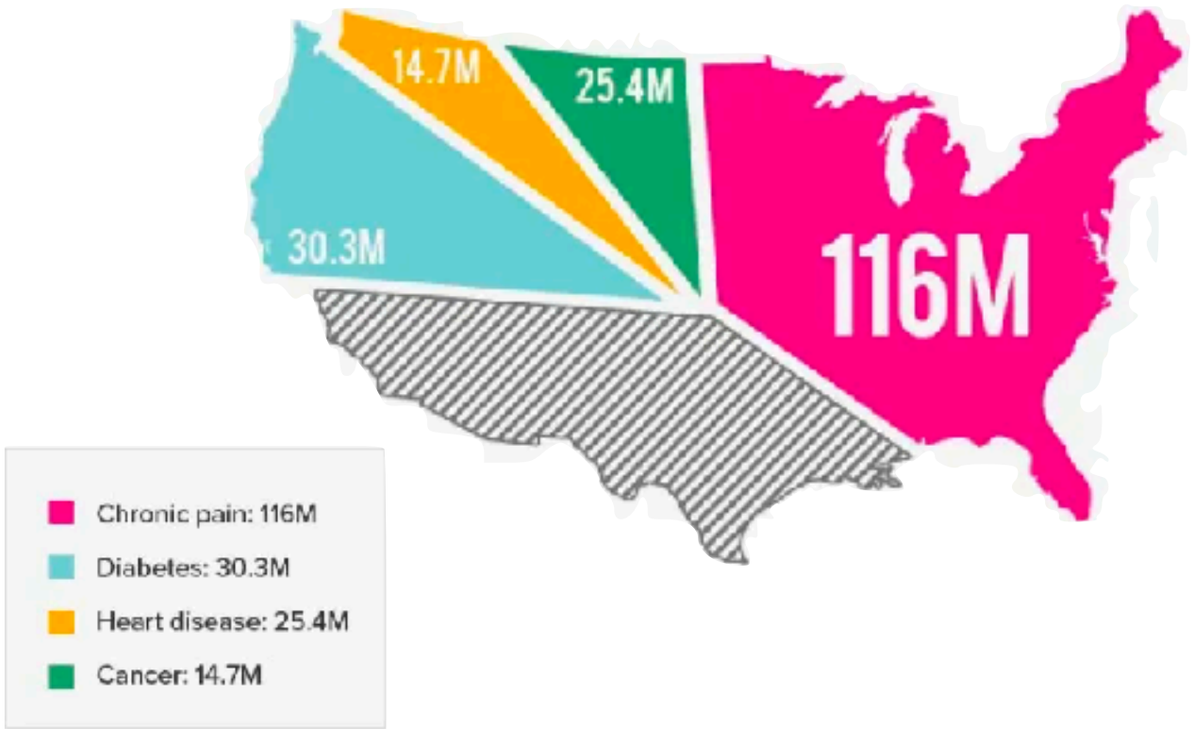


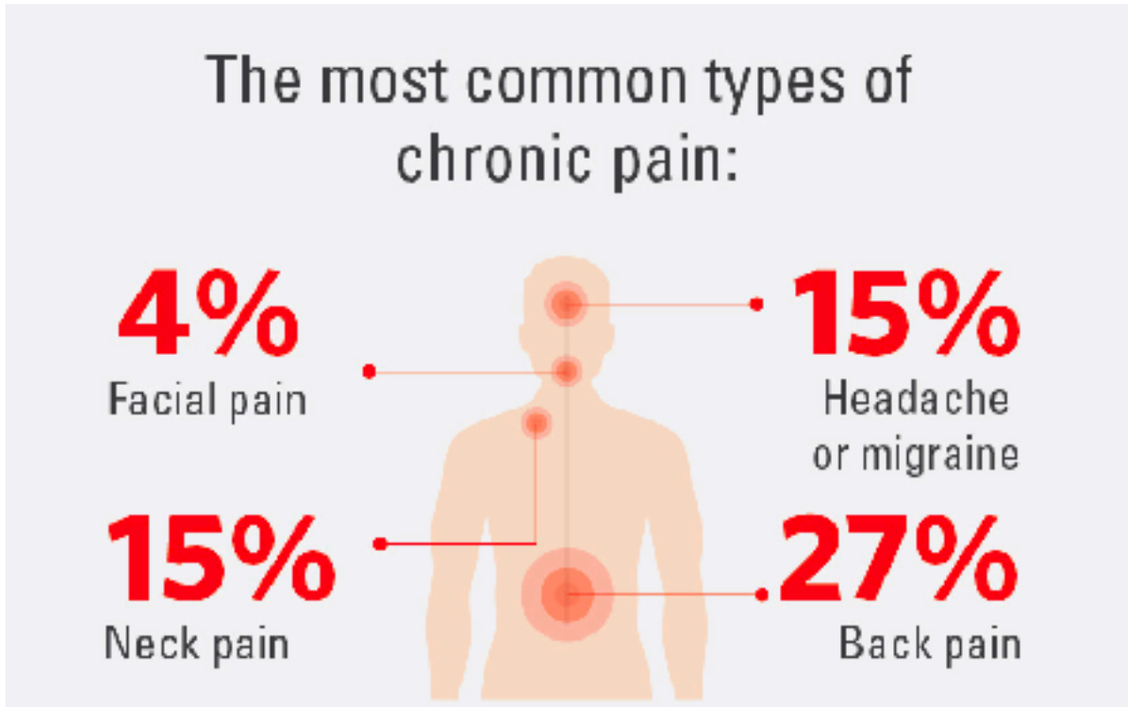
Neuropathic pain

Damage to nerve results in pain signals being sent without stimuli

Commonly caused by:
Injury
Multiple sclerosis
Diabetes
Cancer

The pain problem



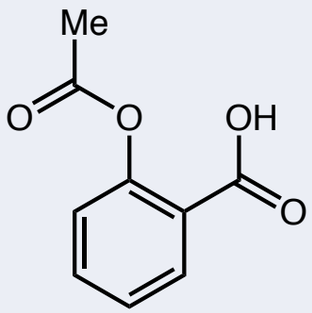


$635 billion of treatment cost and lost productivity annually

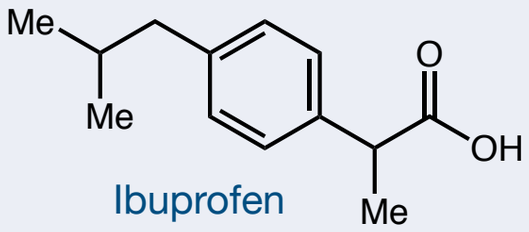
Yong, R.J.; Mullins, P.M. Bhattacharyya, N. The prevalence of chronic pain among adults in the United States. *Pain*, **2021**

Current state of pain medication

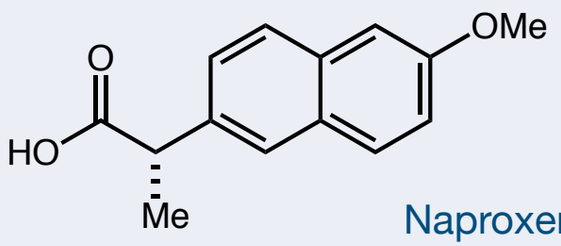
Non-steroidal anti-inflammatory drugs (NSAIDs)



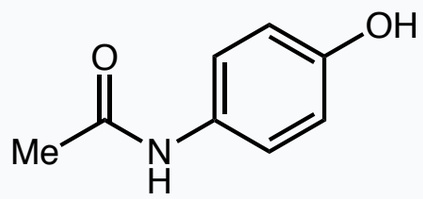
Aspirin



Ibuprofen

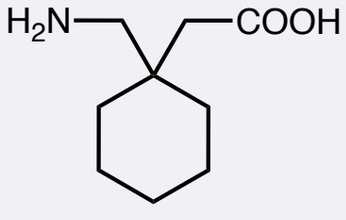


Naproxen



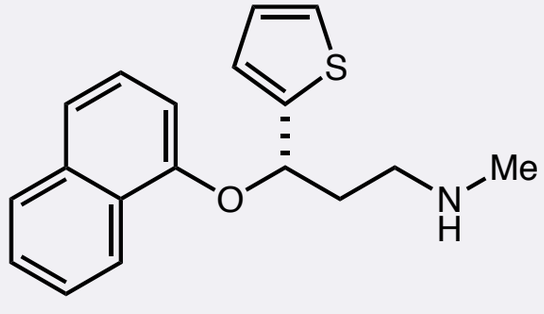
Acetaminophen

Anticonvulsants



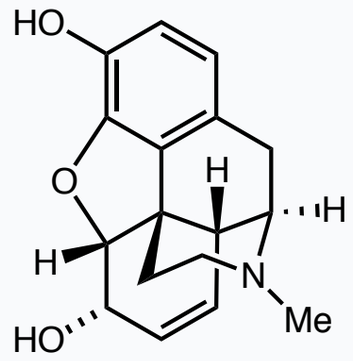
Gabapentin

Antidepressants

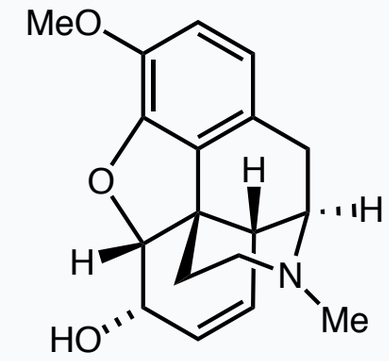


Duloxetine

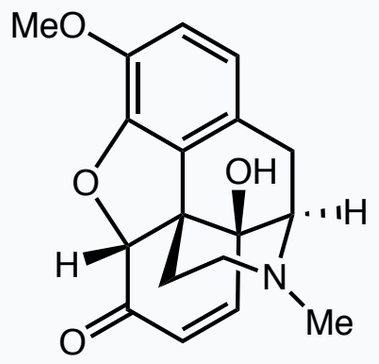
Opioids



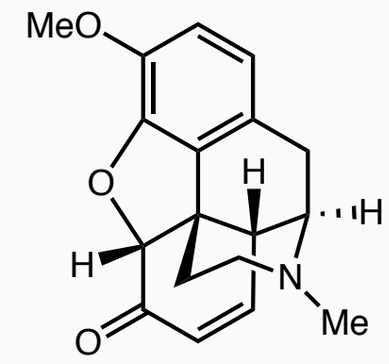
Morphine



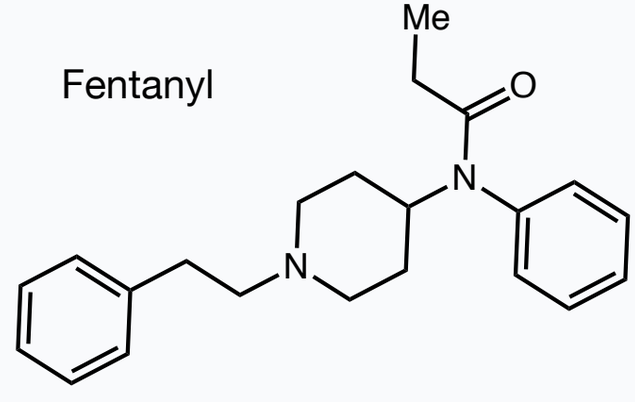
Codeine



Oxycodone



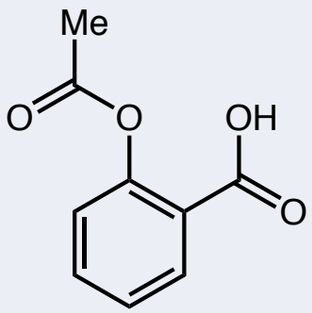
Hydrocodone



Fentanyl

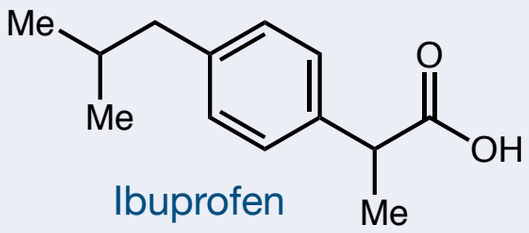
Current state of pain medication

Non-steroidal anti-inflammatory drugs (NSAIDs)



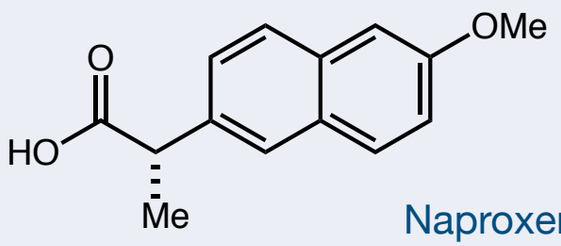
Aspirin

1897



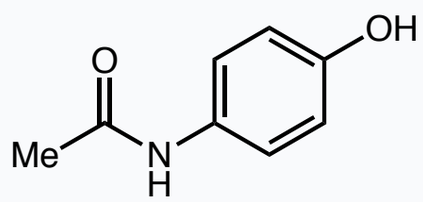
Ibuprofen

1961



Naproxen

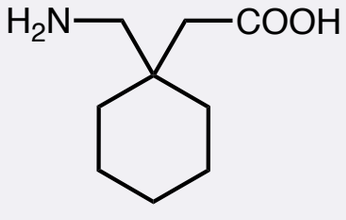
1976



Acetaminophen

1878

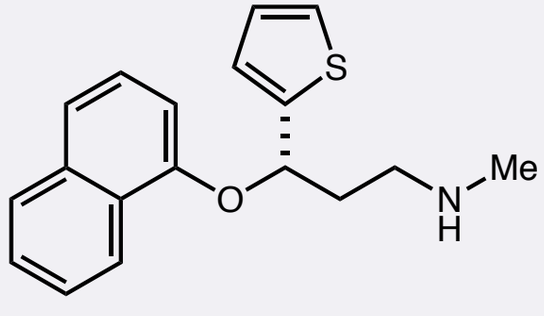
Anticonvulsants



Gabapentin

1993

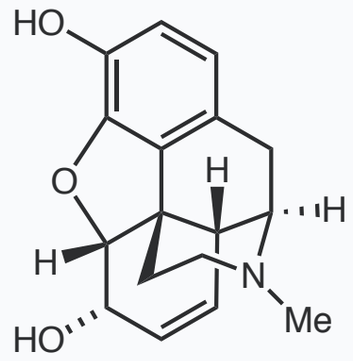
Antidepressants



Duloxetine

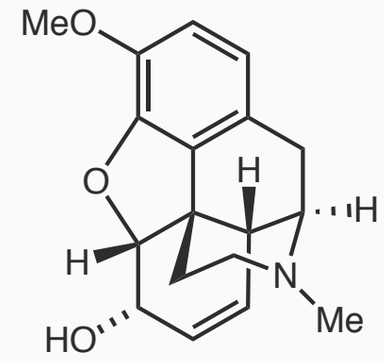
1993

Opioids



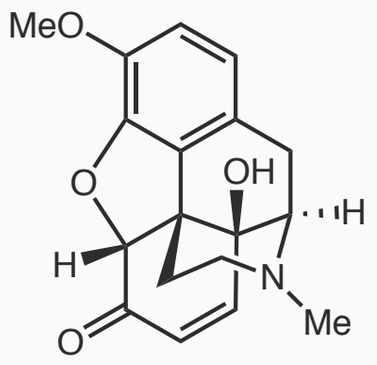
Morphine

“1804”



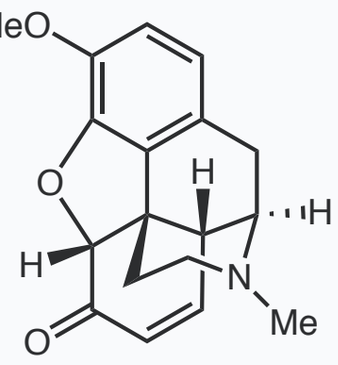
Codeine

“1813”



Oxycodone

1916

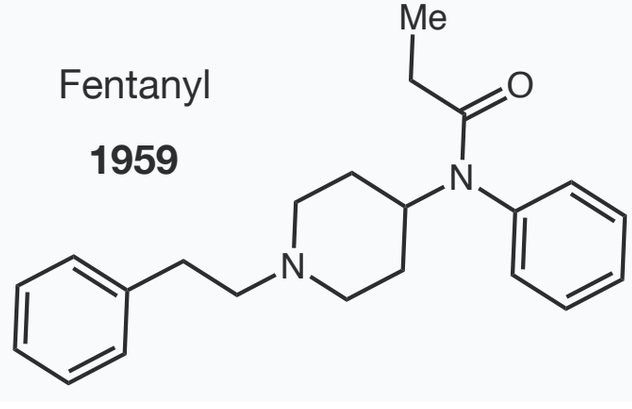


Hydrocodone

1920

Fentanyl

1959



Current state of pain medication

"After 100 years of pain research—old scaffolds, minor improvements?"

ELSEVIER

Bioorganic & Medicinal Chemistry Letters

Volume 26, Issue 4, 15 February 2016, Pages 1103-1119

Digest paper

New approaches to treating pain

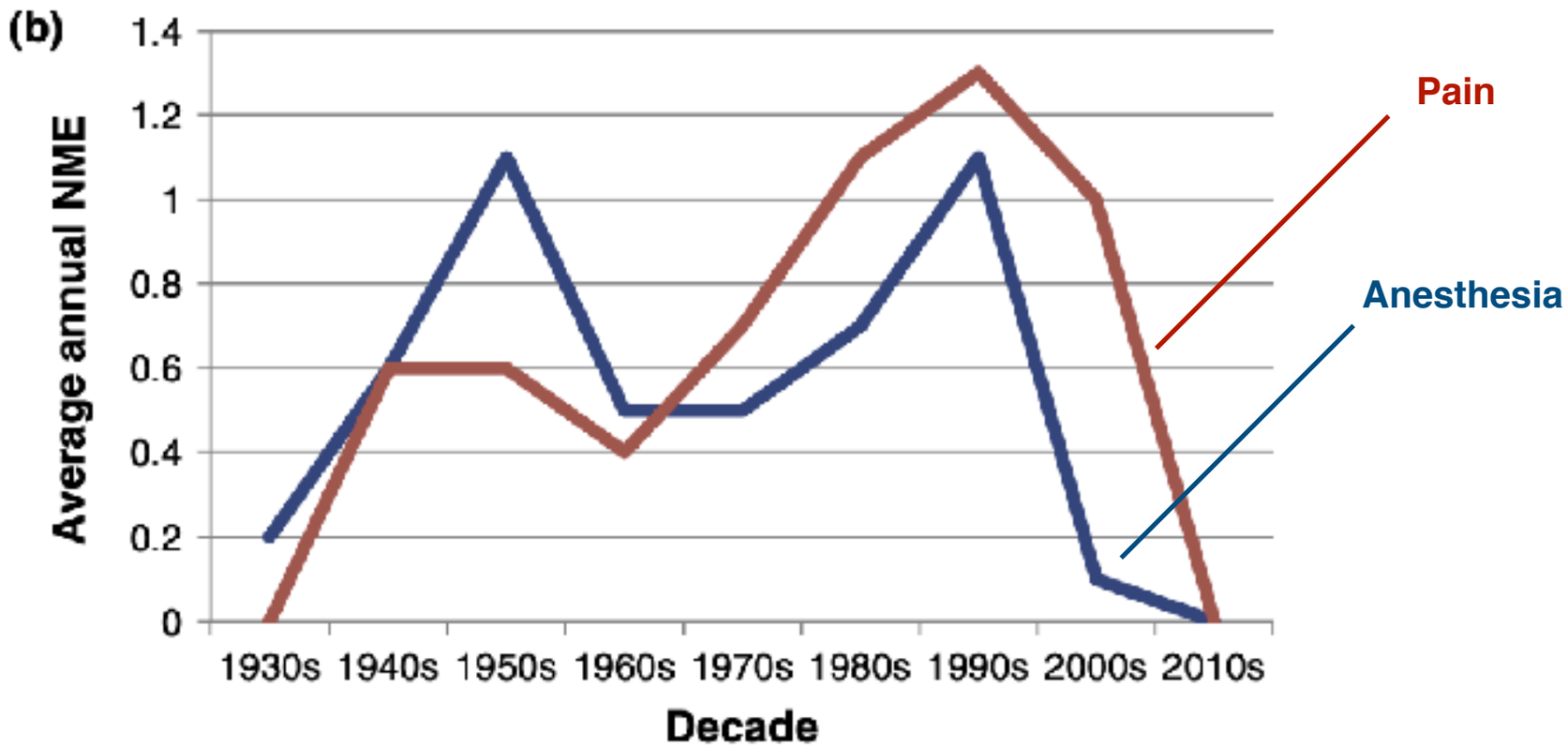
Andrea Wolkerstorfer [a], Norbert Handler [a], Helmut Buschmann [b]

"In recent years, efforts to identify novel analgesic agents has been disappointing."

Wolkerstorfer, A.; Handler, N. Buschmann, New approaches to treating pain. *Bioorg. Med. Chem. Lett*, **2016**, *26,* 1103–1119.

Current state of pain medication

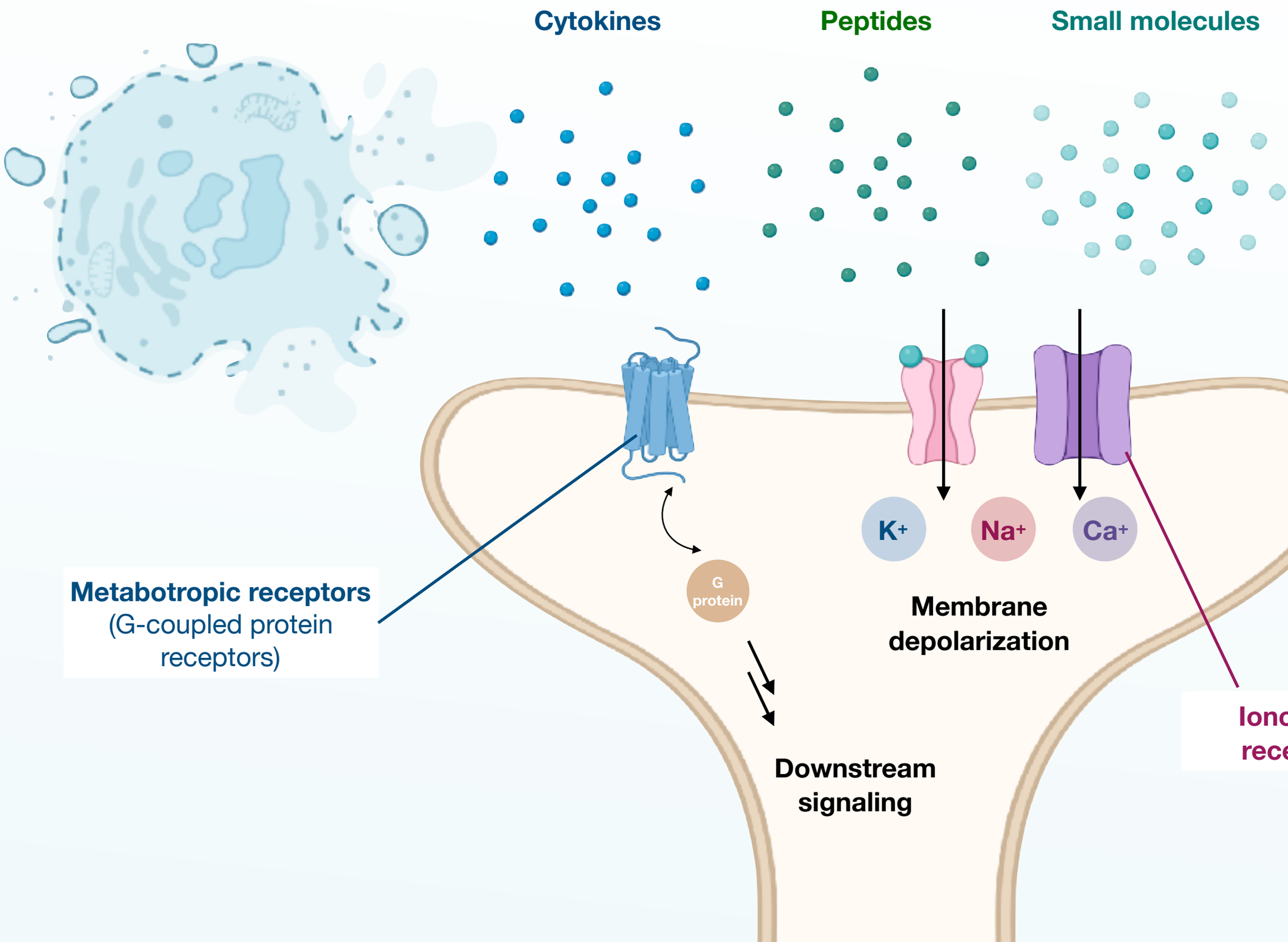
"After 100 years of pain research—old scaffolds, minor improvements?"



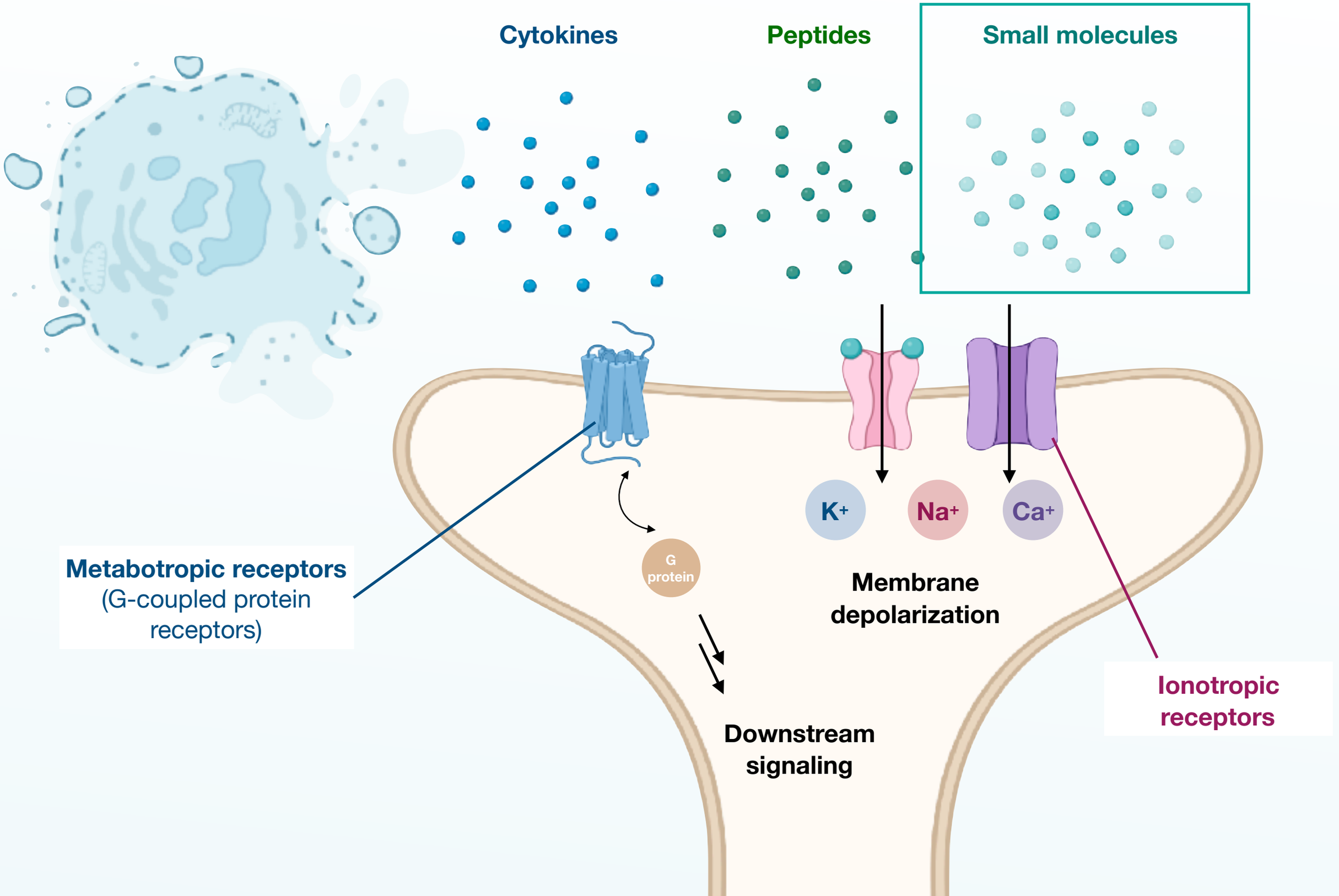
"In recent years, efforts to identify novel analgesic agents has been disappointing."

Kinch, S.K. An overview of FDA-approved new molecular entities. *Drug Discov. Today*, **2015**, *20,* 3–6.

Targets for pain relief



Targets for pain relief

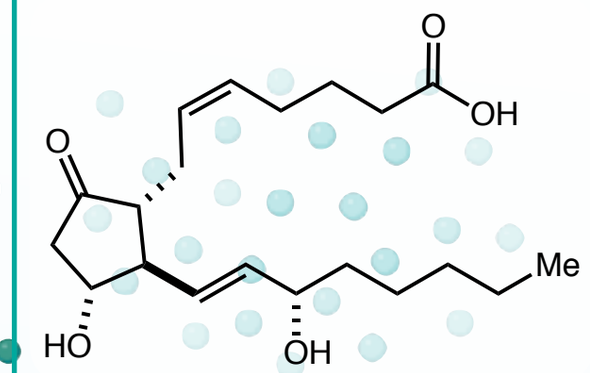


Targets for pain relief

Cytokines

Peptides

Small molecules



Metabotropic receptors
(G-coupled protein receptors)

G protein

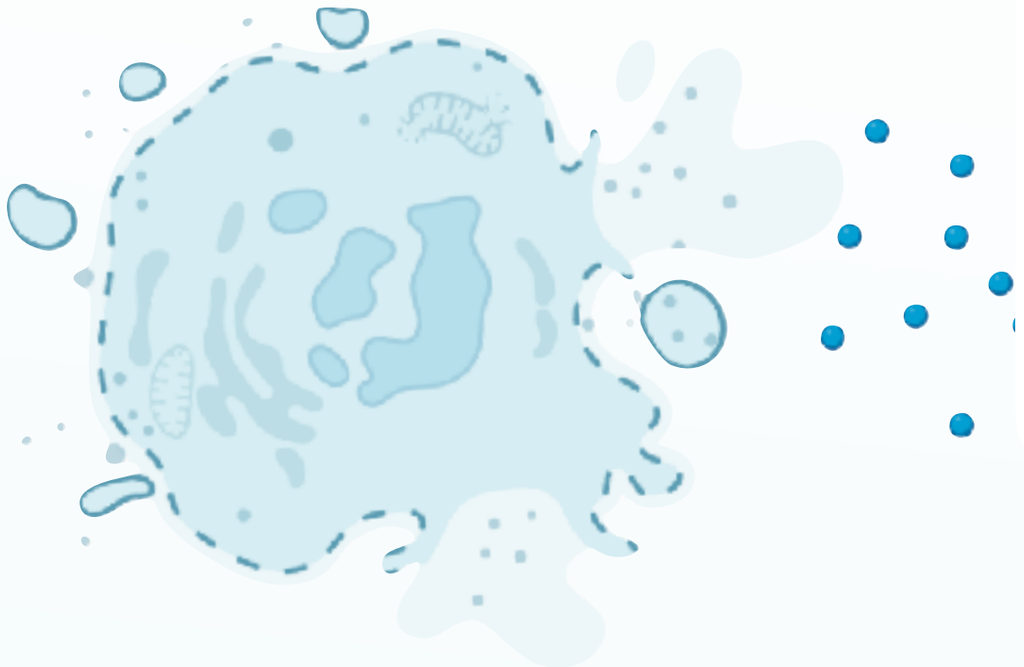
K^+ Na^+ Ca^+

Membrane depolarization

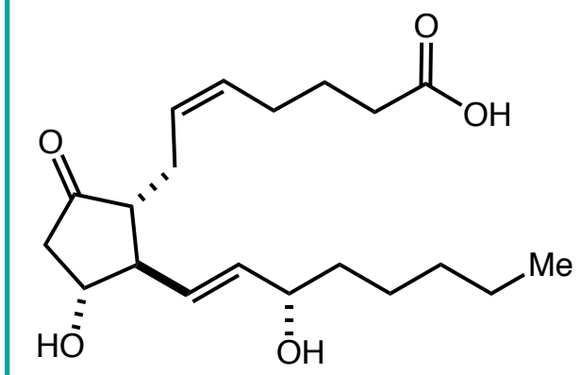
Downstream signaling

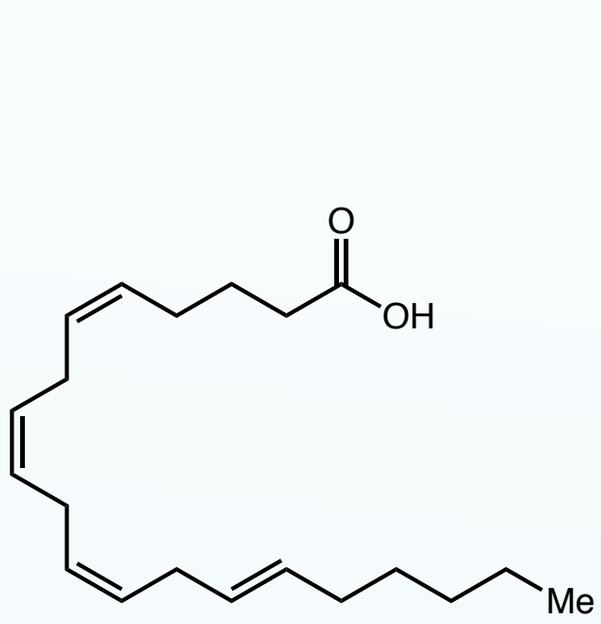
Ionotropic receptors

Targets for pain relief



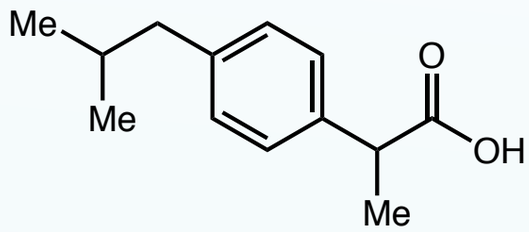
Prostaglandin E_2





Arachidonic acid

X **Cyclooxygenase (COX) enzymes**

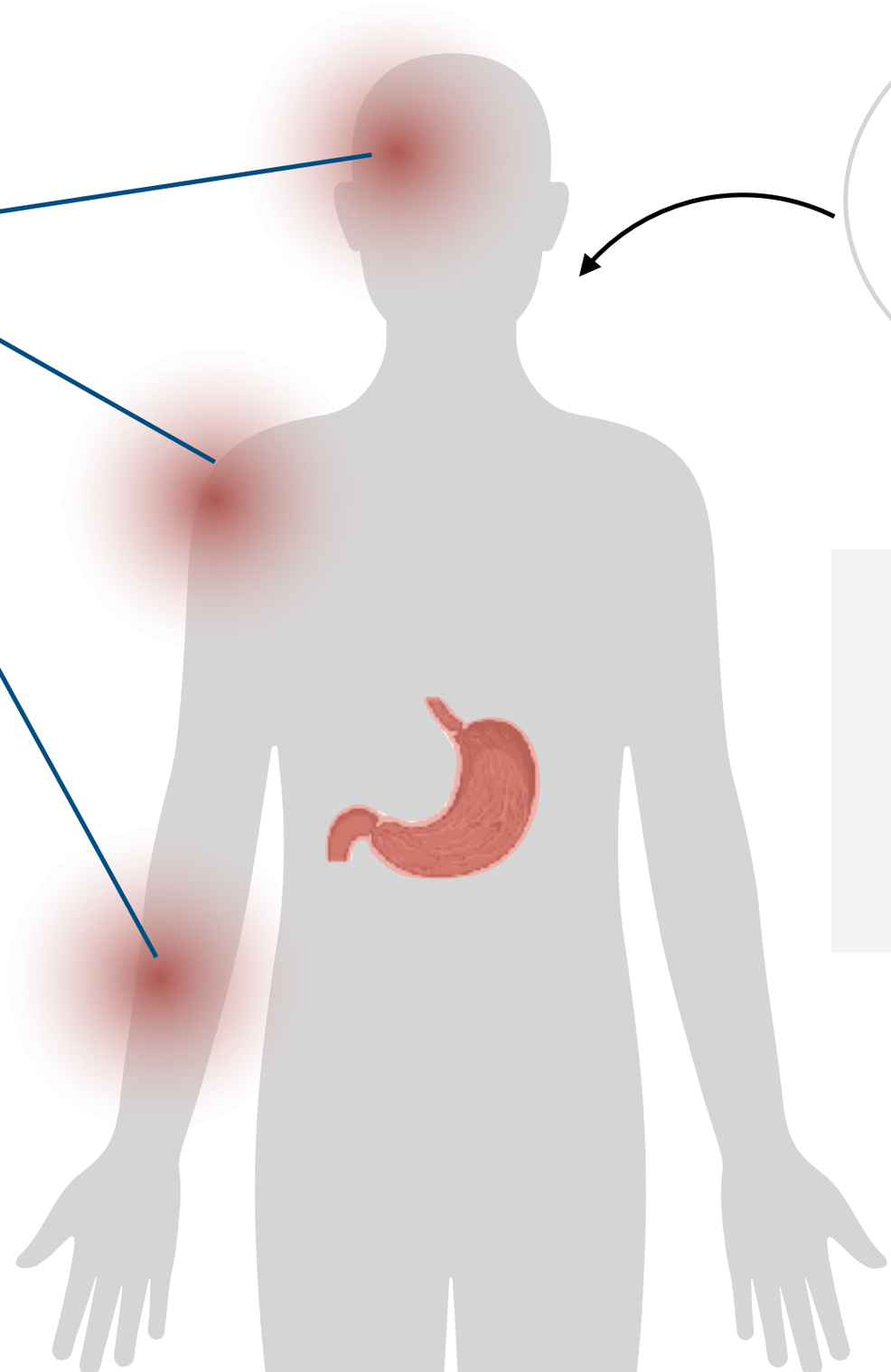


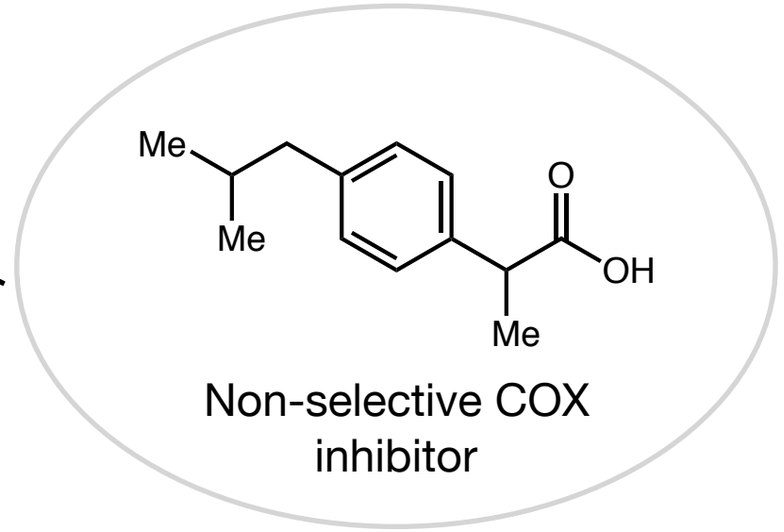
Ibuprofen

NSAIDs

COX-2

Expression induced in sites of inflammation





Non-selective COX inhibitor

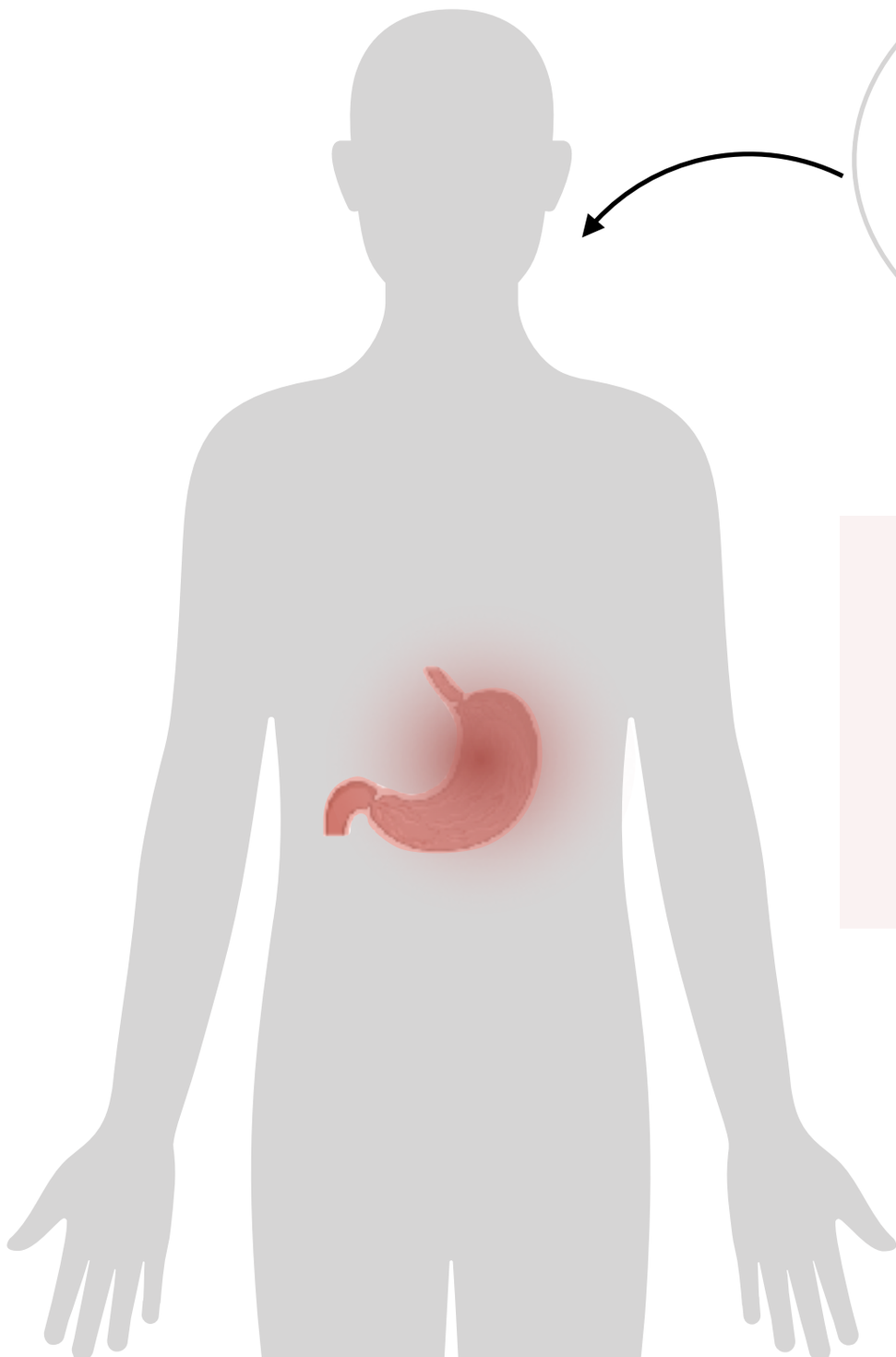
COX-1

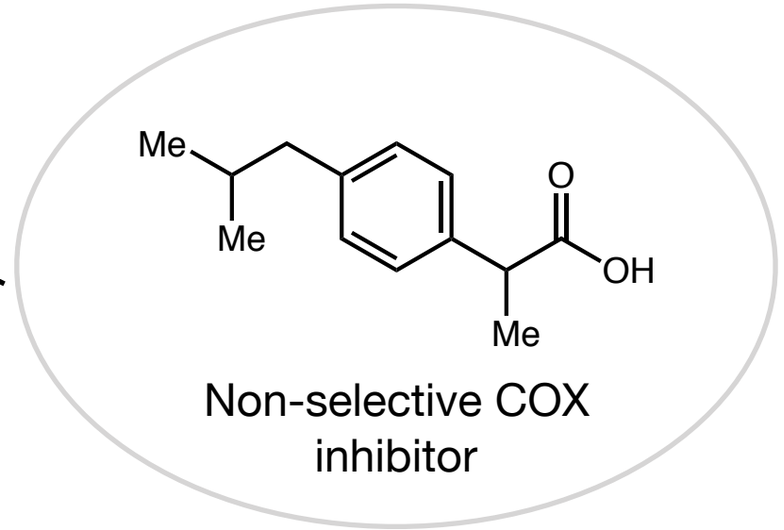
- Expressed evenly throughout body tissue
- “Housekeeping” roles include maintaining stomach mucosa

NSAIDs

COX-2 inhbited

Pain reduced





Non-selective COX inhibitor

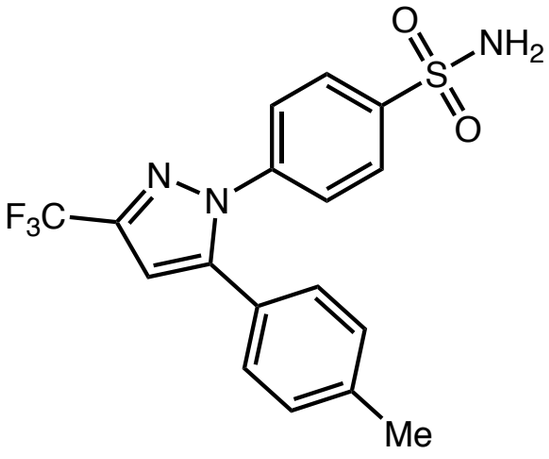
COX-1 inhibited

Gastrointestinal side effects

Ulcers, acid reflux

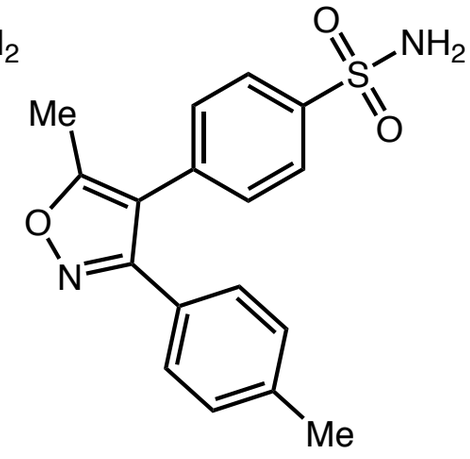
Renal dysfunction

Selective COX-2 inhibitors



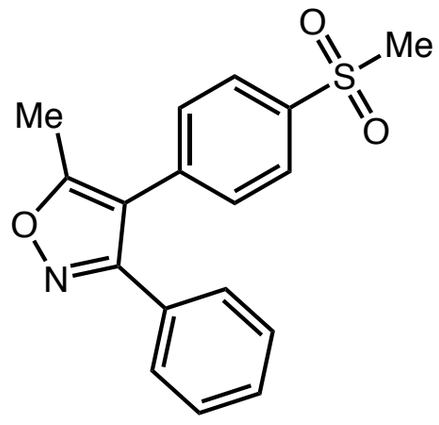
Celecoxib

Approved 1998



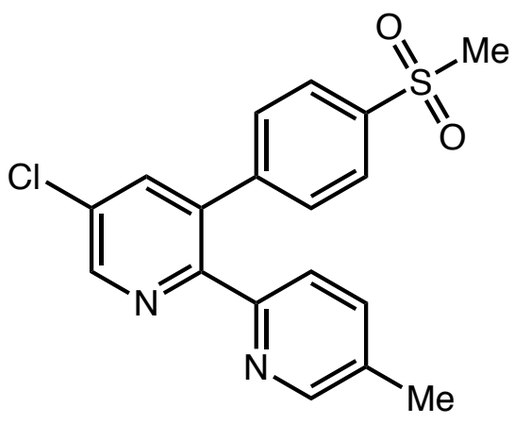
Rofecoxib

Approved 1999



Valdecoxib

Approved 2001



Etoricoxib

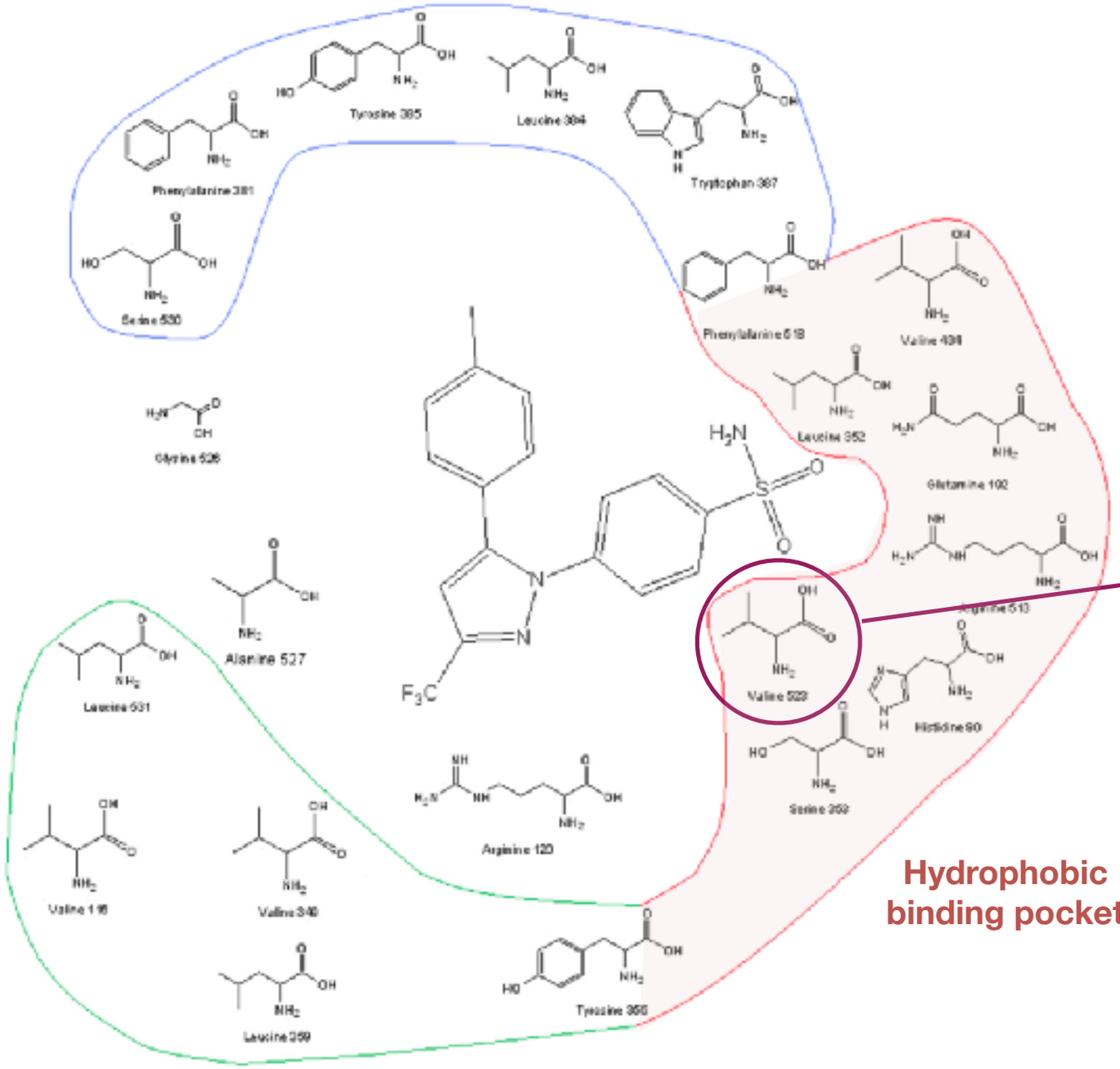
Approved 2002*

COX-2/COX-1 selectivity	**30**	**272**	**61**	**344**

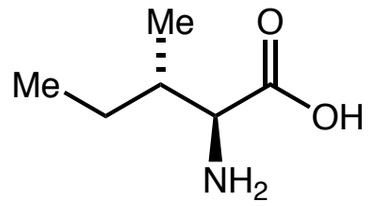
Values for non-selective NSAIDS:	**Naproxen**	**Ibuprofen**	**Aspirin**
	0.7	1.5	0.007

Birmingham, B.; Buvanendran, A. Nonsteroidal Anti-inflammatory Drugs, Acetaminophen, and COX-2 Inhibitors. *Practical Management of Pain* **2014** *553–568.*

Selective COX-2 inhibitors

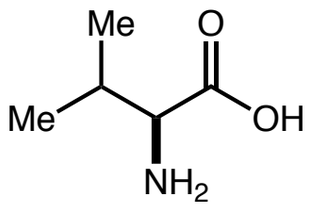


COX-1



Ile-523

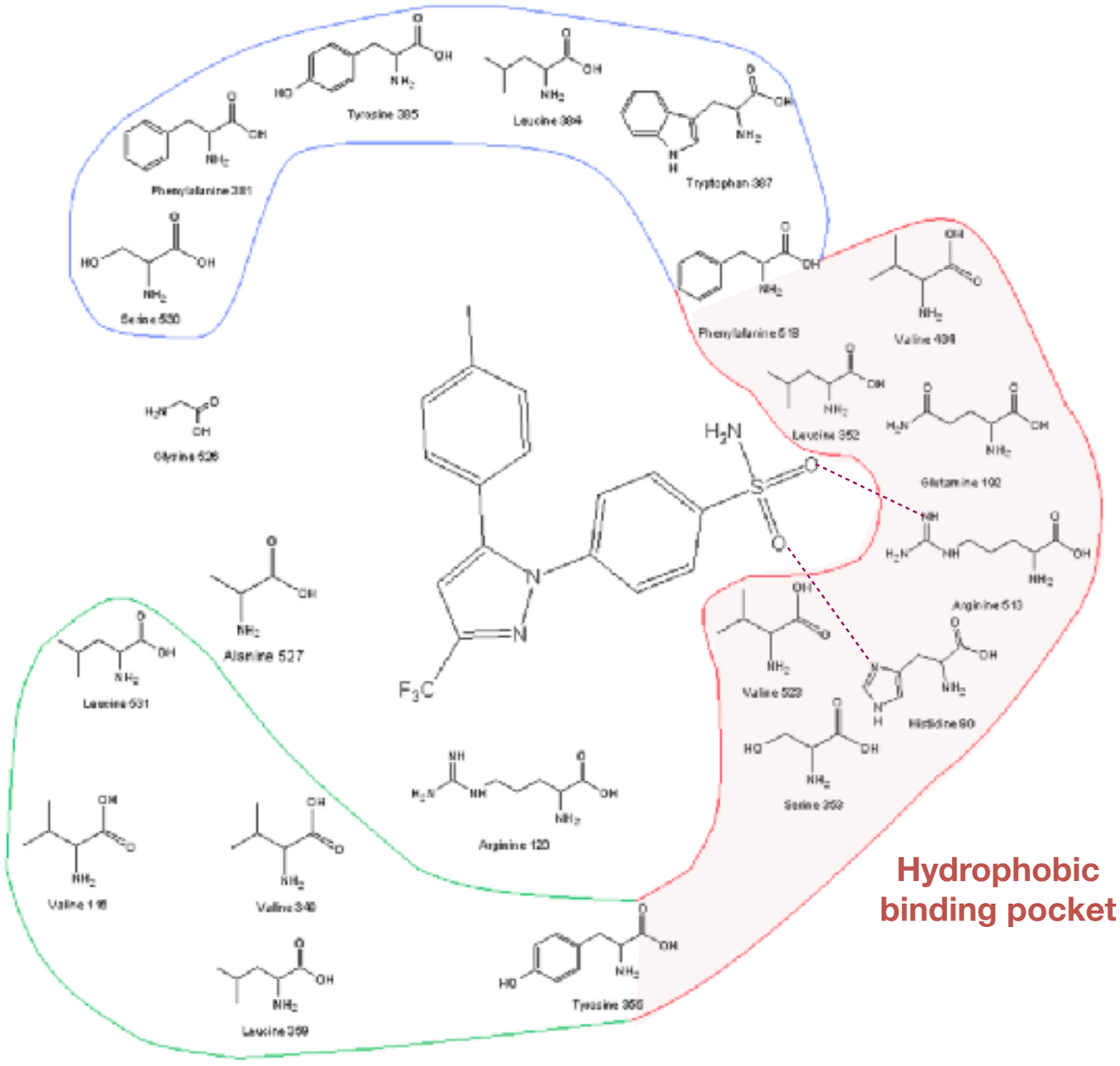
COX-2



Val-523

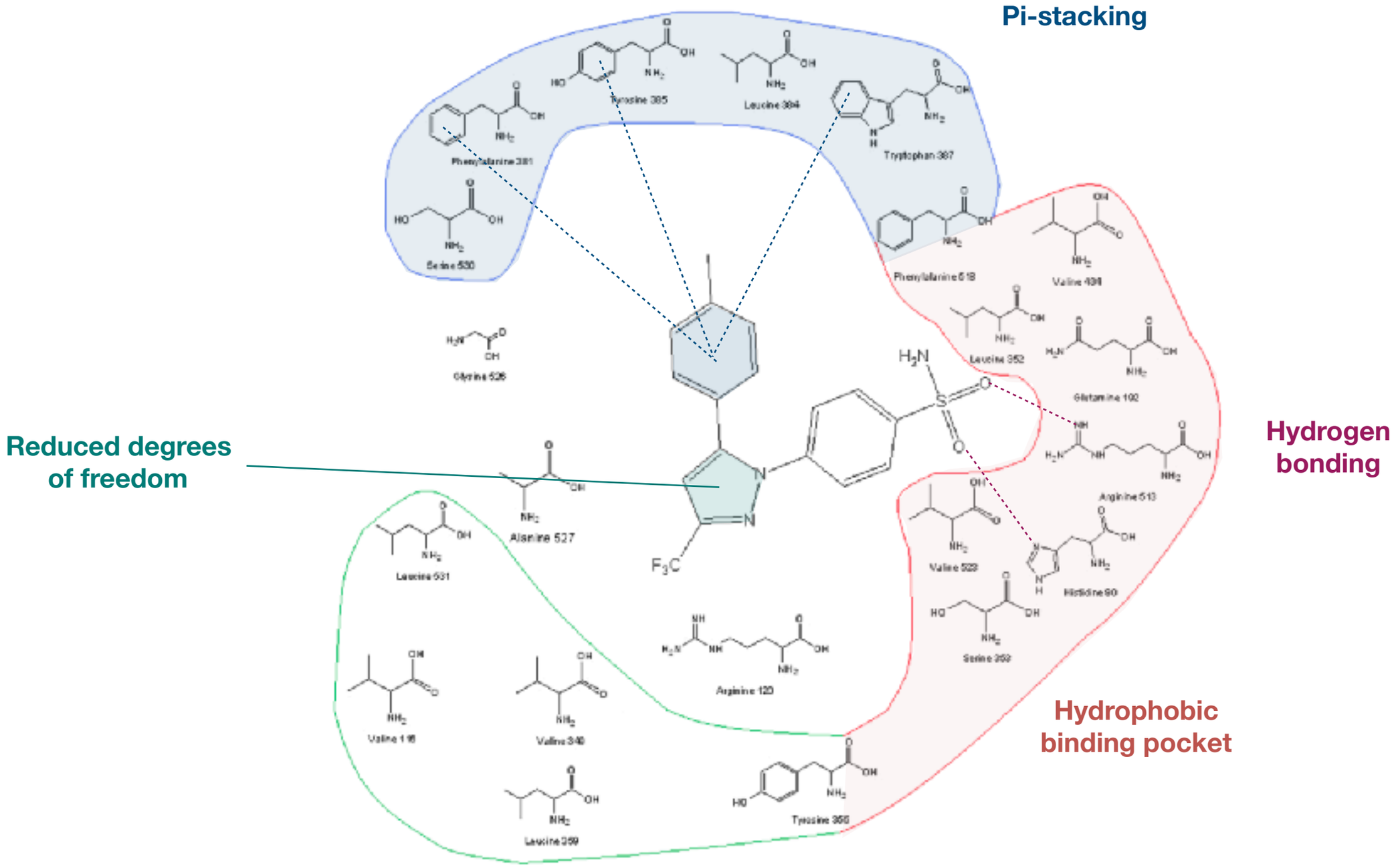
Llorens, O; Perez, J. J.; Palomer, A; Mauleon, D. Structural basis of the dynamic mechanism of ligand binding to cyclooxygenase. **1999,** *Bioorg. Med. Chem. Lett. 9,* 2779–2784.

Selective COX-2 inhibitors



Llorens, O; Perez, J. J.; Palomer, A; Mauleon, D. Structural basis of the dynamic mechanism of ligand binding to cyclooxygenase. **1999,** *Bioorg. Med. Chem. Lett. 9,* 2779–2784.

Selective COX-2 inhibitors

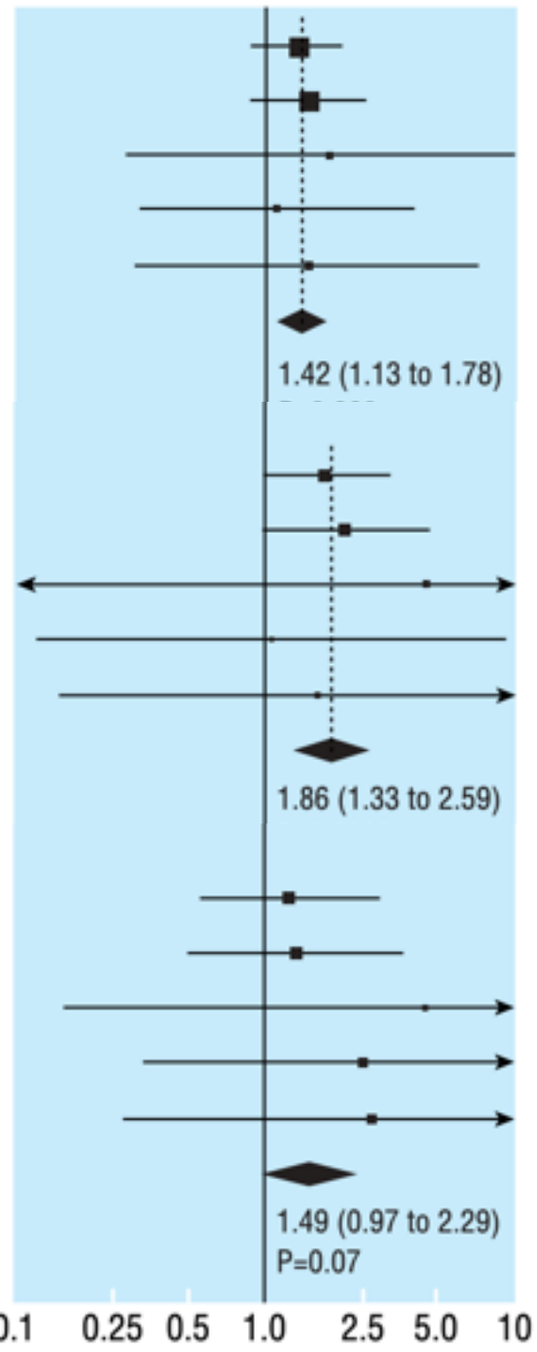


Llorens, O; Perez, J. J.; Palomer, A; Mauleon, D. Structural basis of the dynamic mechanism of ligand binding to cyclooxygenase. **1999,** *Bioorg. Med. Chem. Lett. 9,* 2779–2784.

Selective COX-2 inhibitors

COX 2 inhibitor	No of trials	Events/person years: Allocated COX 2 inhibitor	Events/person years: Allocated placebo
Vascular events			
Rofecoxib	37	98/6638	72/6415
Celecoxib	41	84/8976	29/4953
Etoricoxib	17	7/753	2/414
Lumiracoxib	12	14/1375	6/584
Valdecoxib	14	13/748	3/273
Subtotal	121	216/18 490	112/12 639
		(1.2%/year)	(0.9%/year)
Myocardial infarction			
Rofecoxib	37	54/6638	30/6415
Celecoxib	41	44/8976	9/4953
Etoricoxib	17	2/753	0/414
Lumiracoxib	12	5/1375	2/584
Valdecoxib	14	8/748	1/273
Subtotal	121	113/18 490	42/12 639
		(0.6%/year)	(0.3%/year)
Vascular death			
Rofecoxib	37	22/6638	19/6415
Celecoxib	41	23/8976	9/4953
Etoricoxib	17	3/753	0/414
Lumiracoxib	12	6/1375	1/584
Valdecoxib	14	6/748	1/273
Subtotal	121	60/18 490	30/12 639
		(0.3%/year)	(0.2%/year)

Heterogeneity between five drugs: χ^2=2.0, df=4, P=0.7



Conclusion:

"Selective COX 2 inhibitors are associated with a moderately increased risk of vascular events, largely attributable to a twofold increased risk of myocardial infarction."

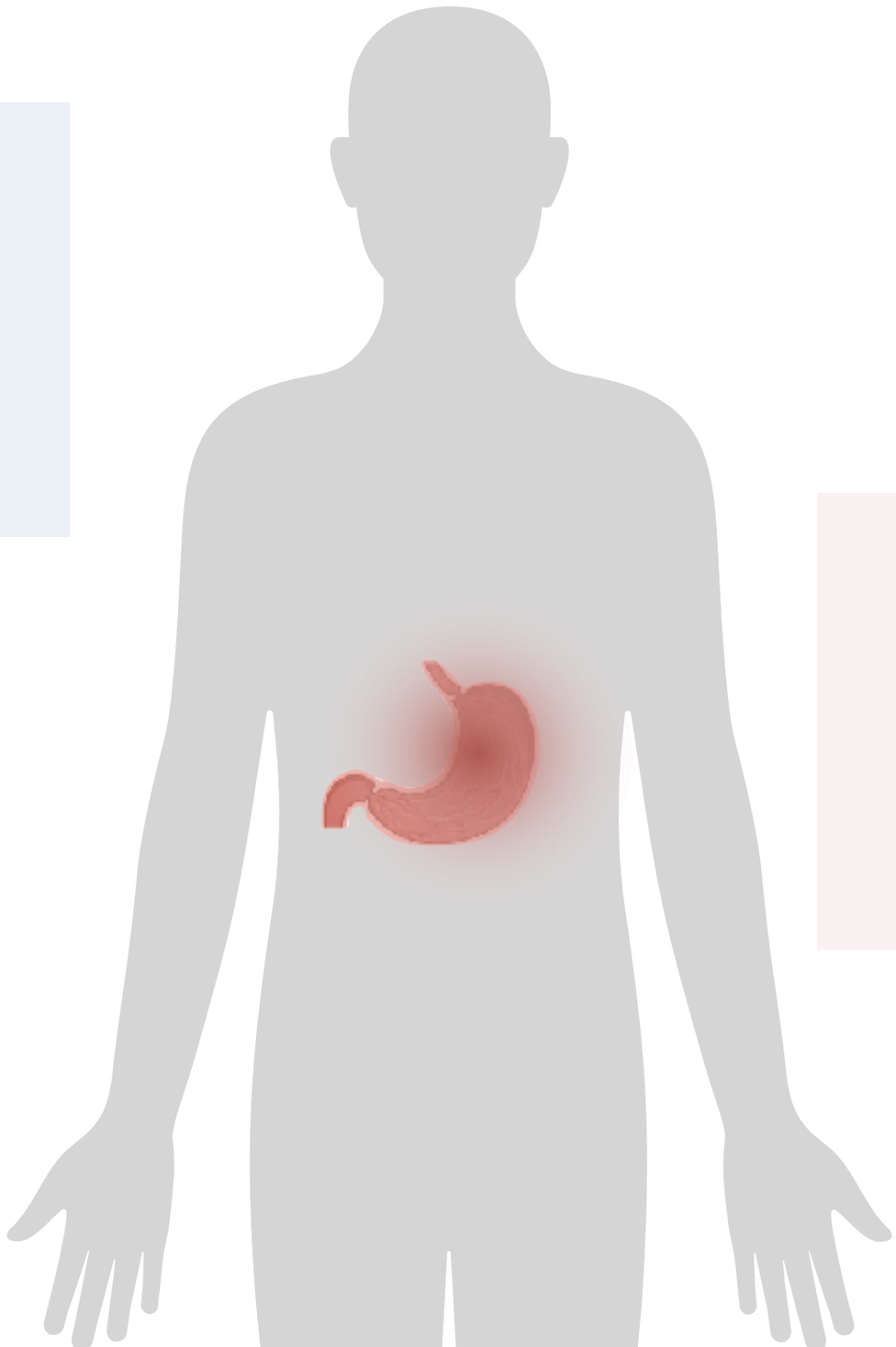
Kearney P. M.; Baigent, C.; Godwin, J.; Halls, H.; Emberson, J.R.; Patrono, C. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. *BMJ,* **2006**, *332,* 1302–1308.

NSAIDs

COX-2

Biosysnthesis of prostacyclin

- Vasodilation
- Decreases platelet aggregation



COX-1

Biosysnthesis of thromboxane

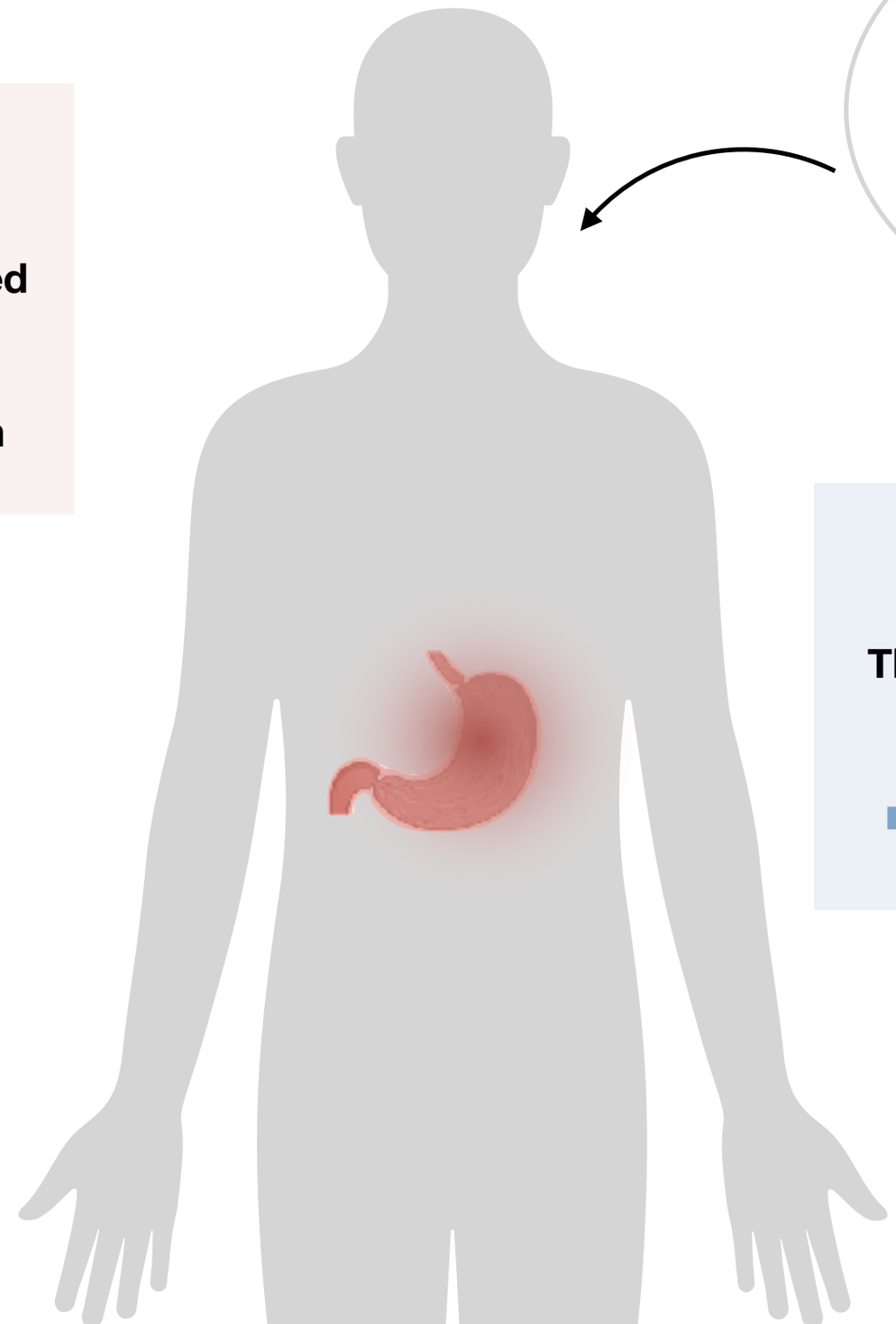
- Vasoconstriction
- Promotes platelet aggregation

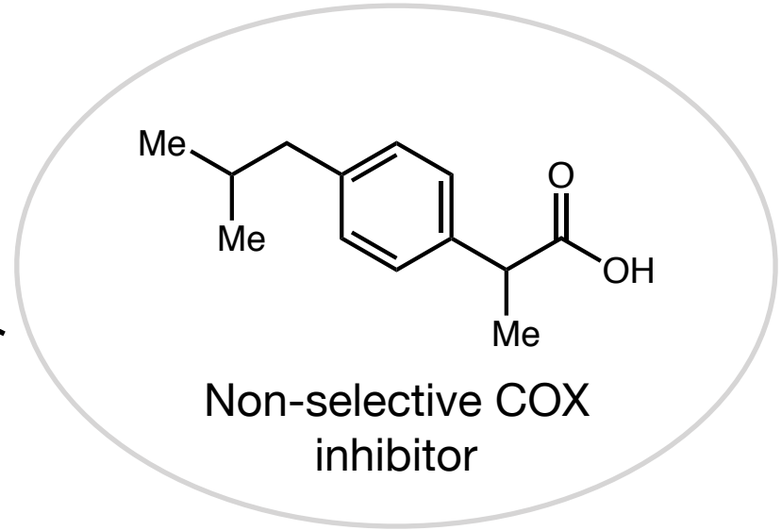
NSAIDs

COX-2 inhibited

Prostaglandin synthesis inhibited

- Vasoconstriction
- Increased platelet aggregation





Non-selective COX inhibitor

COX-1 inhibited

Thromboxane synthesis inhibited

- Vasodilation
- Decreased platelet aggregation

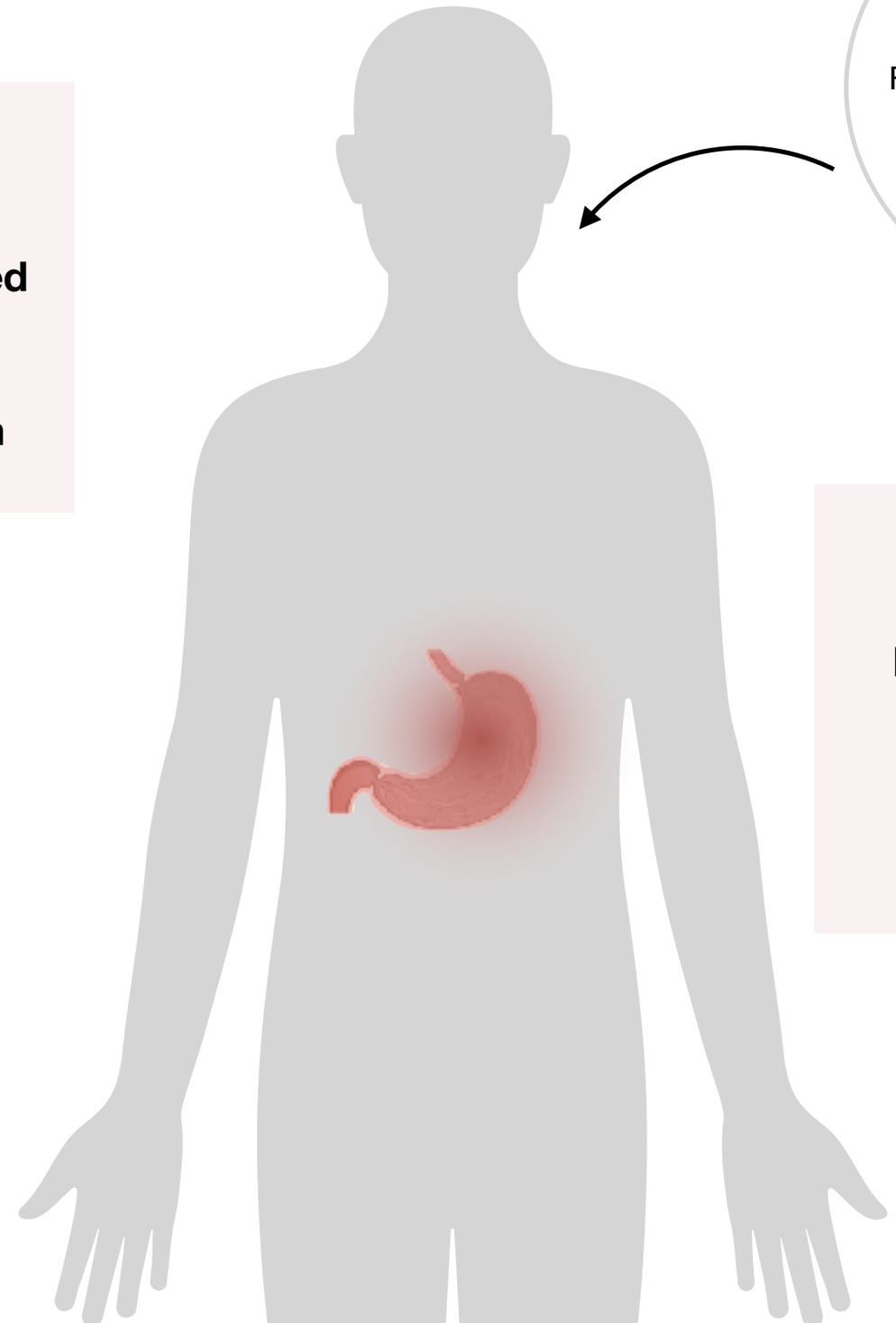
NSAIDs

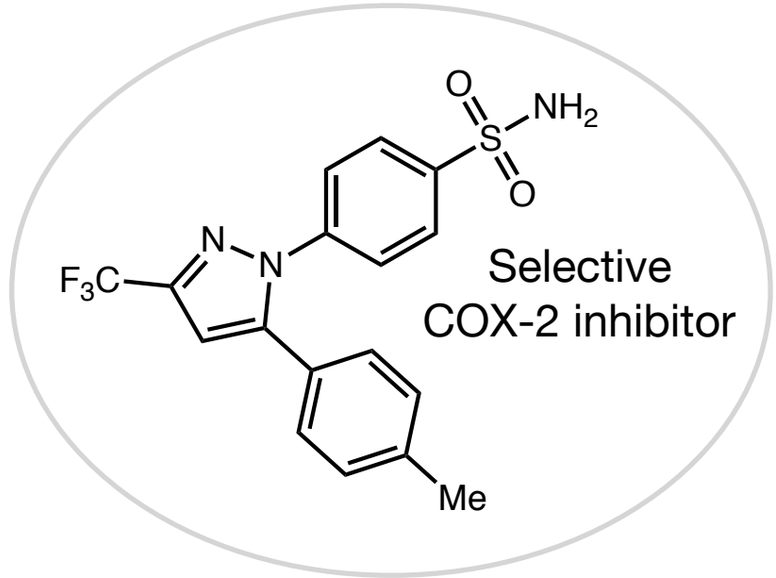
COX-2 inhibited

Prostaglandin synthesis inhibited

- Vasoconstriction
- Increased platelet aggregation

Increased risk of hypertension, thrombosis, and cardiovascular events





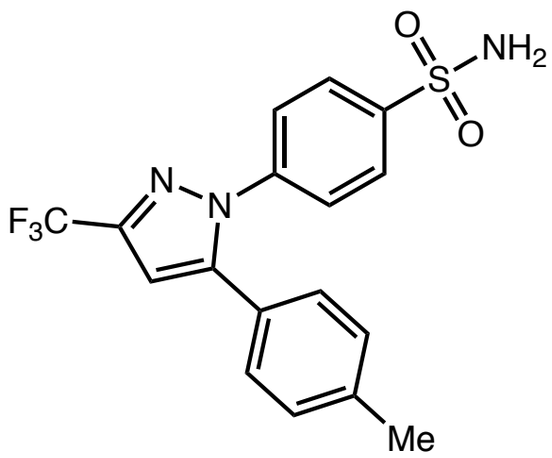
Selective COX-2 inhibitor

COX-1

Biosysnthesis of thromboxane

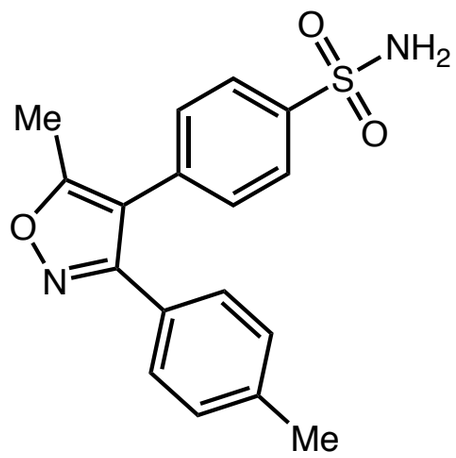
- Vasoconstriction
- Promotes platelet aggregation

Selective COX-2 inhibitors



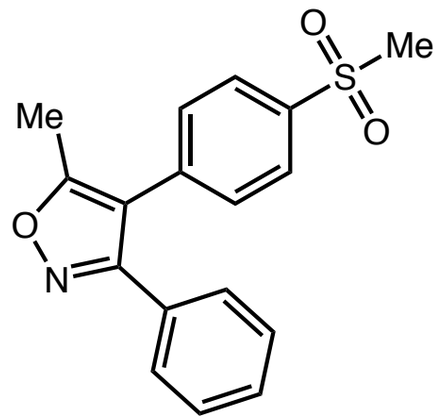
Celecoxib

Black box warning



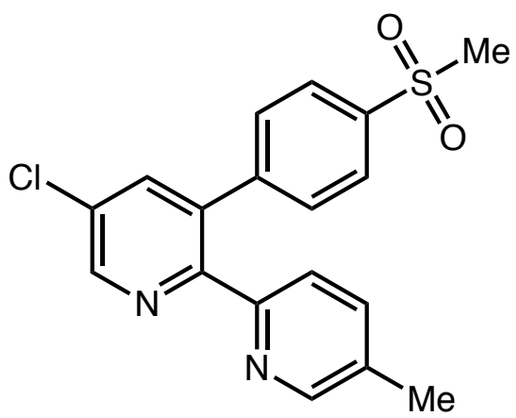
Rofecoxib

Merck voluntarily withdraws from market in 2004, faces multiple lawsuits



Valdecoxib

Pfizer withdraws from market in 2005 and is fined $2.3 billion



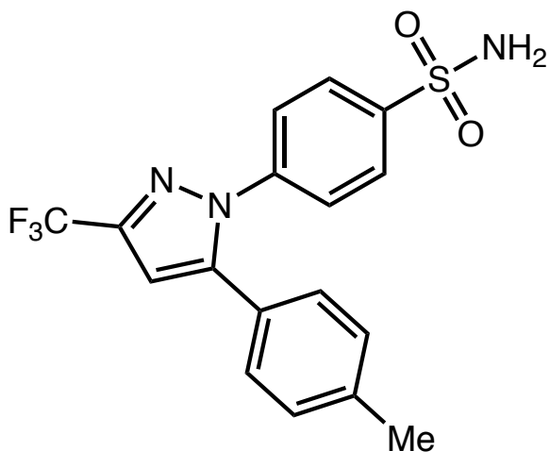
Etoricoxib

Never approved in US, approved in >80 countries worldwide

Cardiovascular Risk

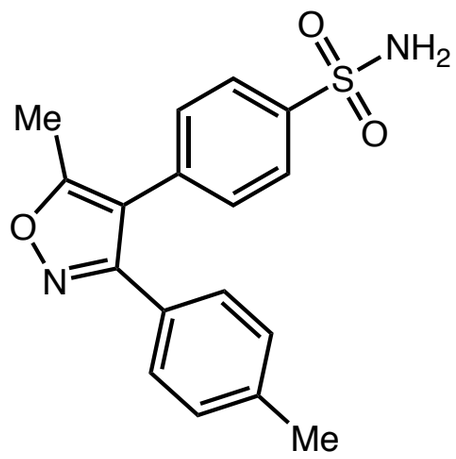
- CELEBREX may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs may have a similar risk. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. (See **WARNINGS** and **CLINICAL TRIALS**).

Selective COX-2 inhibitors



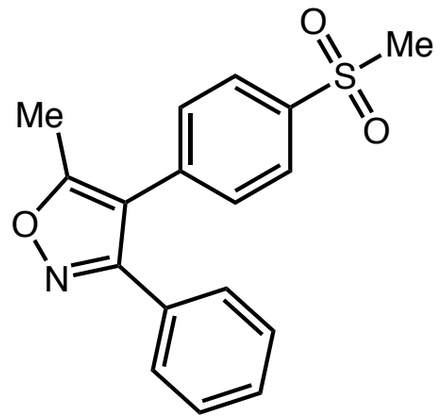
Celecoxib

102nd most prescribed medication in 2019



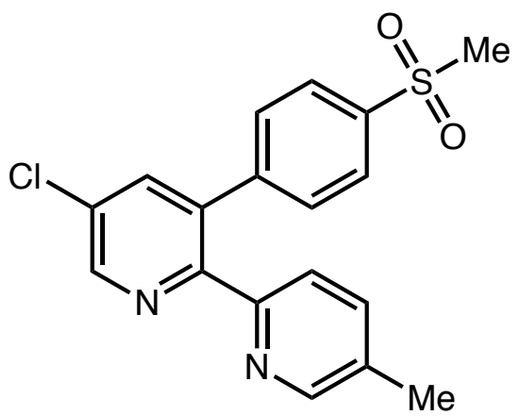
Rofecoxib

FDA encourages return to market



Valdecoxib

Prodrug version available in EU



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Targets for pain relief

Cytokines

Peptides

Small molecules

Metabotropic receptors
(G-coupled protein receptors)

G protein

K^+ Na^+ Ca^+

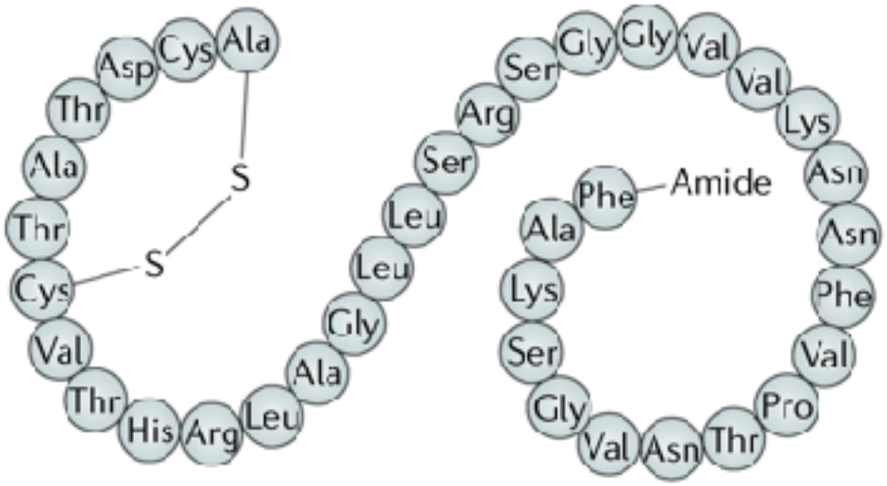
Membrane depolarization

Downstream signaling

Ionotropic receptors

Migraines

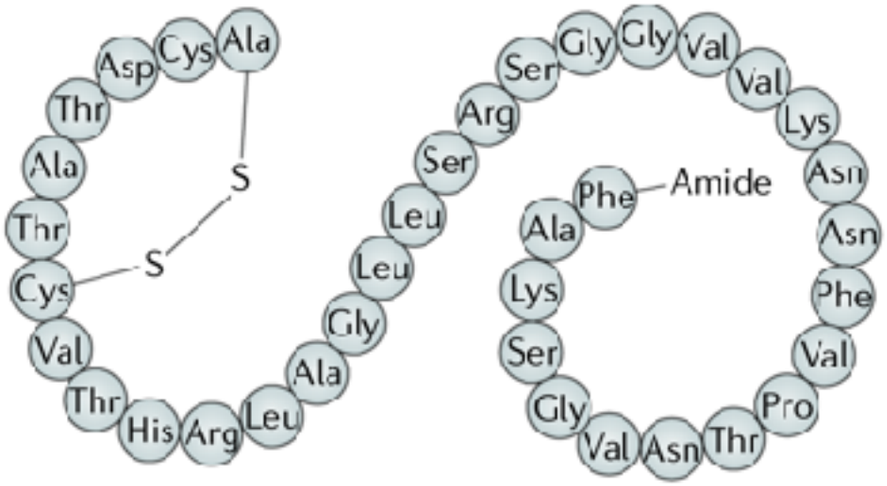
Discovery of CGRP



Calcitonin-gene-related-peptide (CGRP)

Ho, T. W.; Edvinsson, L.; Goadsby, P. J. CGRP and its receptors provide new insights into migraine pathophysiology. *Nat. Rev. Neurology,* **2010,** *6,* 573–582.

Discovery of CGRP



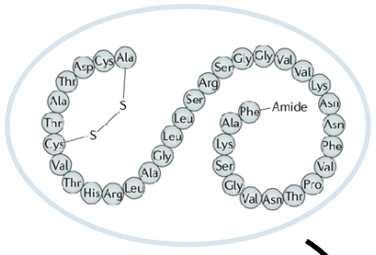
Calcitonin-gene-related-peptide (CGRP)

Pioneering work in the 1990's demonstrated CGRP's role in migraine pathophysiology

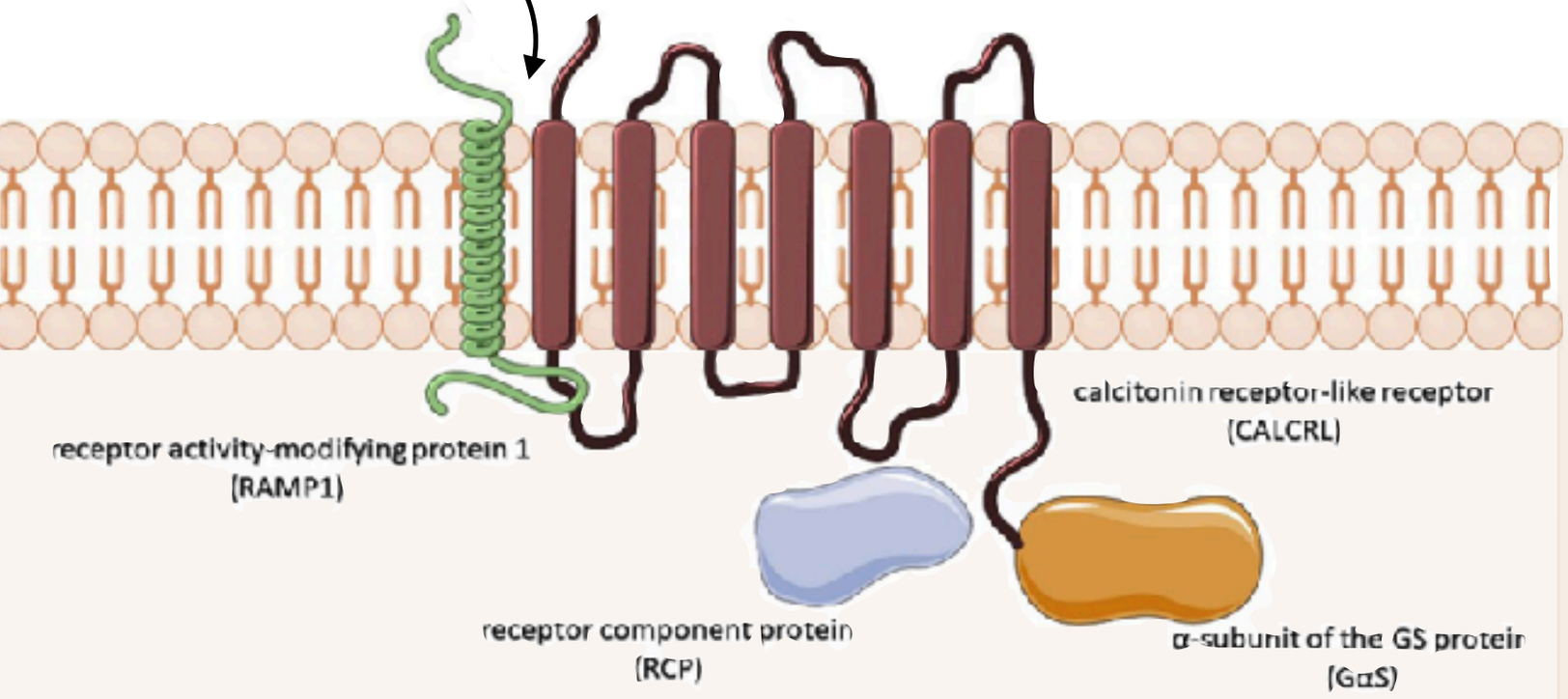
- CGRP levels are increased in saliva and plasma during migraine
- Chronic migraine patients show increased levels of CGRP in blood even when pain-free
- CGPR levels return to normality after triptans administration and headache resolution
- IV infusion of CGRP can induce migraine-like attacks in patients

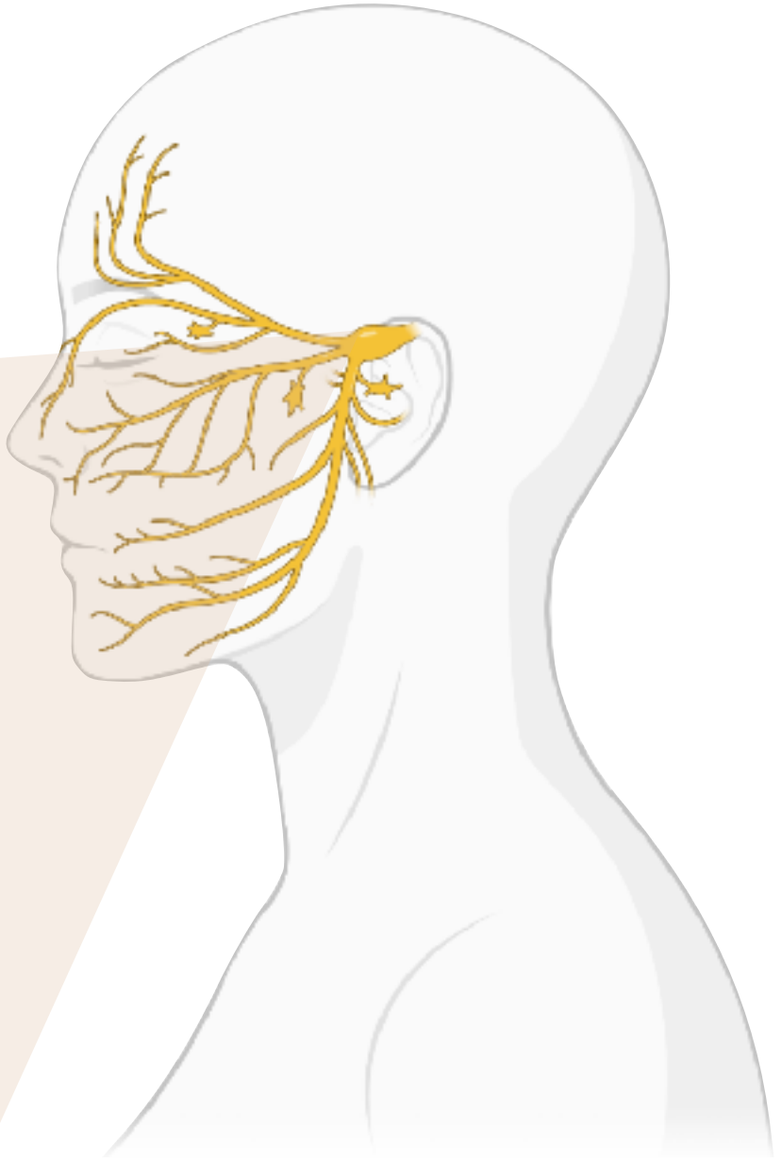
Ho, T. W.; Edvinsson, L.; Goadsby, P. J. CGRP and its receptors provide new insights into migraine pathophysiology. *Nat. Rev. Neurology,* **2010,** *6,* 573–582.

Receptor physiology



CGRP





Trigeminal nerve:
Primary site of migraine pain

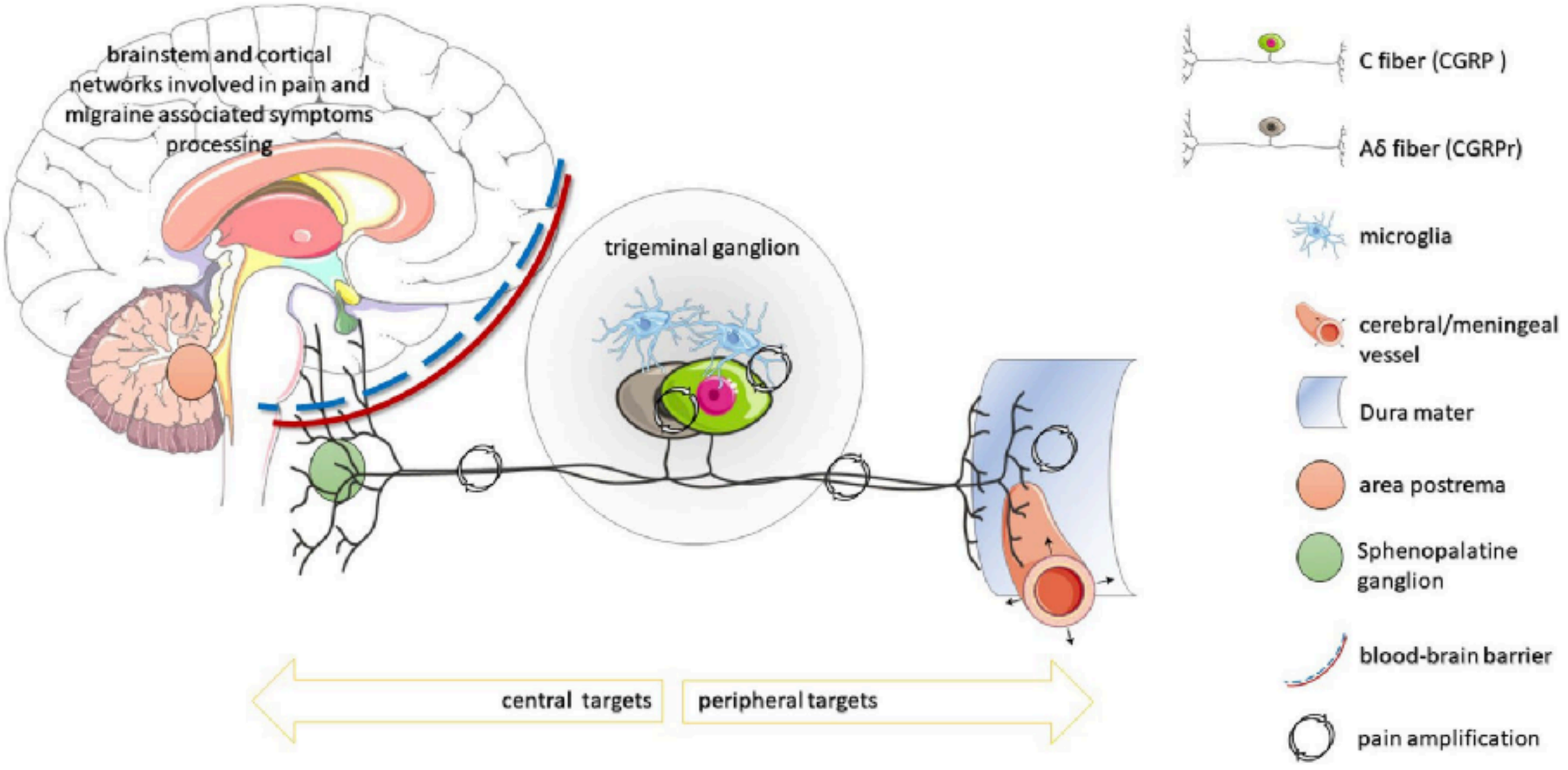
CGRP

Pain-signaling neurotransmitters

Substance P

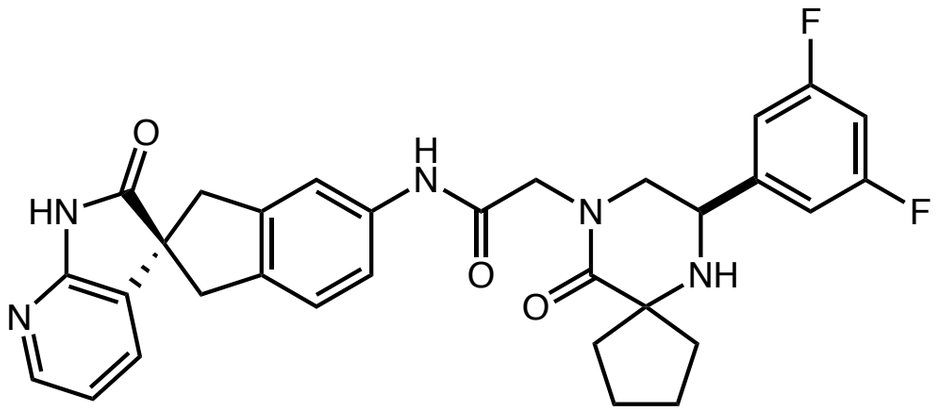
Ho, T. W.; Edvinsson, L.; Goadsby, P. J. CGRP and its receptors provide new insights into migraine pathophysiology. *Nat. Rev. Neurology,* **2010,** *6,* 573–582.

Migraine pain amplification circuitry



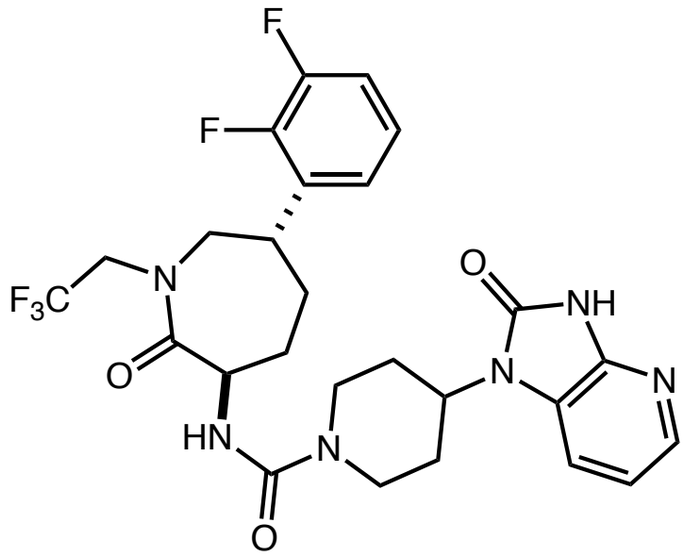
Ho, T. W.; Edvinsson, L.; Goadsby, P. J. CGRP and its receptors provide new insights into migraine pathophysiology. *Nat. Rev. Neurology,* **2010,** *6,* 573–582.

First small molecule antagonist of CGRP receptors



MK-3207

Discontinued during Phase I trials in 2011



Telcagepant (MK-0974)

Prematurely terminated during Phase II clinical trials in 2014

Heightened aminotransferase levels found in patients:

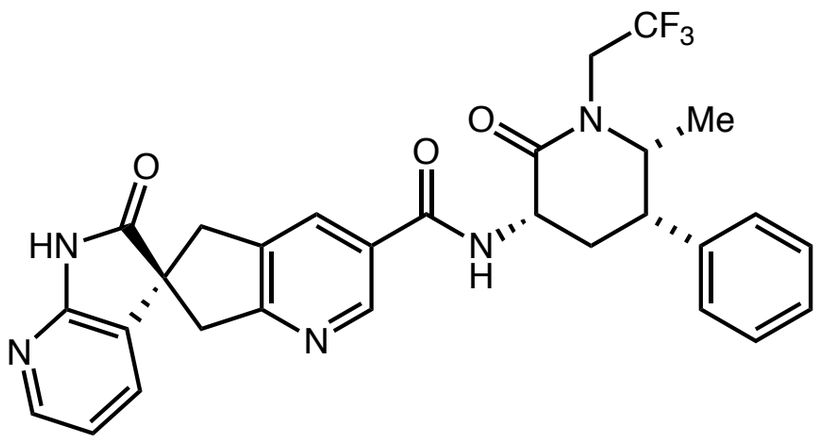
Red flag for potential liver toxicity

Altamura, C., Brunelli, N., Marcosano, M. Fofi, L.; Vernieri, F. Gepants — a long way to cure: a narrative review. *Neurol. Sci.* **2022,** *43*, 5697–5708.

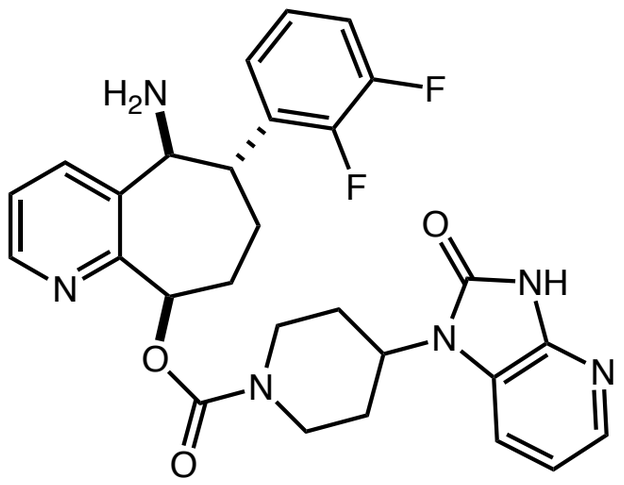
Ho T.W.; Connor, K.M.; Zhang, Y. *et al.* Randomized controlled trial of the CGRP receptor antagonist telcagepant for migraine prevention. *Neurology,* **2014,** *83,* 958–966.

CGRP receptor antagonists

The “gepants”



Ubrogepant
Approved 2019

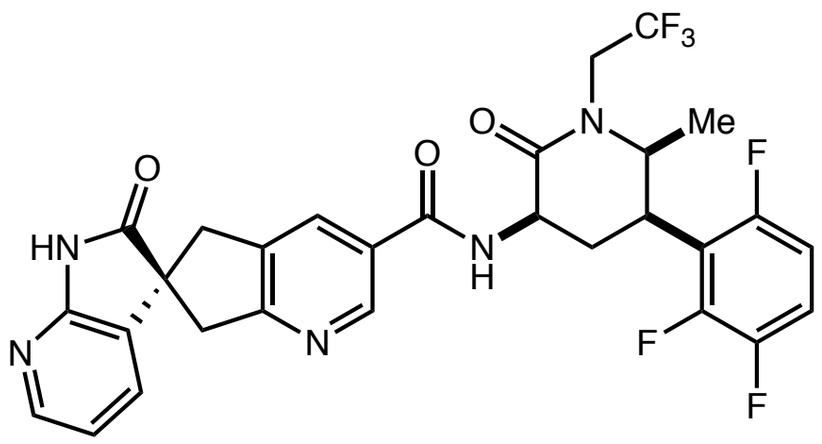


Rimegepant
Approved 2020

Monoclonal antibodies

Erenumab (Approved 2018)
Fremanezumab* (Approved 2018)
Galcanezumab* (Approved 2018)

***Preventative**

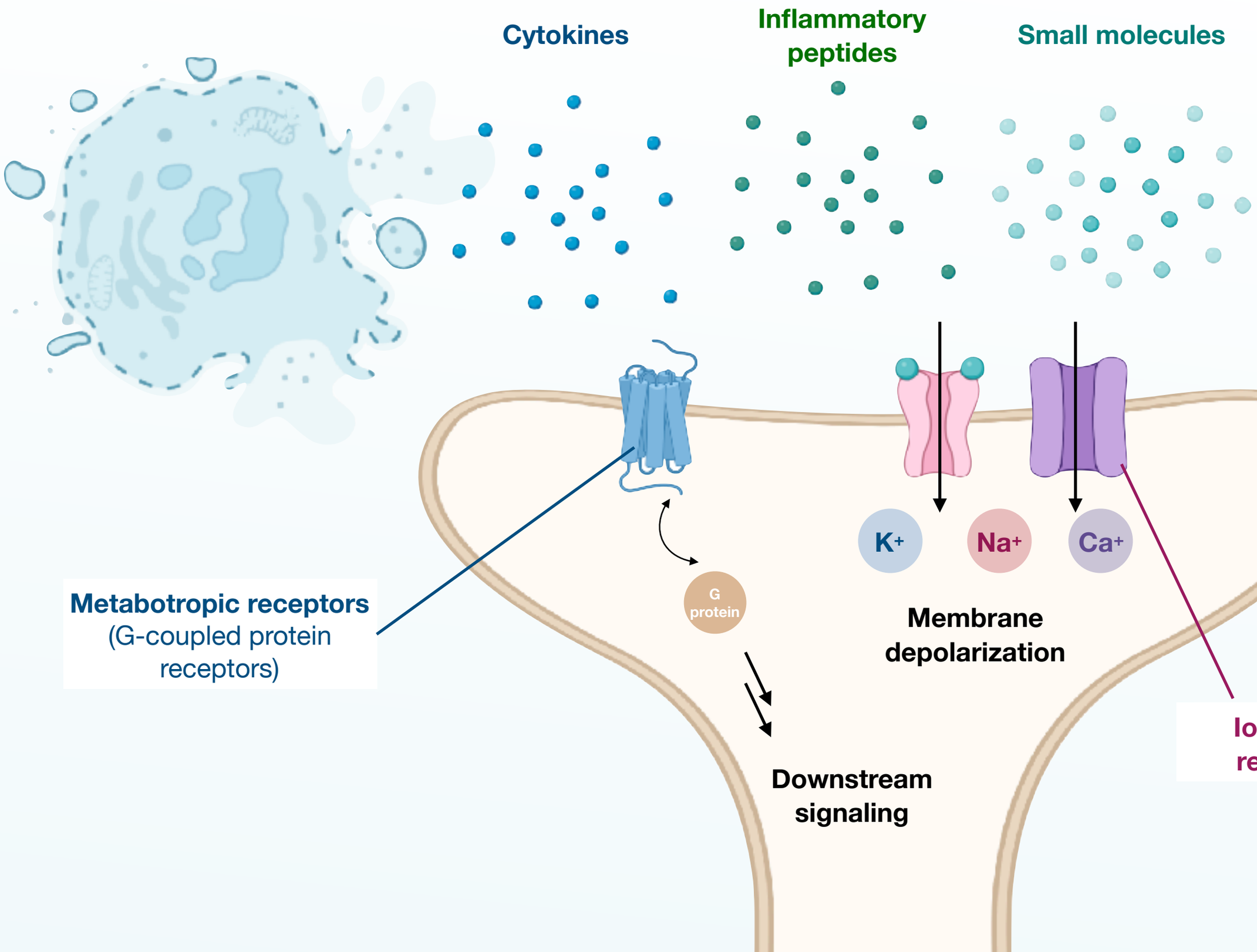


Atogepant*
Approved 2021

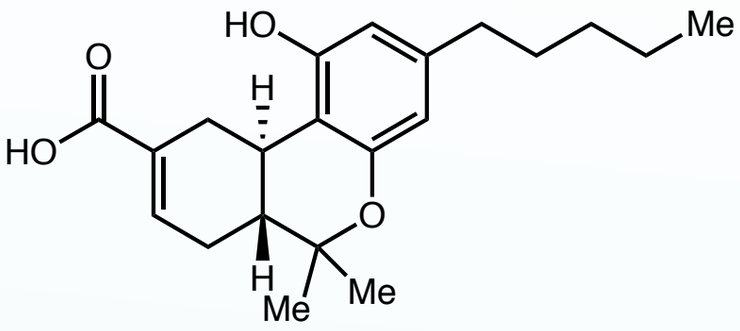
Altamura, C., Brunelli, N., Marcosano, M. Fofi, L.; Vernieri, F. Gepants — a long way to cure: a narrative review. *Neurol. Sci.* **2022,** *43*, 5697–5708.

Ho T.W.; Connor, K.M.; Zhang, Y. *et al.* Randomized controlled trial of the CGRP receptor antagonist telcagepant for migraine prevention. *Neurology,* **2014,** *83,* 958–966.

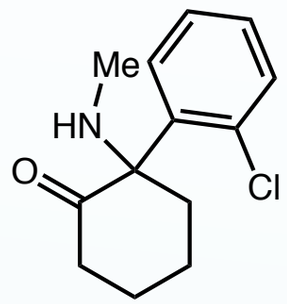
Targets for pain relief



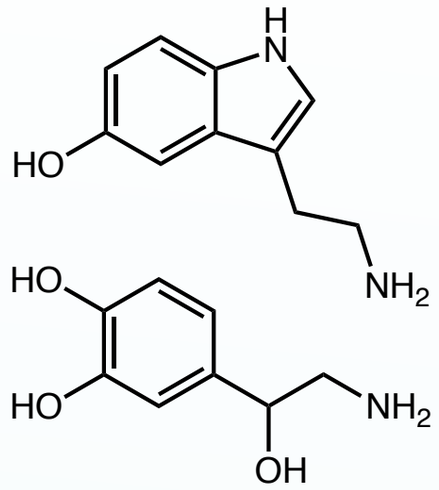
Targets for pain relief

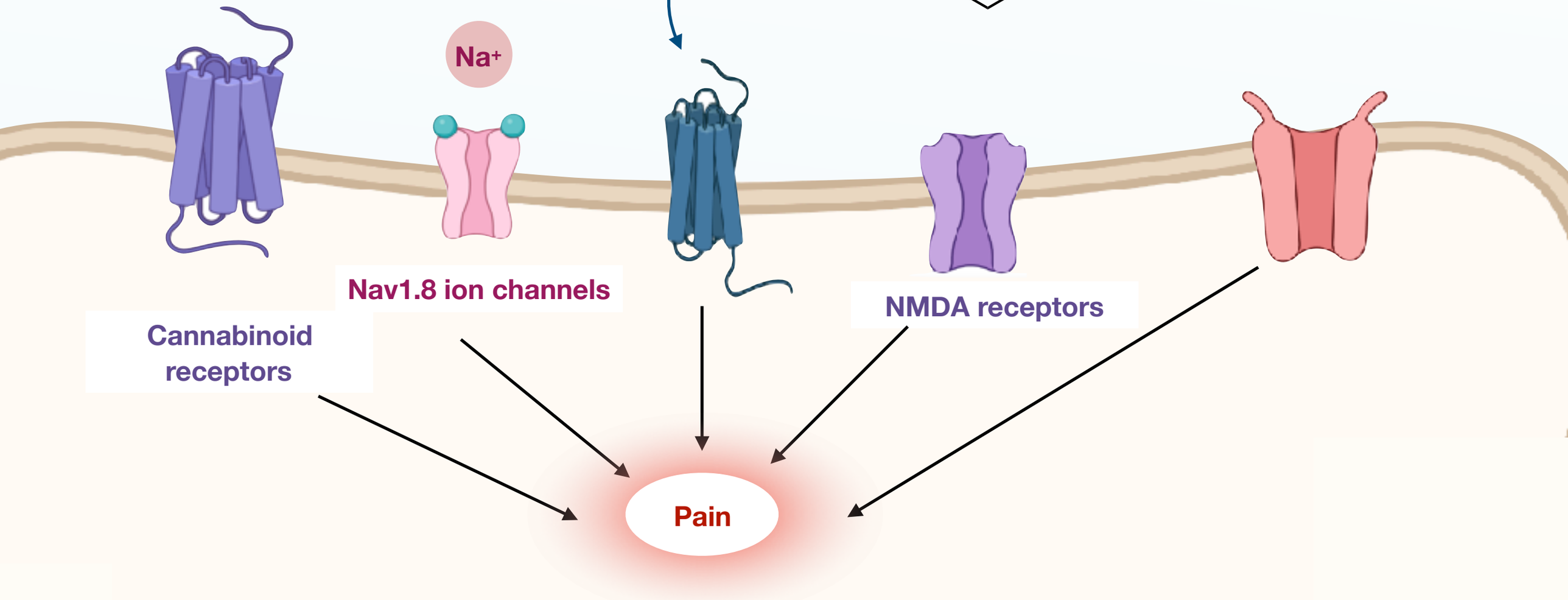


Nerve growth factor/ TrkA signaling pathway



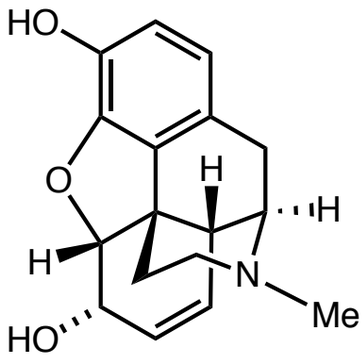
Neurotransmitters





Obeng, S.; Hiranita, T.; León, F.; McMahon, L.R.; McCurdy, C. R. Novel Approaches, Drug Candidates, and Targets in Pain Drug Discovery. *J. Med. Chem*. **2021** *64*, 6523-6548.

Opioids



Morphine

“the world’s oldest drug”

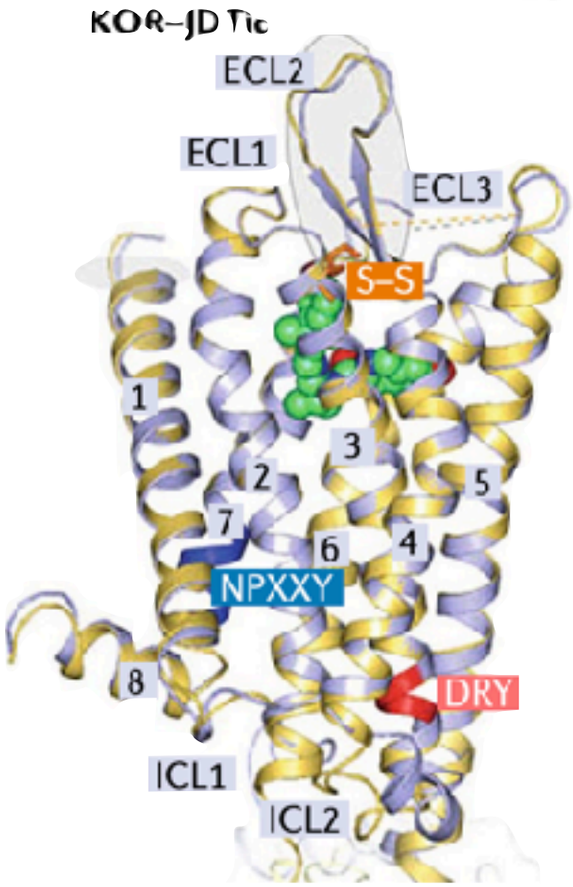
Isolated in 1804 as active ingredient in opium

Papaver somniferum

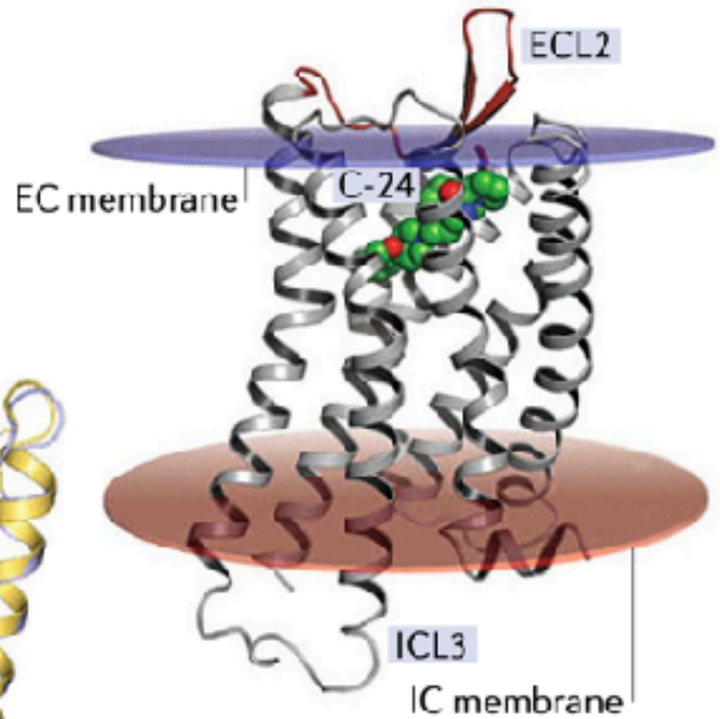
Main classes of opioid receptors

μ opioid receptor (MOR)

δ opioid receptor (DOR)



κ opioid receptor (KOR)



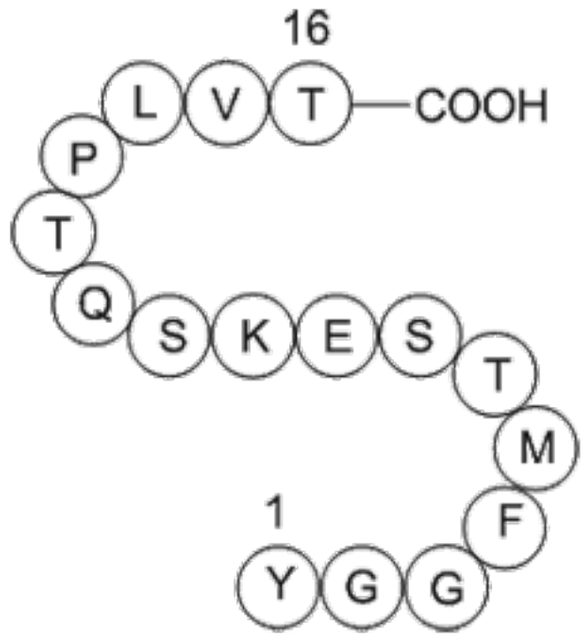
Nociceptin opioid peptide receptor (NOR)

Darcq, E., Kieffer, B.L. Opioid receptors: drivers to addiction?. *Nat Rev Neurosci.* **2018,** *19*, 499–514.

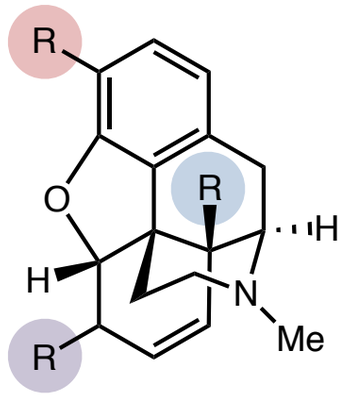
The μ opioid receptors

μ opioid receptor (MOR)

Ligands



Endorphin peptides



Opioids

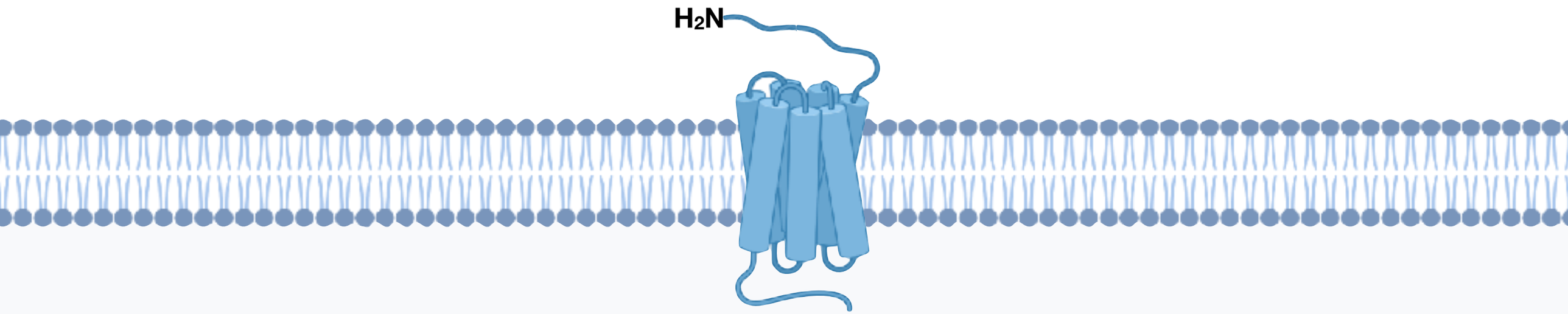
Involved in the regulation of:

- Mood and nociception
- Reward and aversion processing

Darcq, E., Kieffer, B.L. Opioid receptors: drivers to addiction?. *Nat Rev Neurosci.* **2018,** *19*, 499–514.

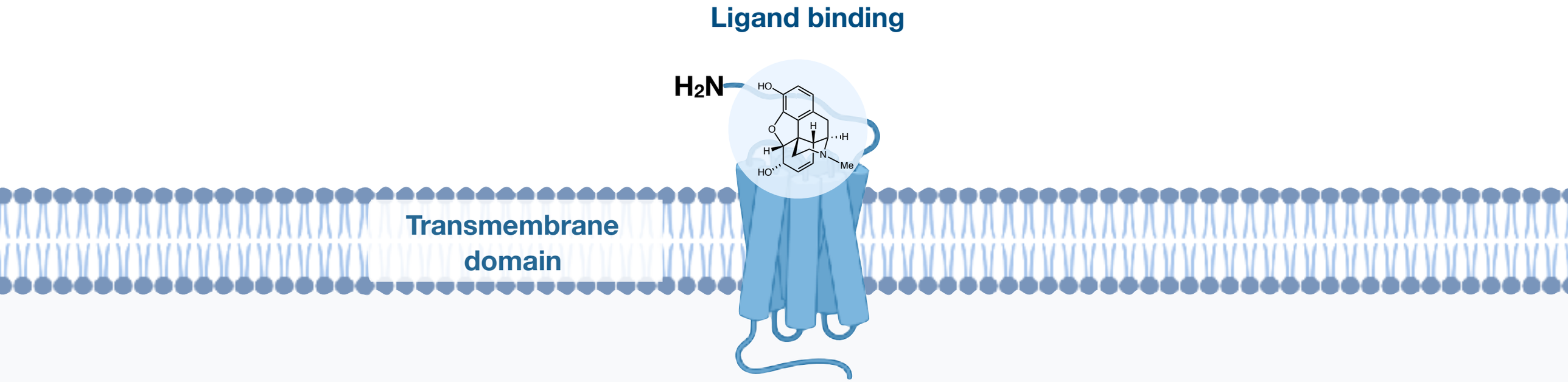
Opioids: Mechanism of action

MOR **“G-coupled-protein receptor”**



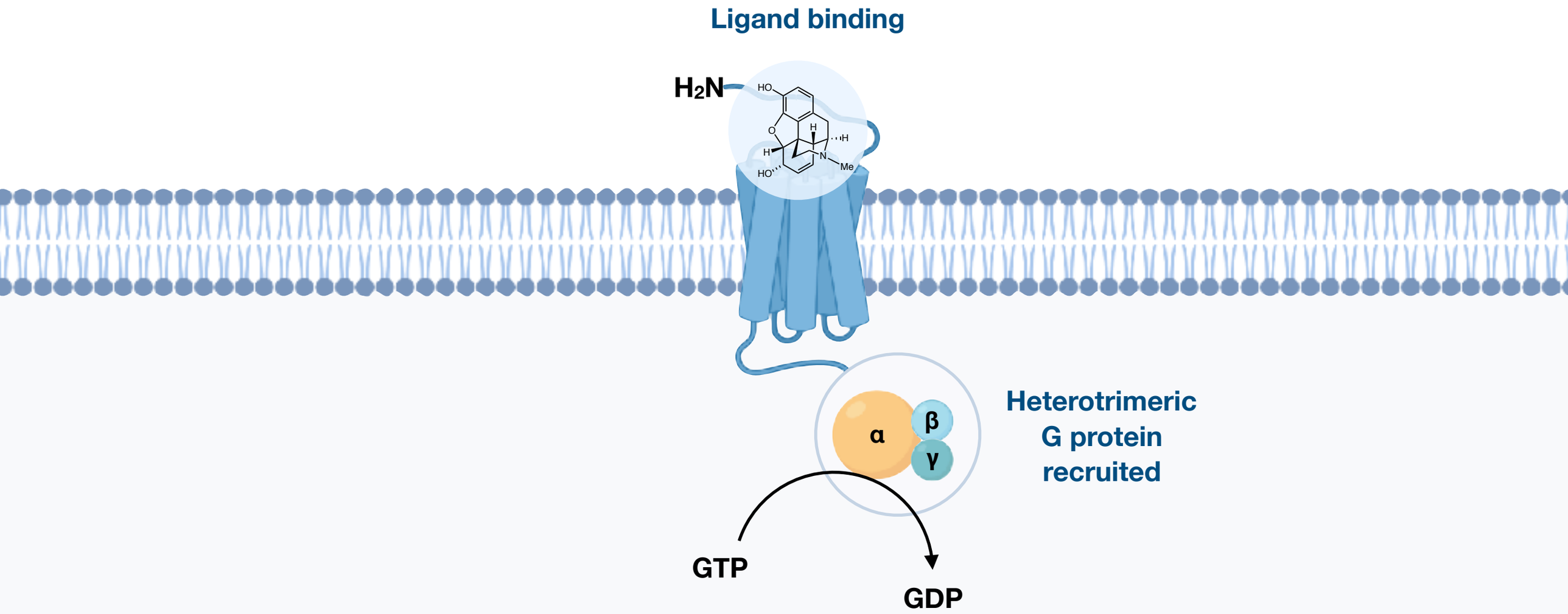
Schäfer, M. Mechanisms of action of opioids. *Anesthetic Pharmacology, 2nd Ed. Cambridge University Press 2011*, 493–508.

Opioids: Mechanism of action



Schäfer, M. Mechanisms of action of opioids. *Anesthetic Pharmacology, 2nd Ed. Cambridge University Press 2011*, 493–508.

Opioids: Mechanism of action



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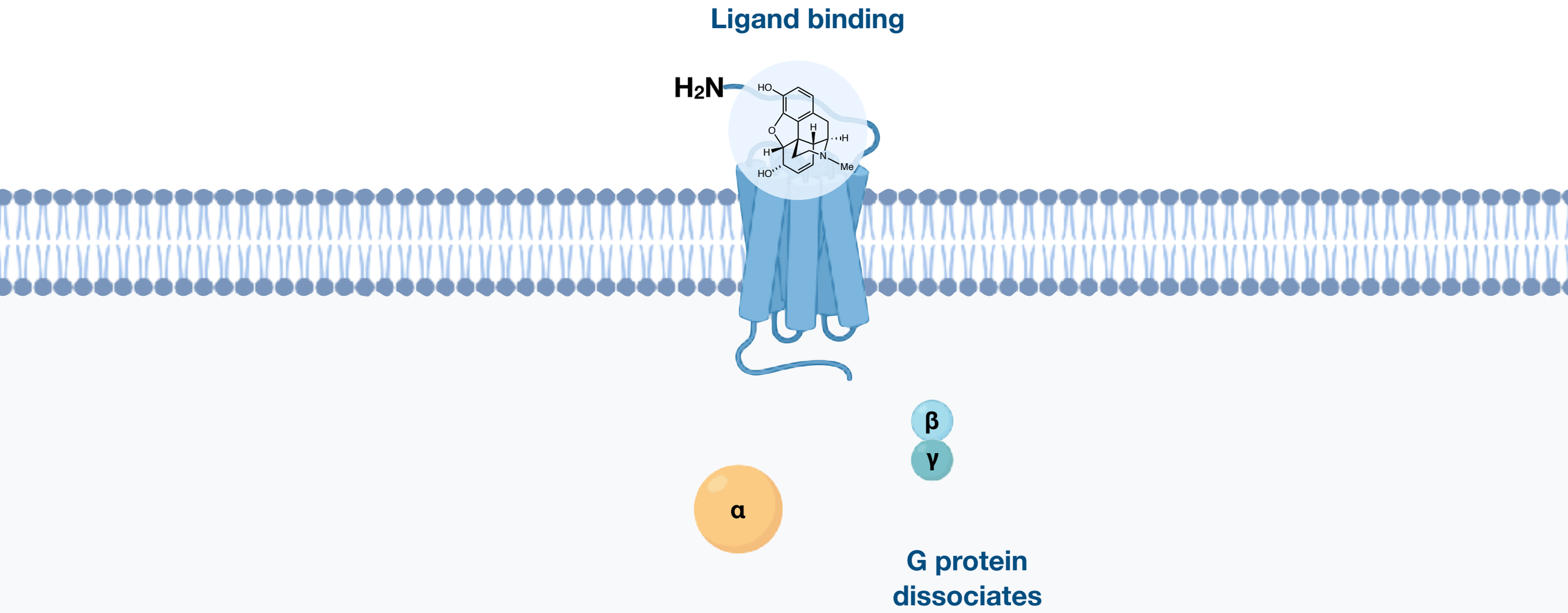
Opioids: Mechanism of action



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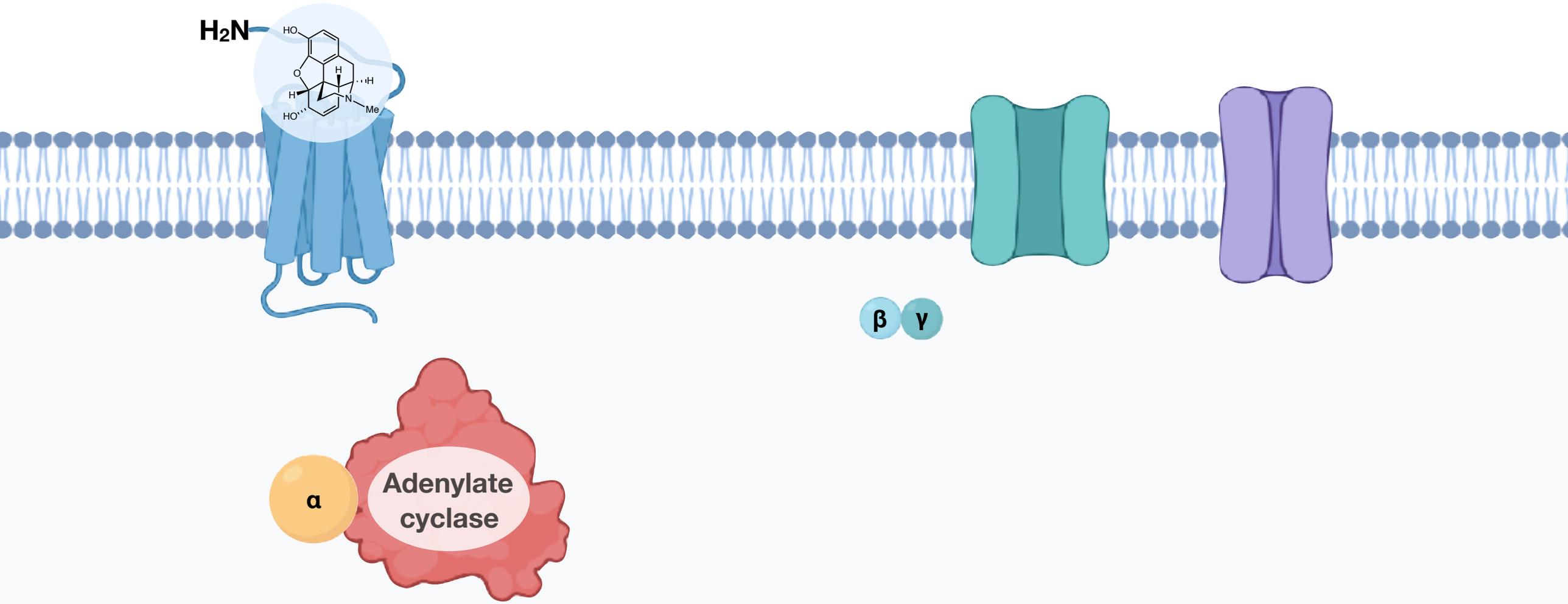

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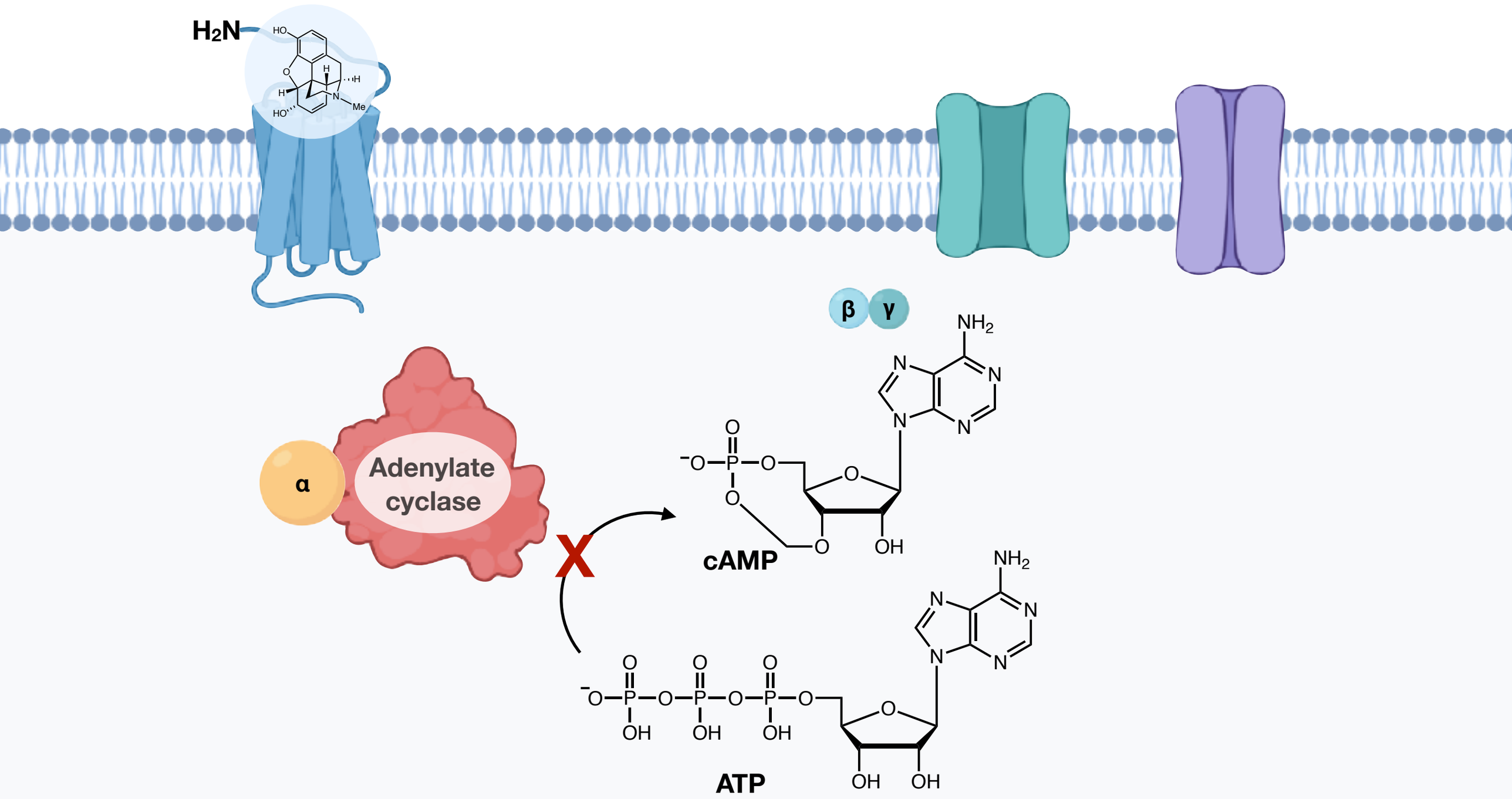
Opioids: Mechanism of action



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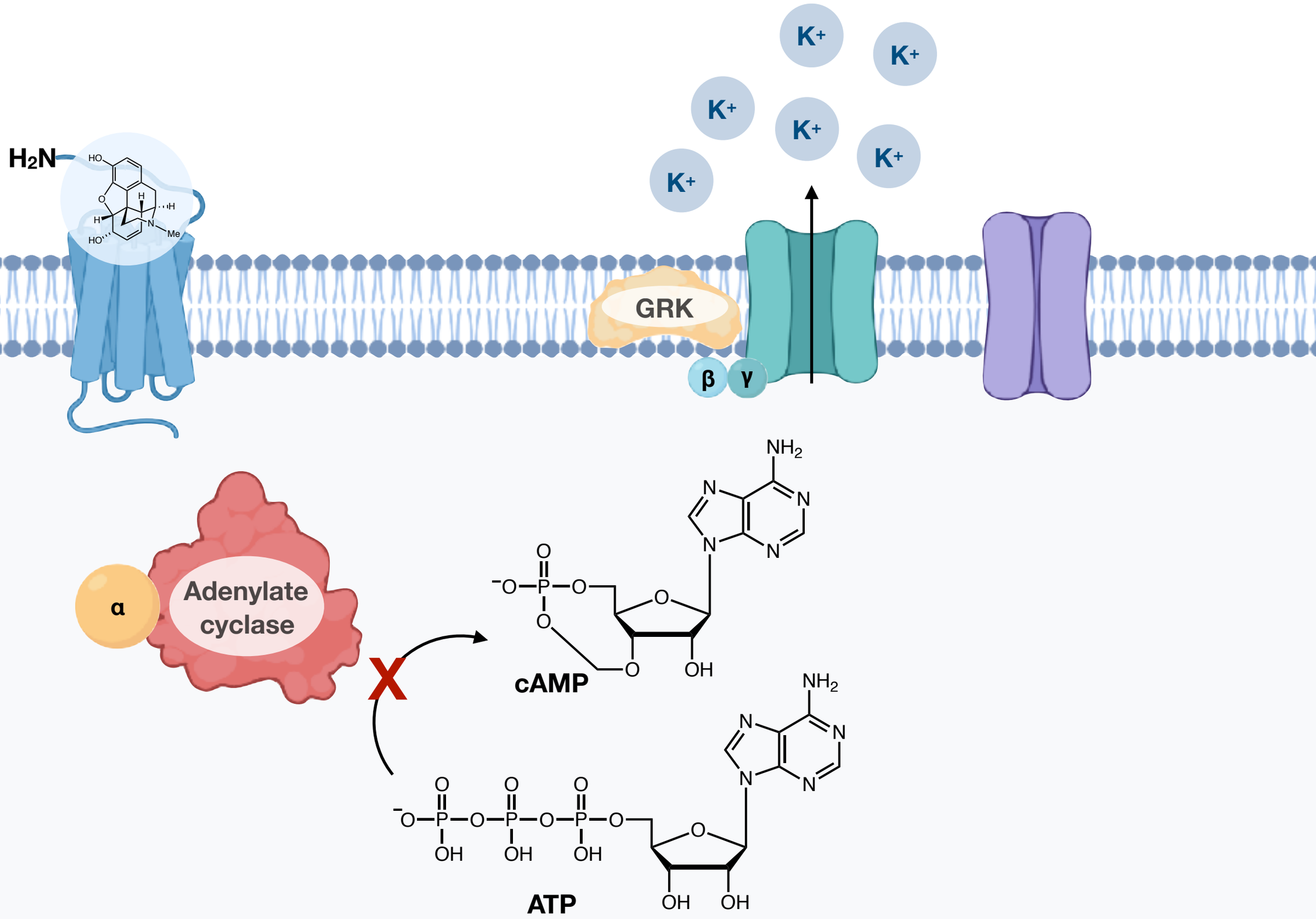

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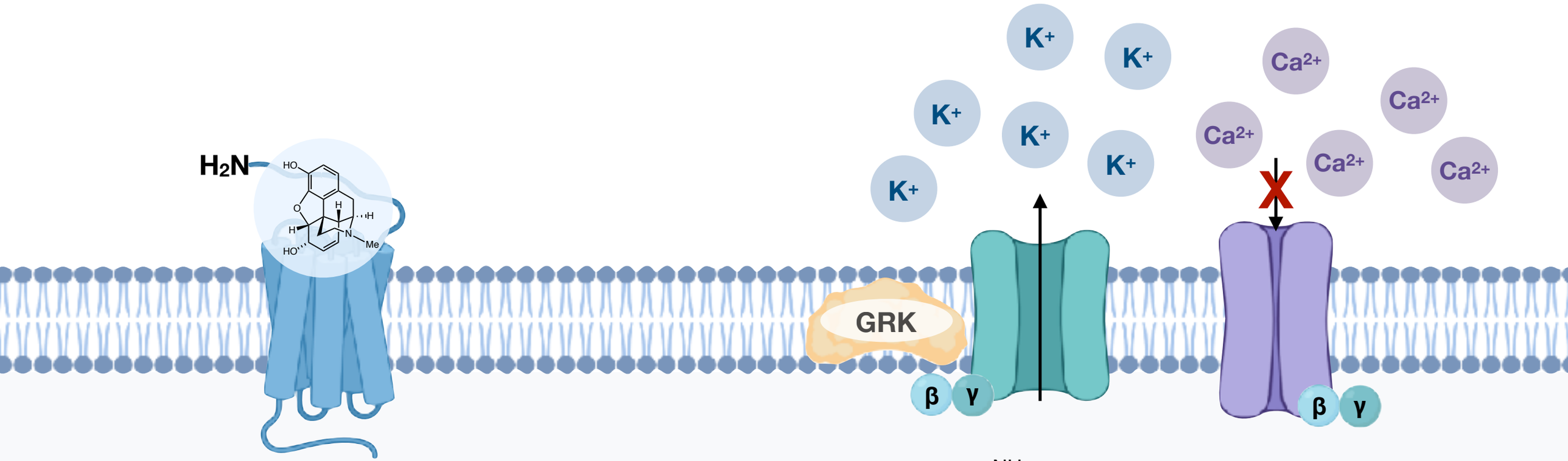
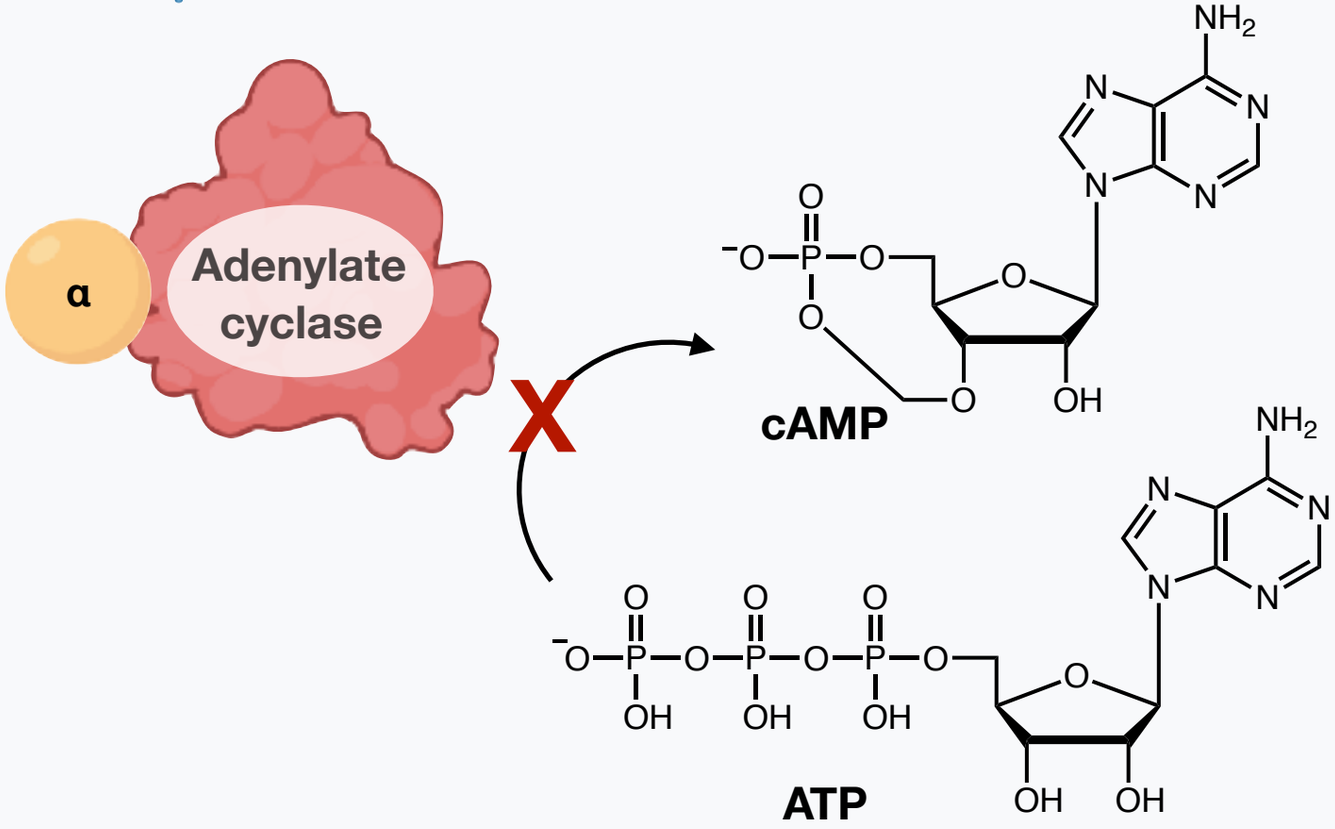
Opioids: Mechanism of action





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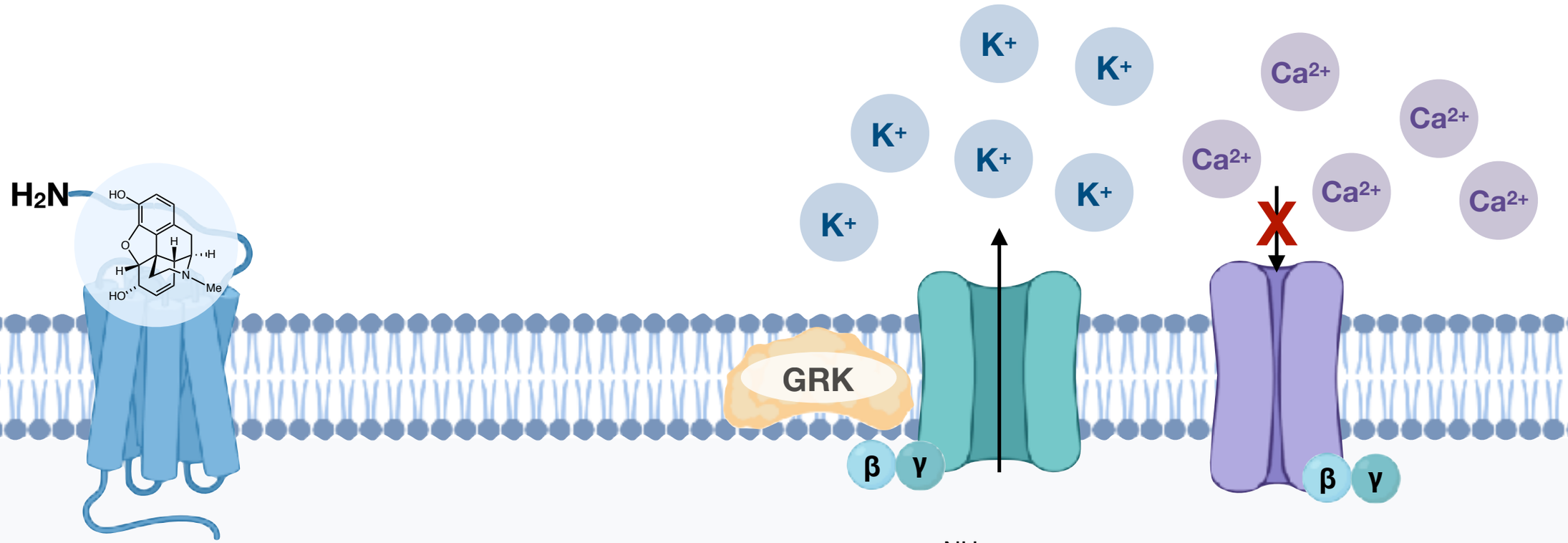
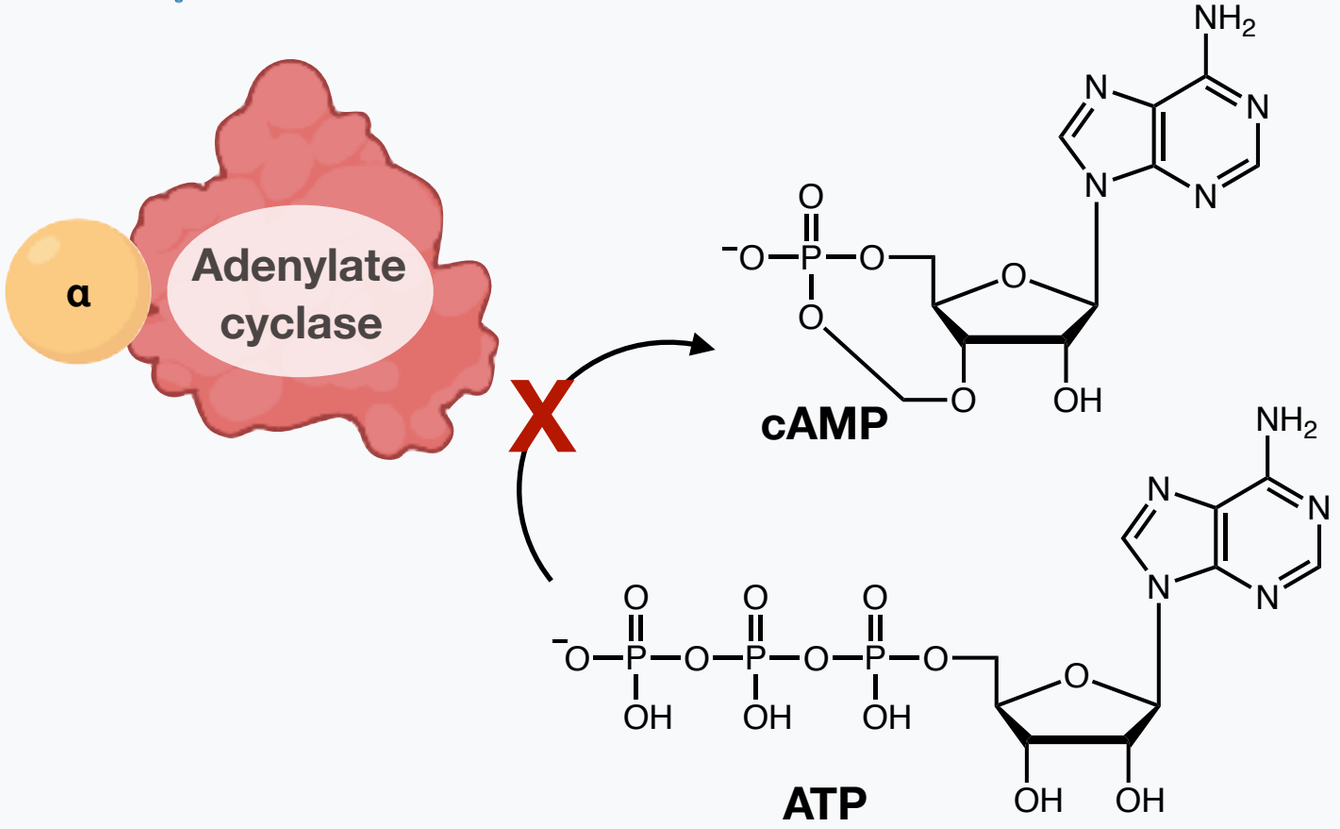




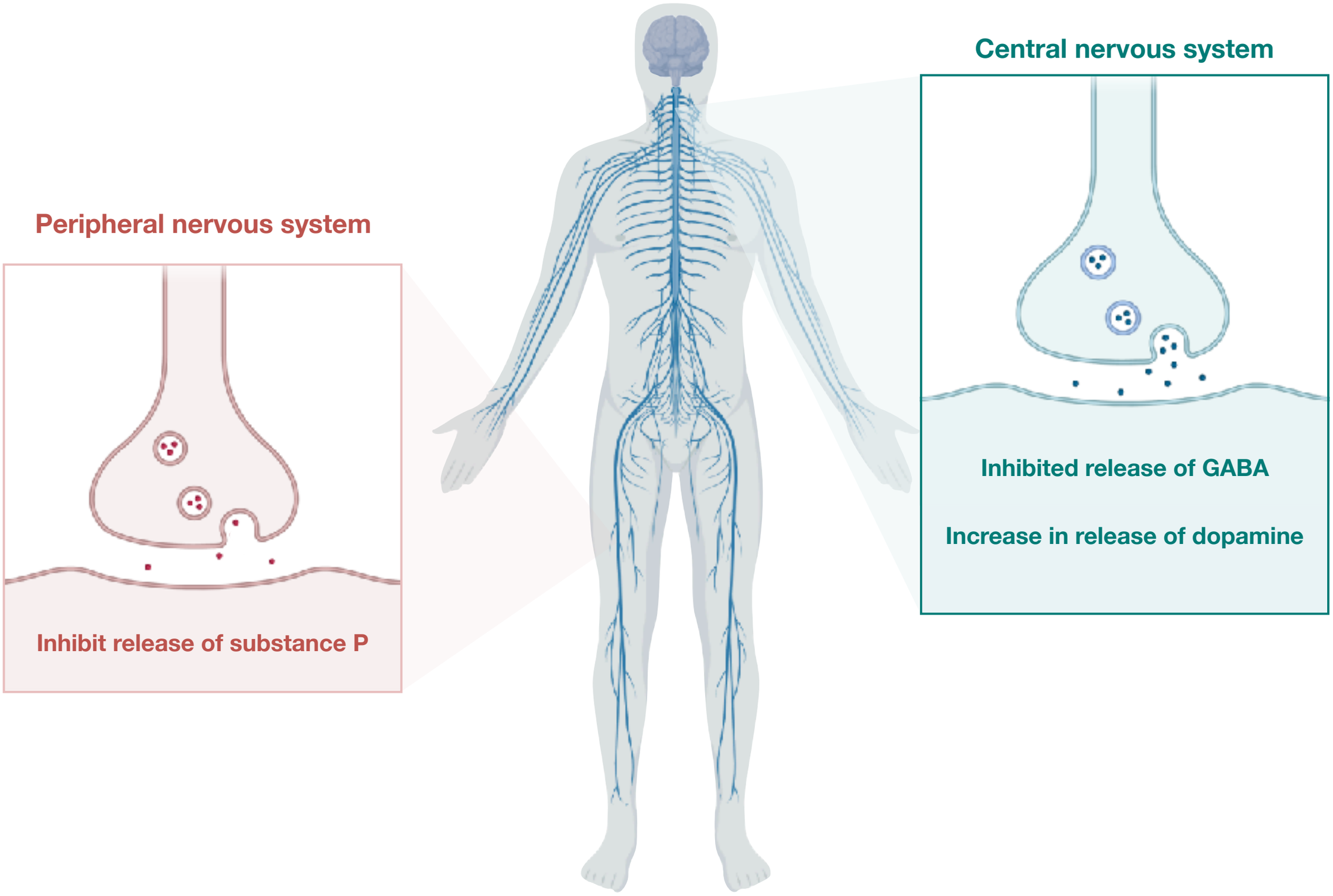
Overall:
Membrane hyperpolarization

↓

Inhibition of neuronal activity

Schäfer, M. Mechanisms of action of opioids. *Anesthetic Pharmacology, 2nd Ed. Cambridge University Press 2011*, 493–508.

Opioids: Mechanism of action

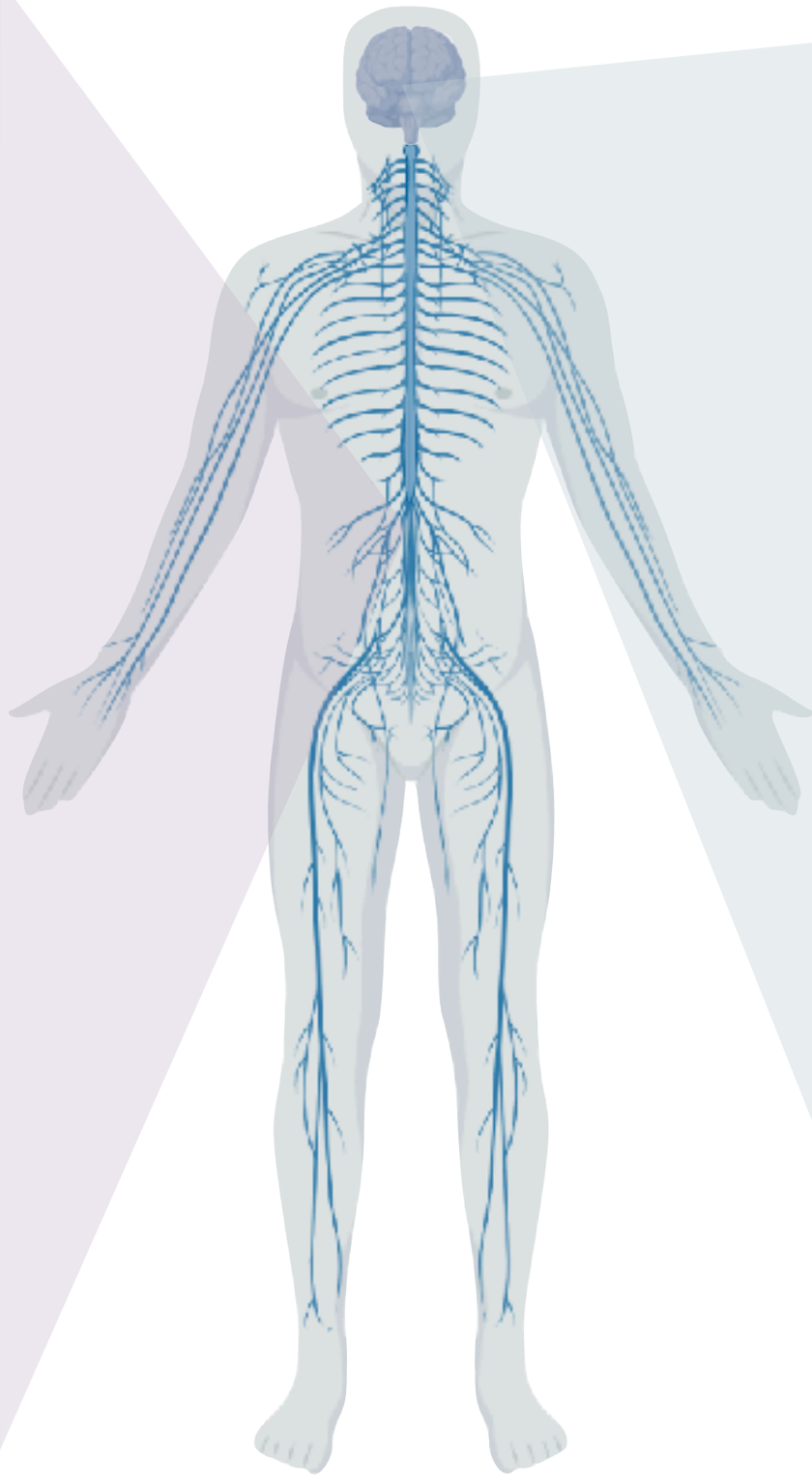


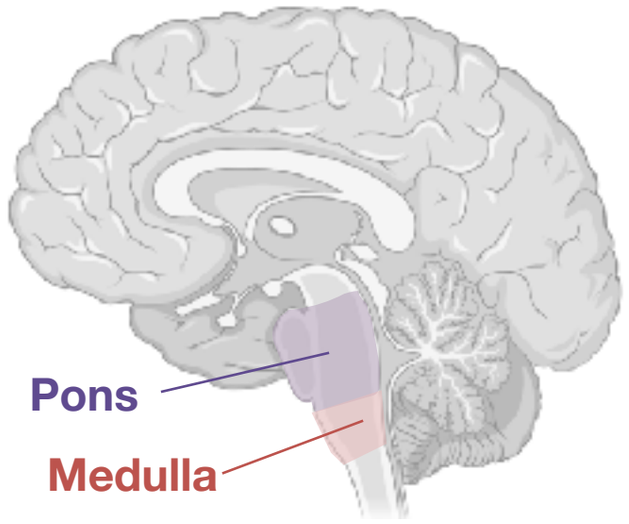
Schäfer, M. Mechanisms of action of opioids. *Anesthetic Pharmacology, 2nd Ed. Cambridge University Press 2011*, 493–508.

Opioids: Mechanism of adverse effects

High expression of MOR in stomach and gastrointestinal track

Opioid actions	Consequences
gastric motility ↓	delayed gastric emptying
pyloric tone ↑	nausea, vomiting
lower esophageal sphincter ↓	gastroesophageal reflux ↑
gastric juice secretion ↓	delayed digestion
pancreatic and biliary secretion ↓	delayed digestion
fluid secretion ↓	delayed transit
propulsion ↓	delayed transit, absorption
propulsion ↓	bloating, distension, constipation
circular smooth muscle contractions↑	spasm, abdominal cramps
fluid absorption ↑	hard, dry stool
anal sphincter tone ↑	incomplete evacuation



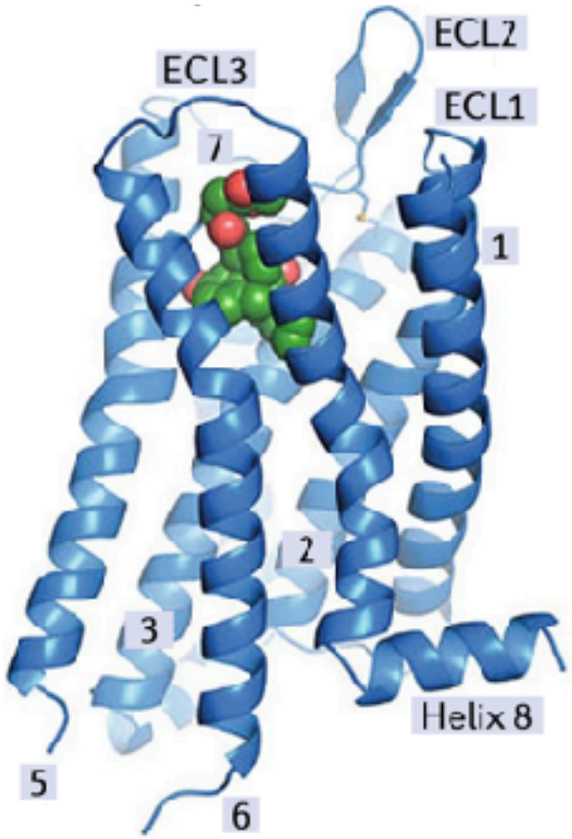


Areas of brainstem which regulate breathing also display high expression of MOR and DOR

Respiratory depression

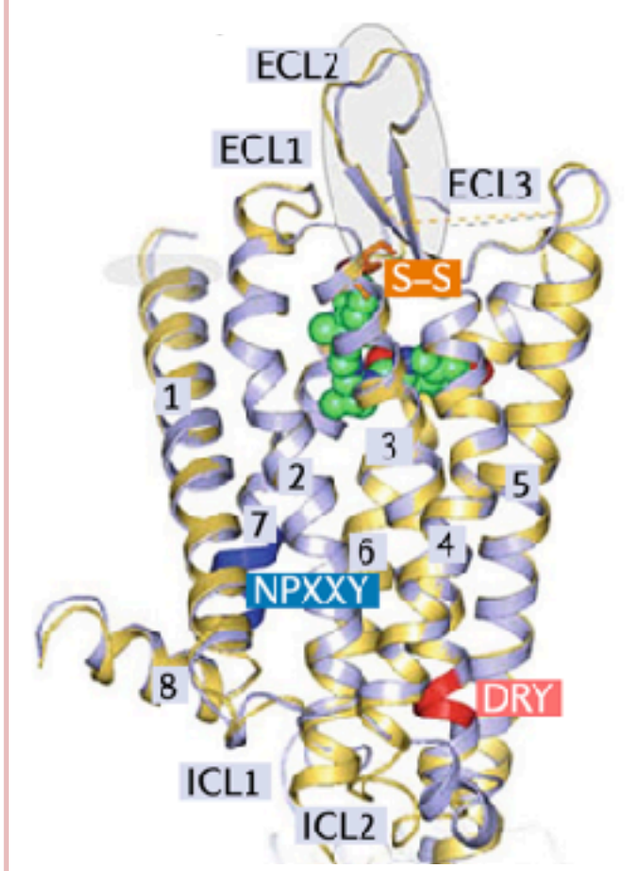
Schäfer, M. Mechanisms of action of opioids. *Anesthetic Pharmacology, 2nd Ed. Cambridge University Press 2011*, 493–508.

Opioids: Mechanism of adverse side effects



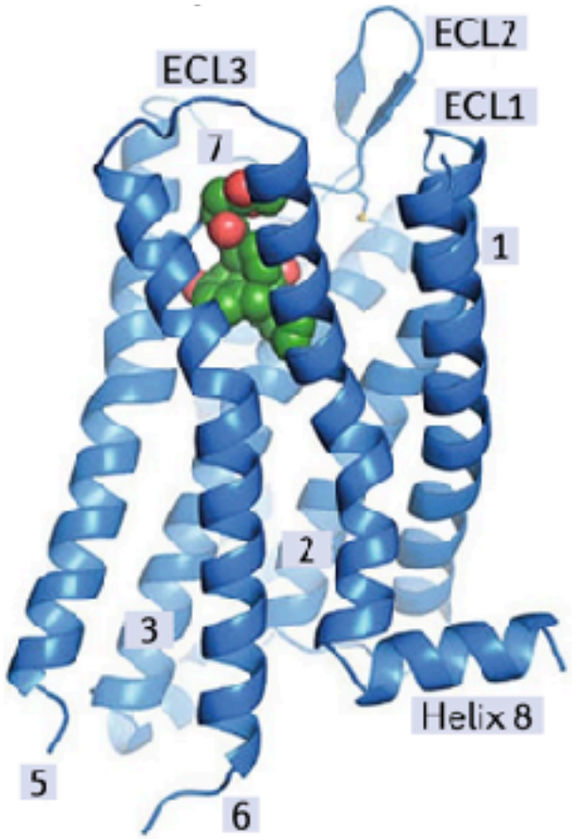
MOR
euphoria and reward

“Hedonic balance”



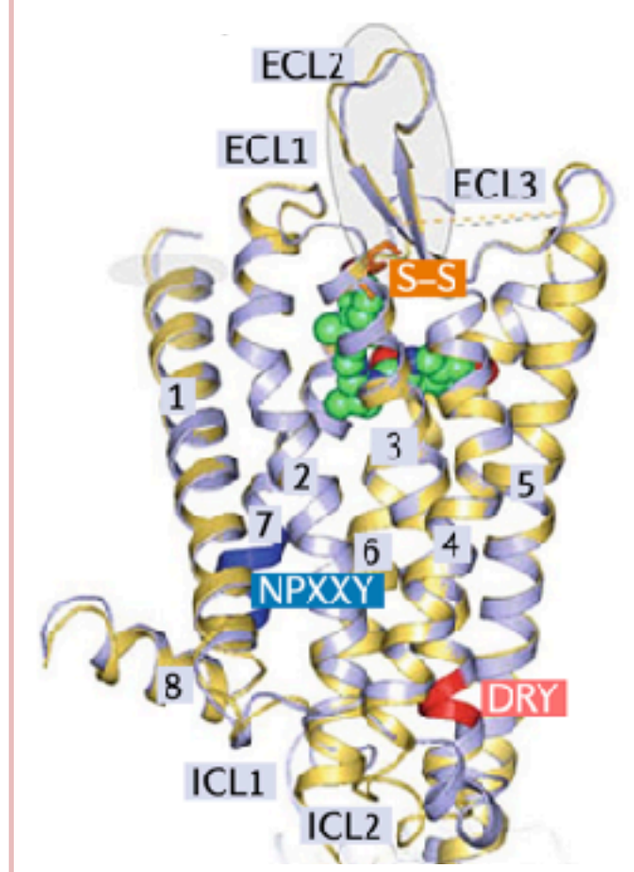
KOR
dysphoria and aversion

Opioids: Mechanism of adverse side effects



MOR
euphoria and reward

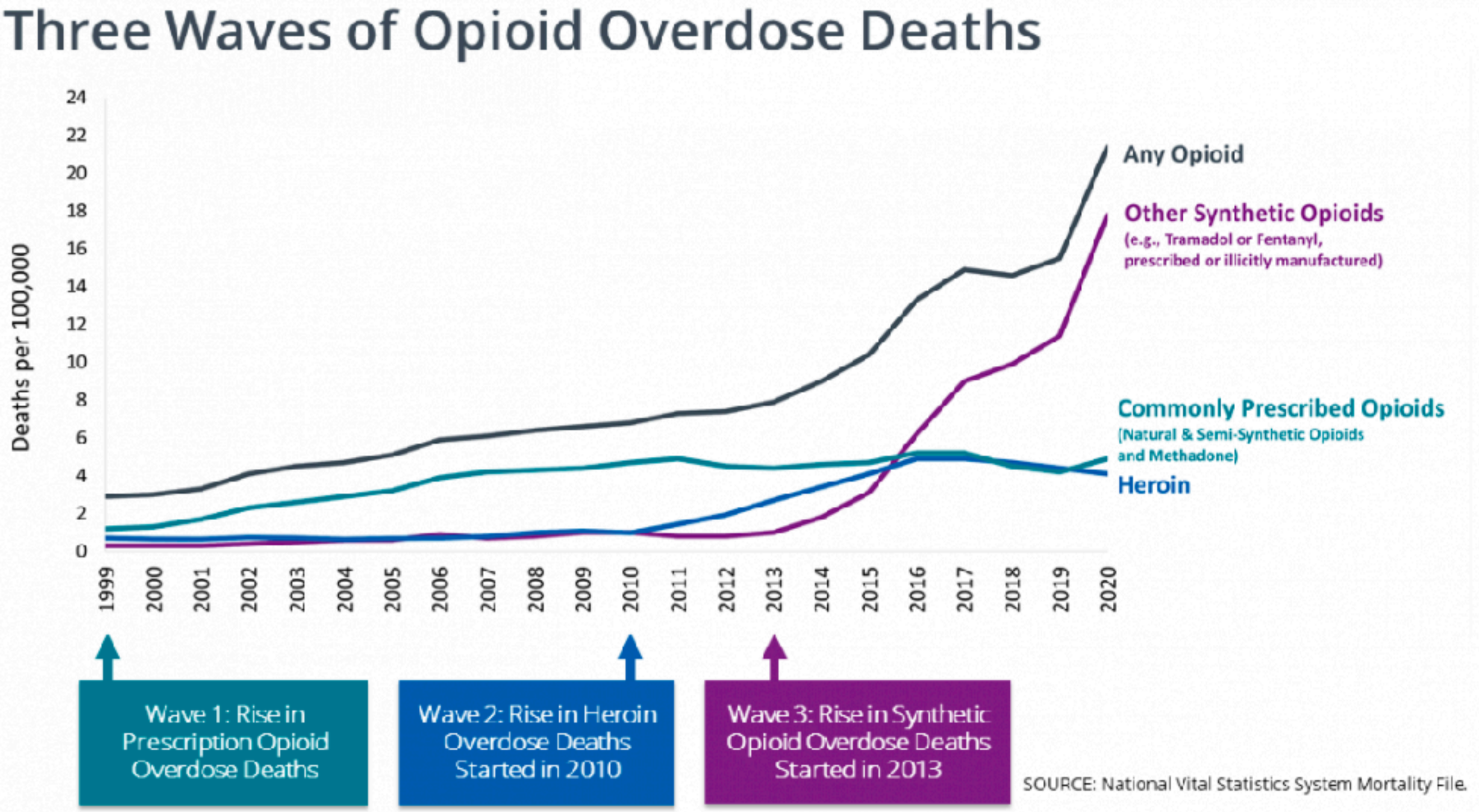
- Chronic activation leads to tolerance
- Euphoric effects diminished



KOR
dysphoria and aversion

- Heightened dysphoric effects
- Withdrawal symptoms

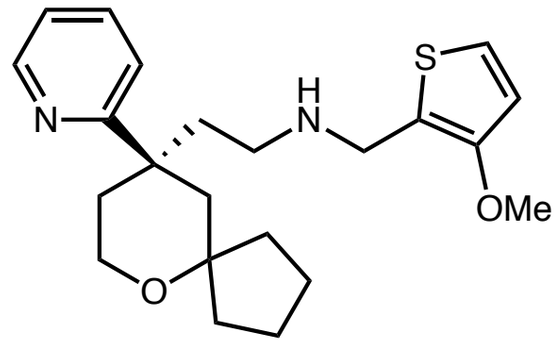
The opioid epidemic



Designing safer opioids

How can we design safer opioid receptor ligands?

Designing safer opioids



Oliceridine

- First approved "**biased opioid receptor agonist**"
- Approved in 2020 for IV use in hospitals to treat moderate to severe acute pain

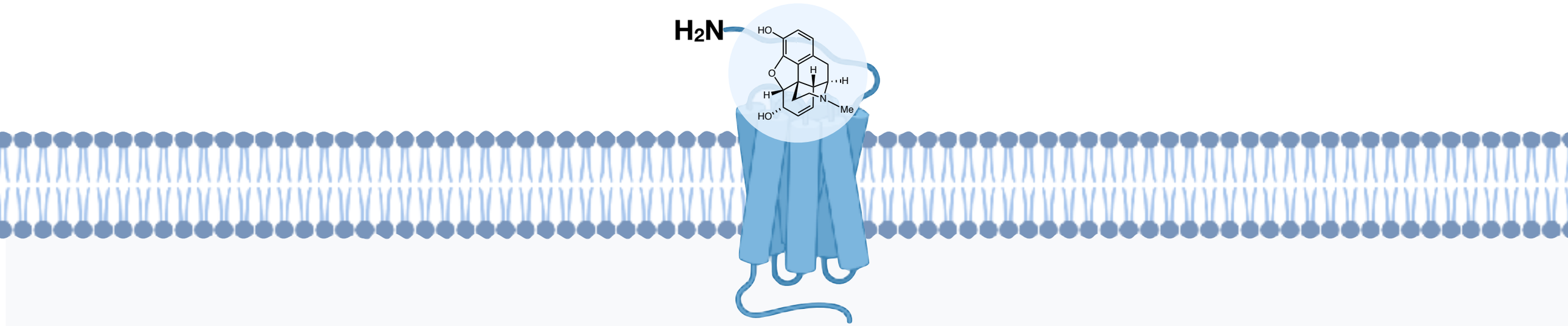
FDA NEWS RELEASE

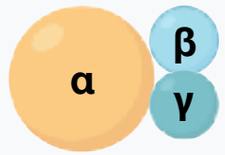
FDA Approves New Opioid for Intravenous Use in Hospitals, Other Controlled Clinical Settings

Share | Tweet | LinkedIn | Email | Print

For Immediate Release: August 07, 2020

Opioids: Mechanism of action



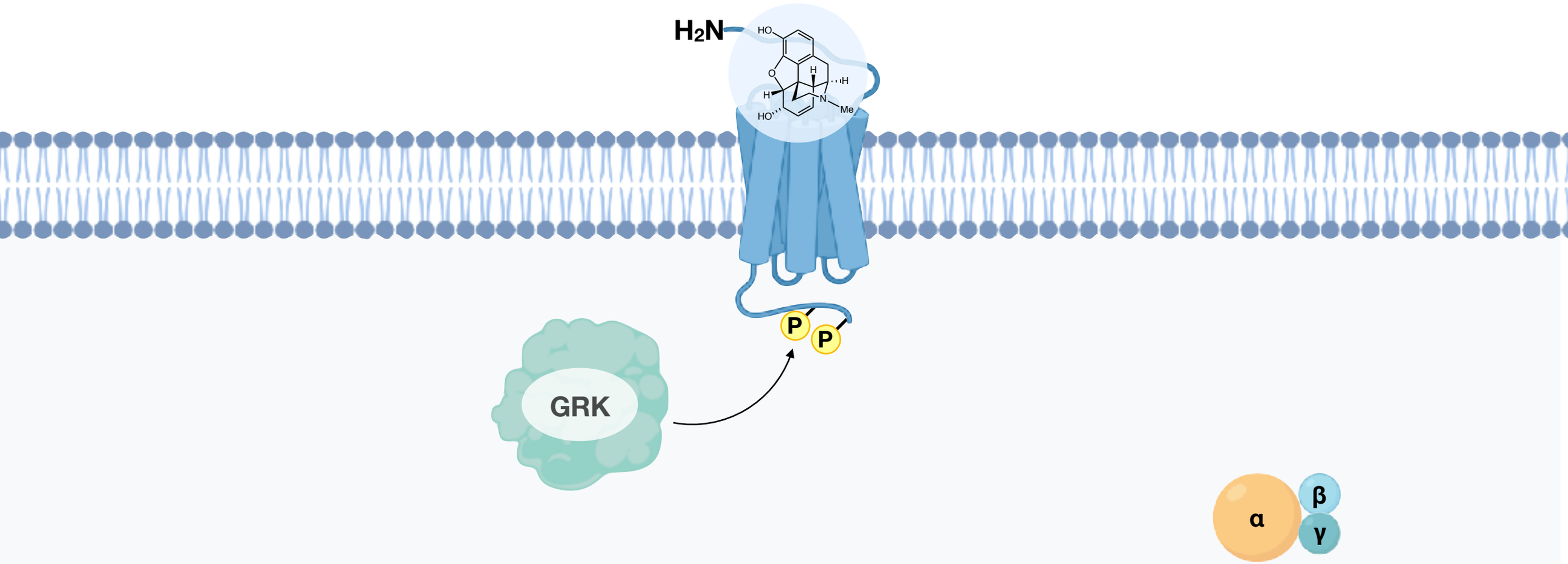


G-protein signaling pathway

Analgesic effects

T. Che, H. Dwivedi-Agnihotri, A.K. Shukla, B.L. Roth. Biased ligands at opioid receptors: Current status and future directions. Sci. Signal., **2021,** *14*, Article eaav0320

Opioids: Mechanism of action



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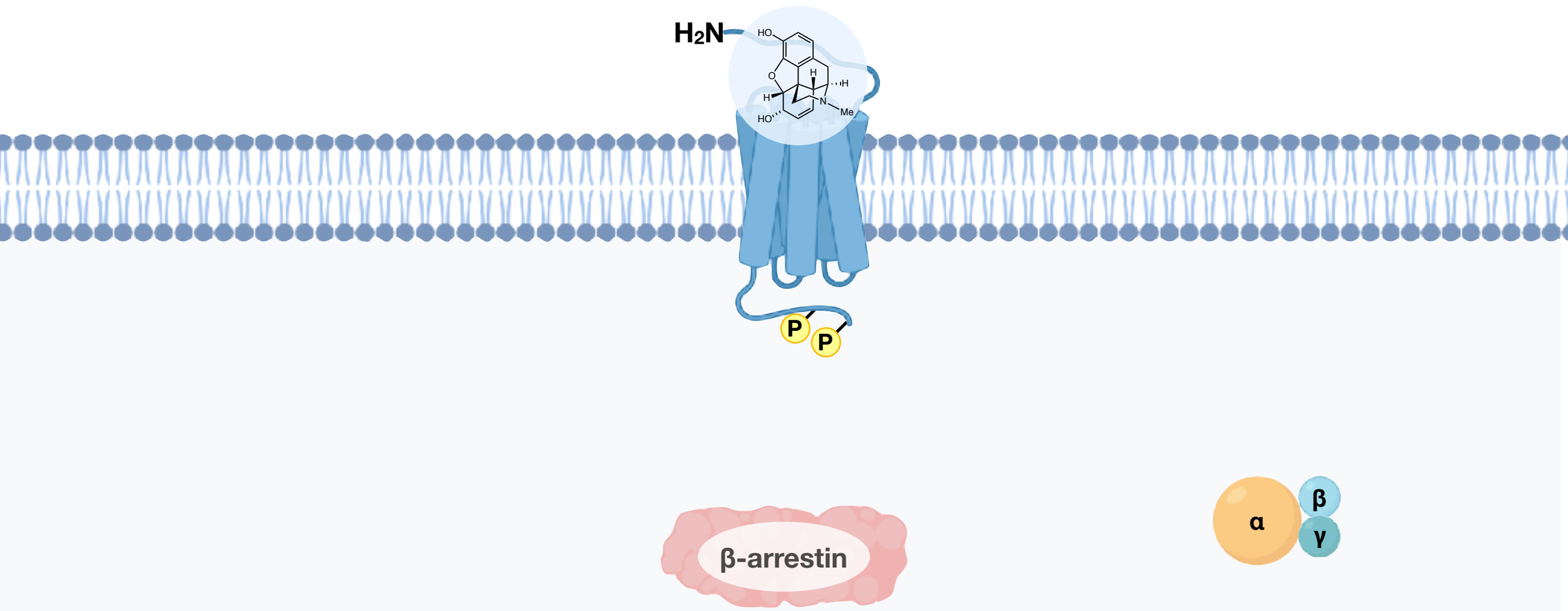

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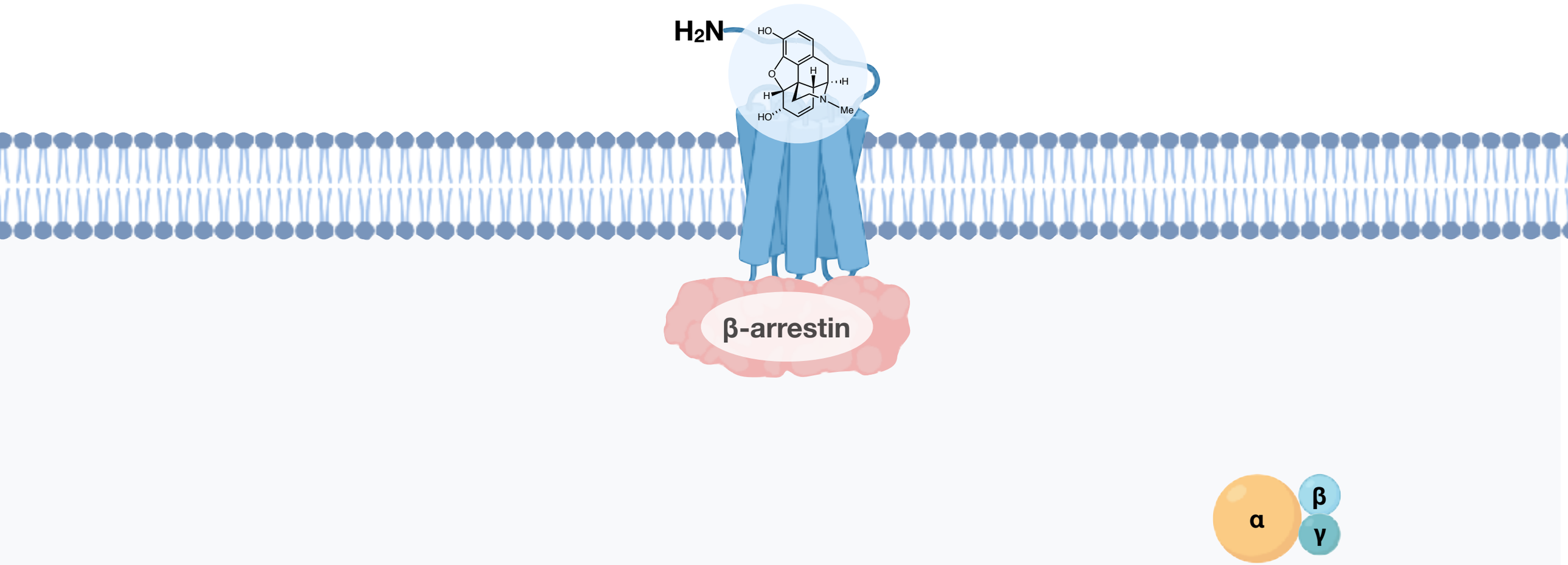

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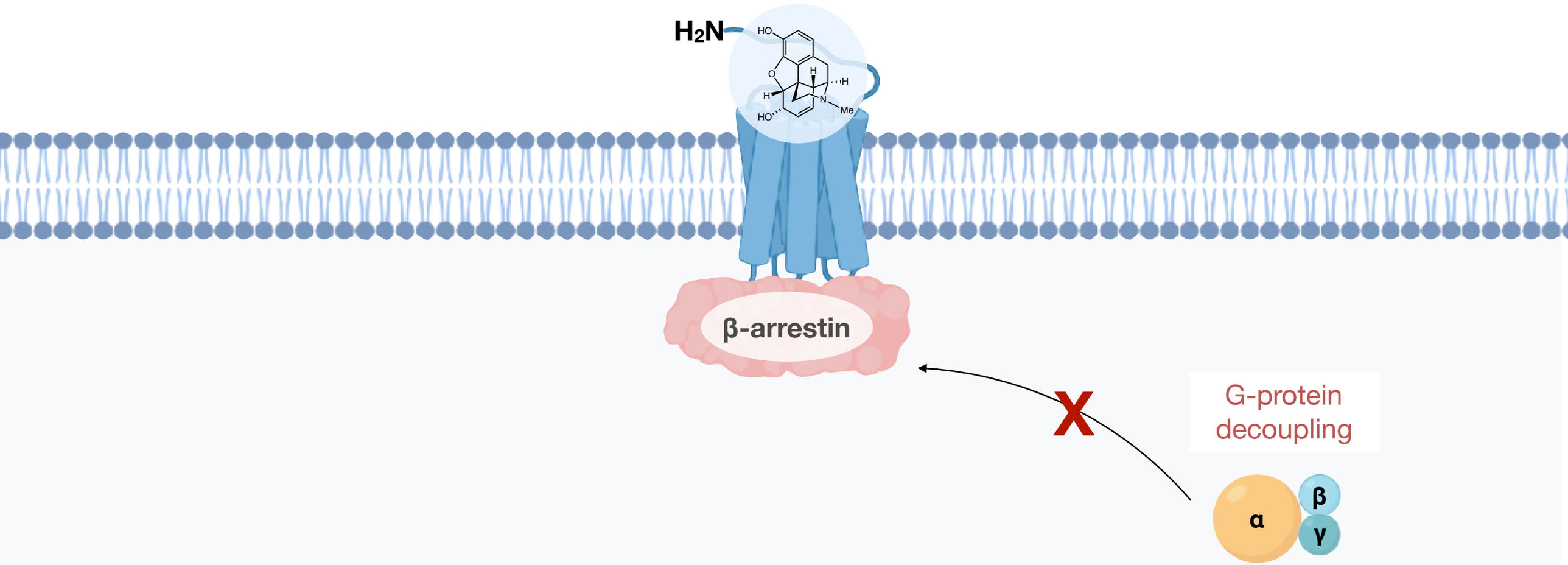
Opioids: Mechanism of action



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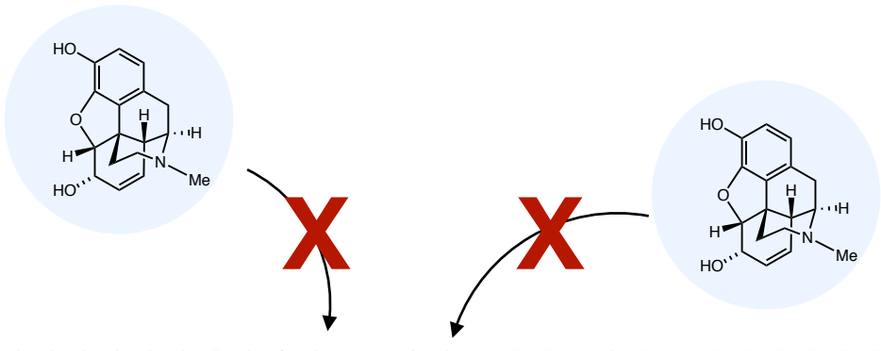
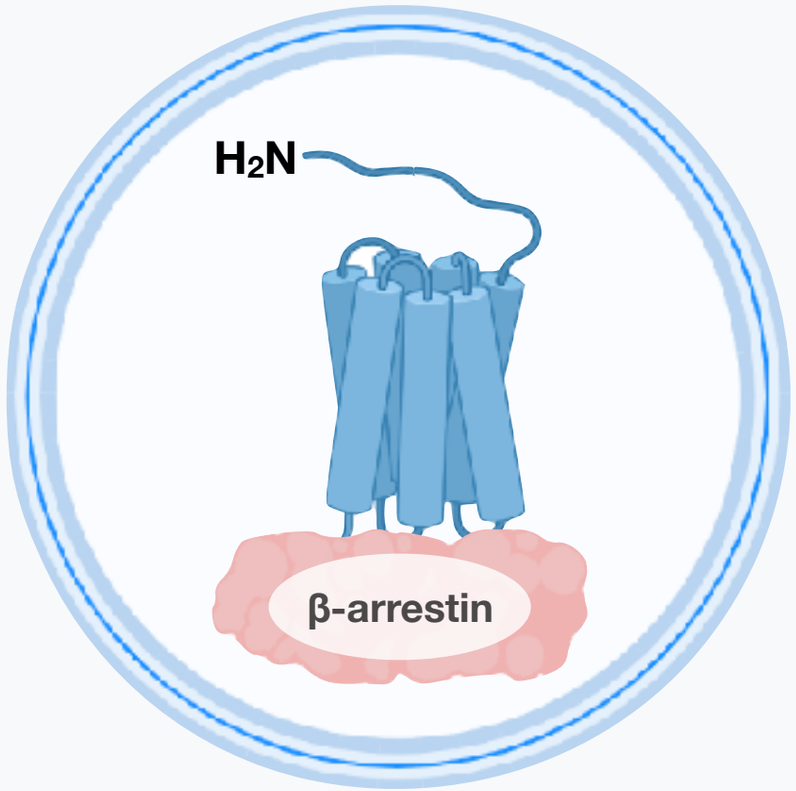
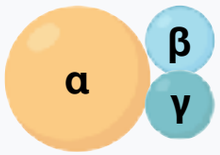
Opioids: Mechanism of action





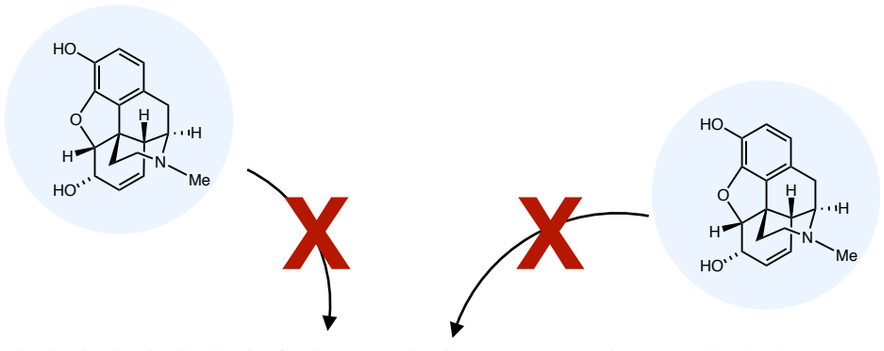
G-protein decoupling



Receptor internalization

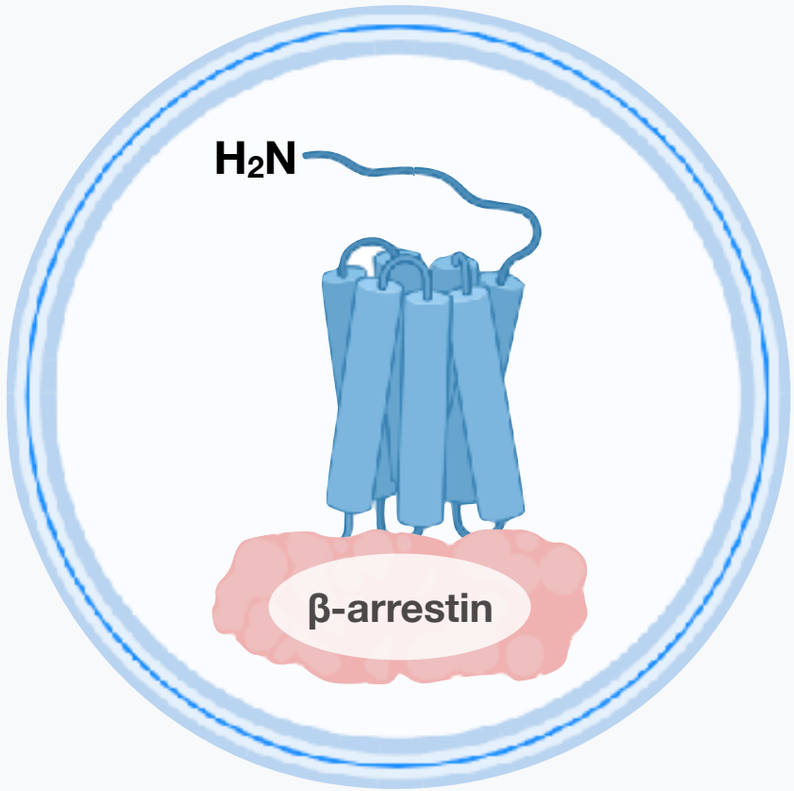
T. Che, H. Dwivedi-Agnihotri, A.K. Shukla, B.L. Roth. Biased ligands at opioid receptors: Current status and future directions. Sci. Signal., **2021,** *14*, Article eaav0320

Opioids: Mechanism of action

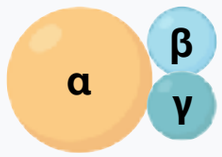


β-arrestin-dependent pathways

Sensitization and tolerance



G-protein decoupling



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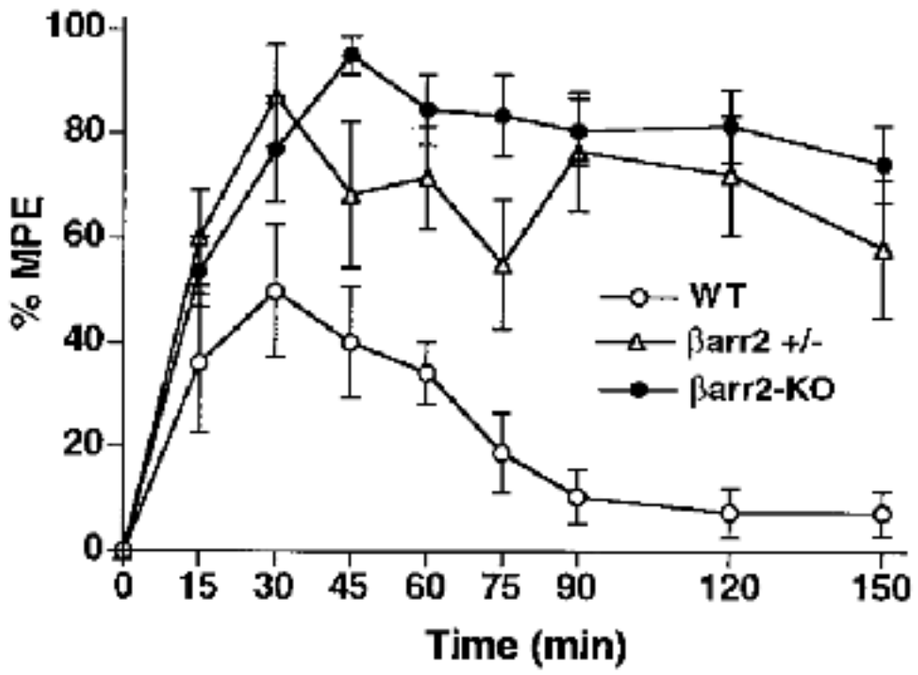
β-arrestin signaling pathway

β-arrestin knockout mice

Hot plate test

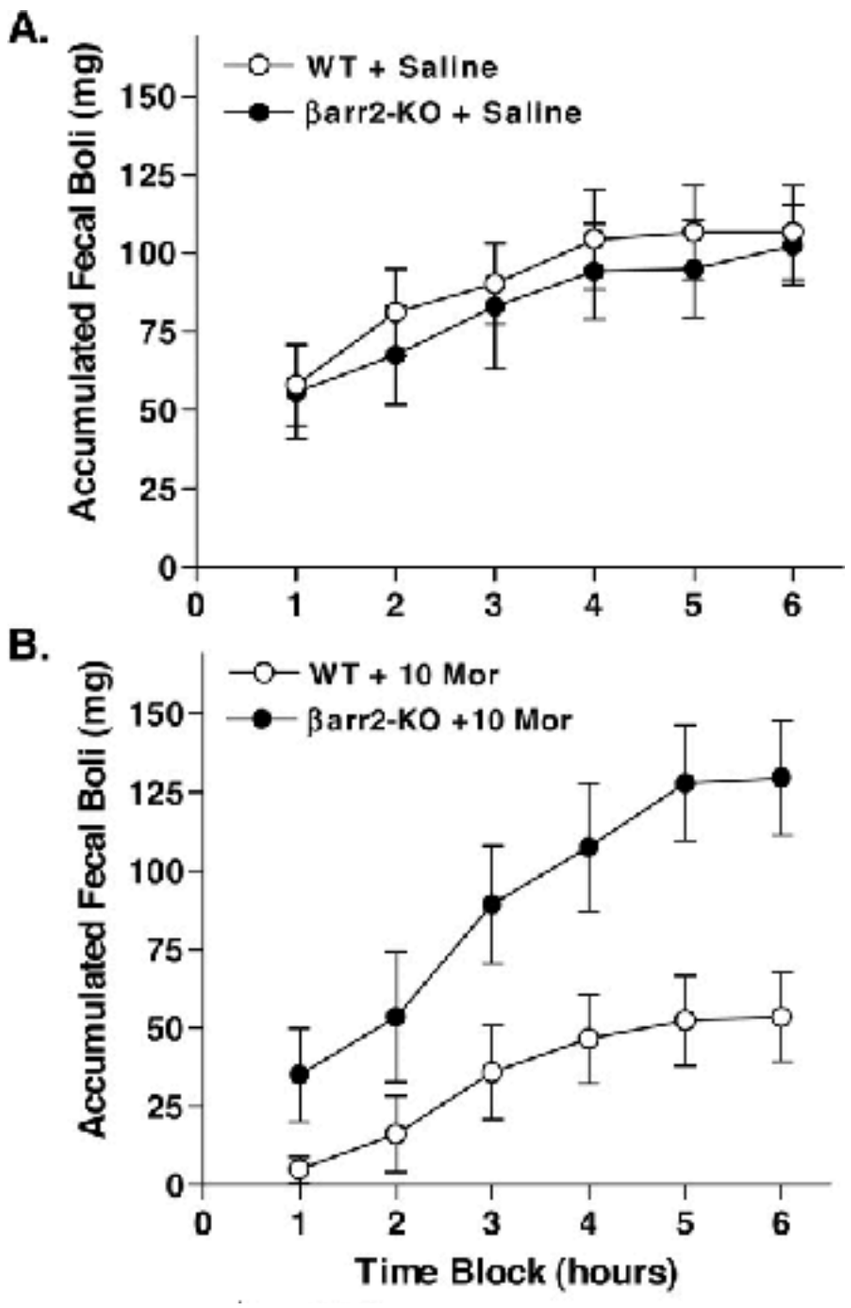
% MPE =
maximum possible effect



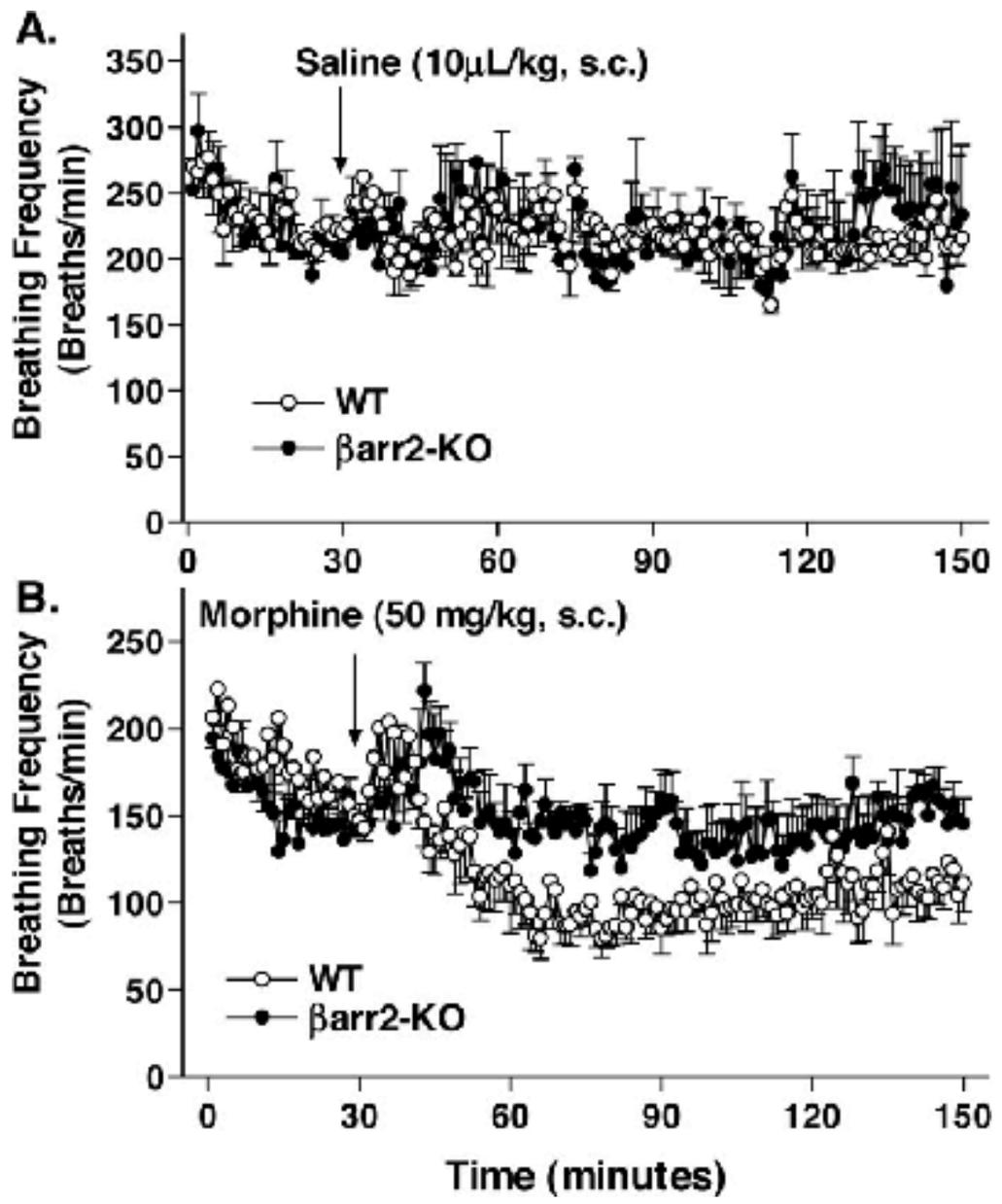
Prolonged anesthesia in
β-arrestin knockout mice

Bohn, L. M.; Lefkowitz, R. J.; Gainetdinov, R. R.; Peppel, K.; Caron, M. G.; Lin, F.-T. Enhanced morphine analgesia in mice lacking β-arrestin 2. Science 1999, 286, 2495–2498.

Decreased adverse effects of morphine in β-arrestin knockout mice



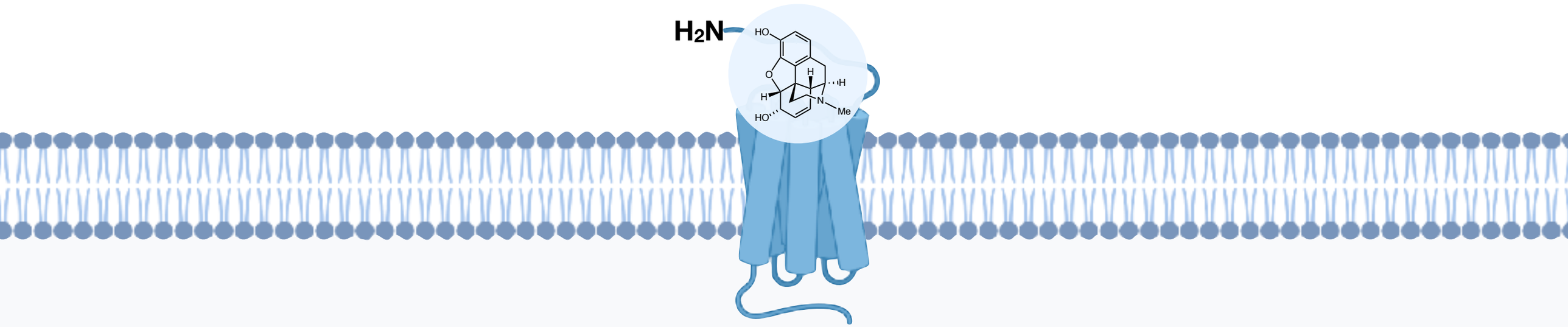
Decreased levels of constipation



Decreased respiratory depression

Raehal, K. M., Walker, J. K. & Bohn, L. M. Morphine side effects in β-arrestin 2 knockout mice. J. Pharmacol. Exp. Ther. 314, 1195–1201 (2005).

Opioids: Mechanism of action



β-arrestin

α
β
γ

G protein-dependent signaling pathway

Sensitization, tolerance, adverse side effects

Analgesic effects

T. Che, H. Dwivedi-Agnihotri, A.K. Shukla, B.L. Roth. Biased ligands at opioid receptors: Current status and future directions. Sci. Signal., **2021,** *14*, Article eaav0320

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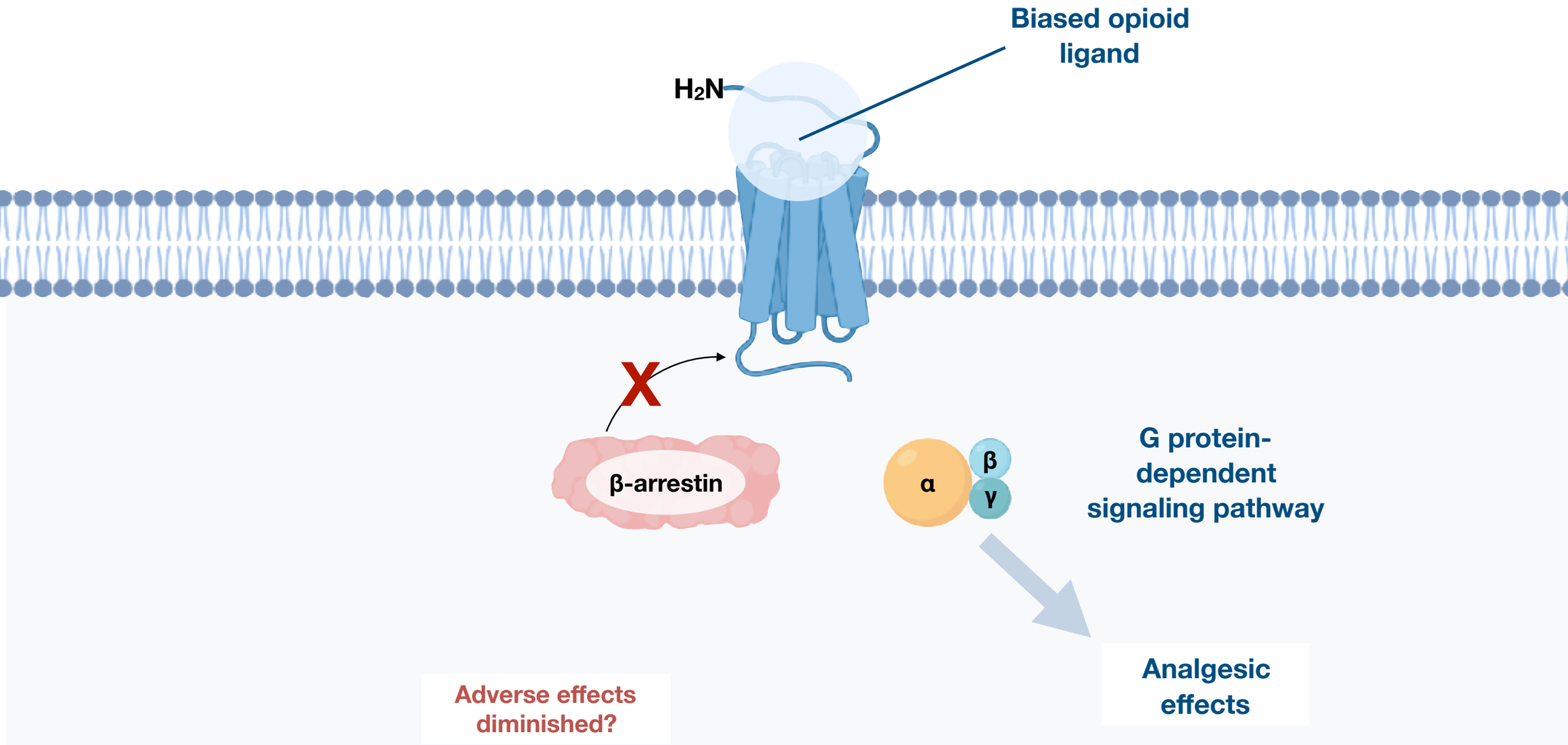
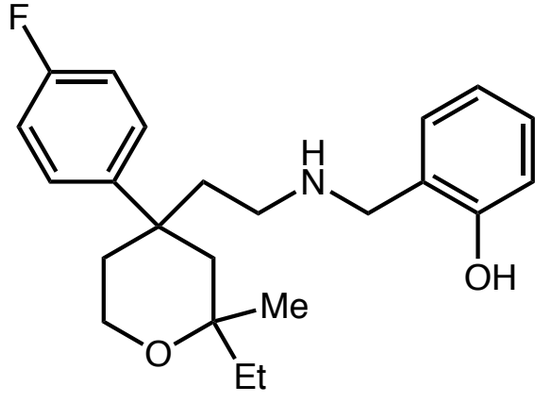
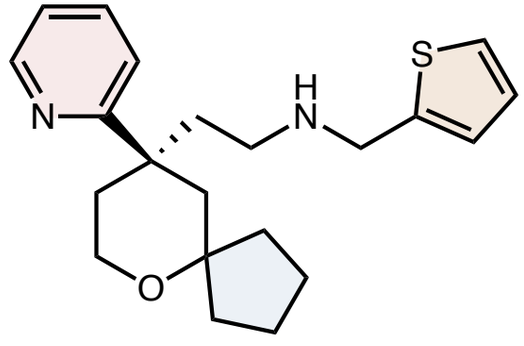
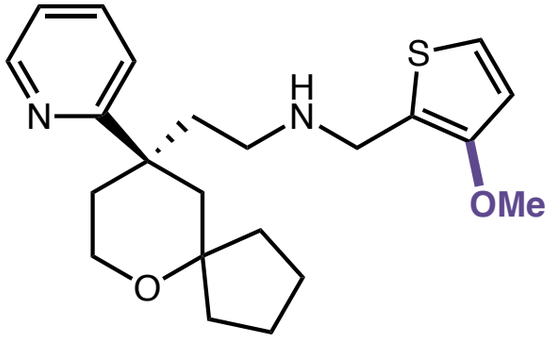


T. Che, H. Dwivedi-Agnihotri, A.K. Shukla, B.L. Roth. Biased ligands at opioid receptors: Current status and future directions. Sci. Signal., **2021,** *14*, Article eaav0320

Back to oliceridine…







TRV130

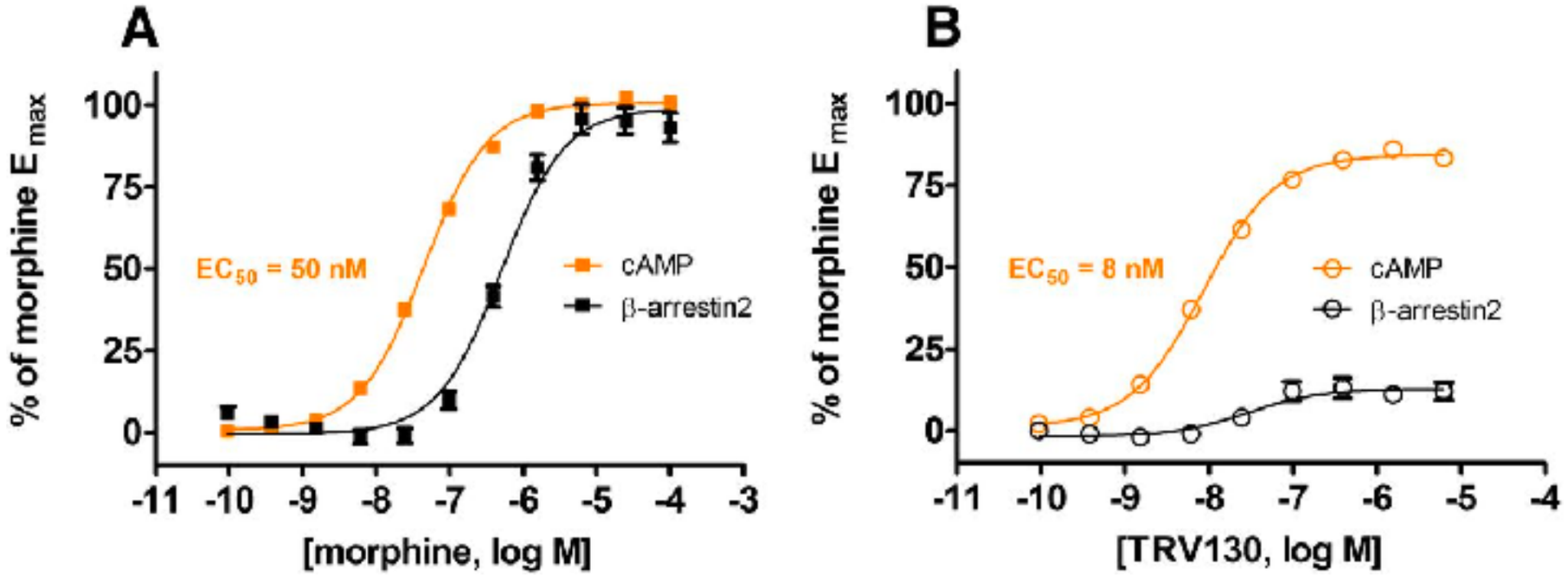
G-protein			
pEC_{50}	7.4	7.8	8.1
Efficacy (rel. to morphine)	108%	95%	84%
β-arrestin			
pEC_{50}	5.8	6.6	7.3
Efficacy (rel. to morphine)	236%	15%	15%

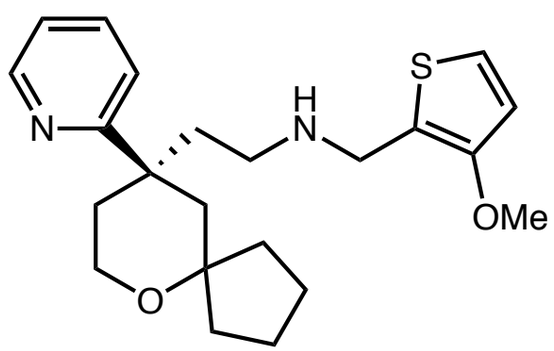
- Increase potency
- Reduce β-arrestin efficacy

Mitigate cardiovascular risk

Chen XT, Pitis P, Liu G, Yuan C, Gotchev D, Cowan CL, et al. "Structure-activity relationships and discovery of a G protein biased μ opioid receptor ligand, [(3-methoxythiophen-2-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro-[4.5]decan-9-yl]ethyl})amine (TRV130), for the treatment of acute severe pain". *J. Med. Chem.* **2013,** *56,* 8019–8031.

Oliceridine in vivo studies





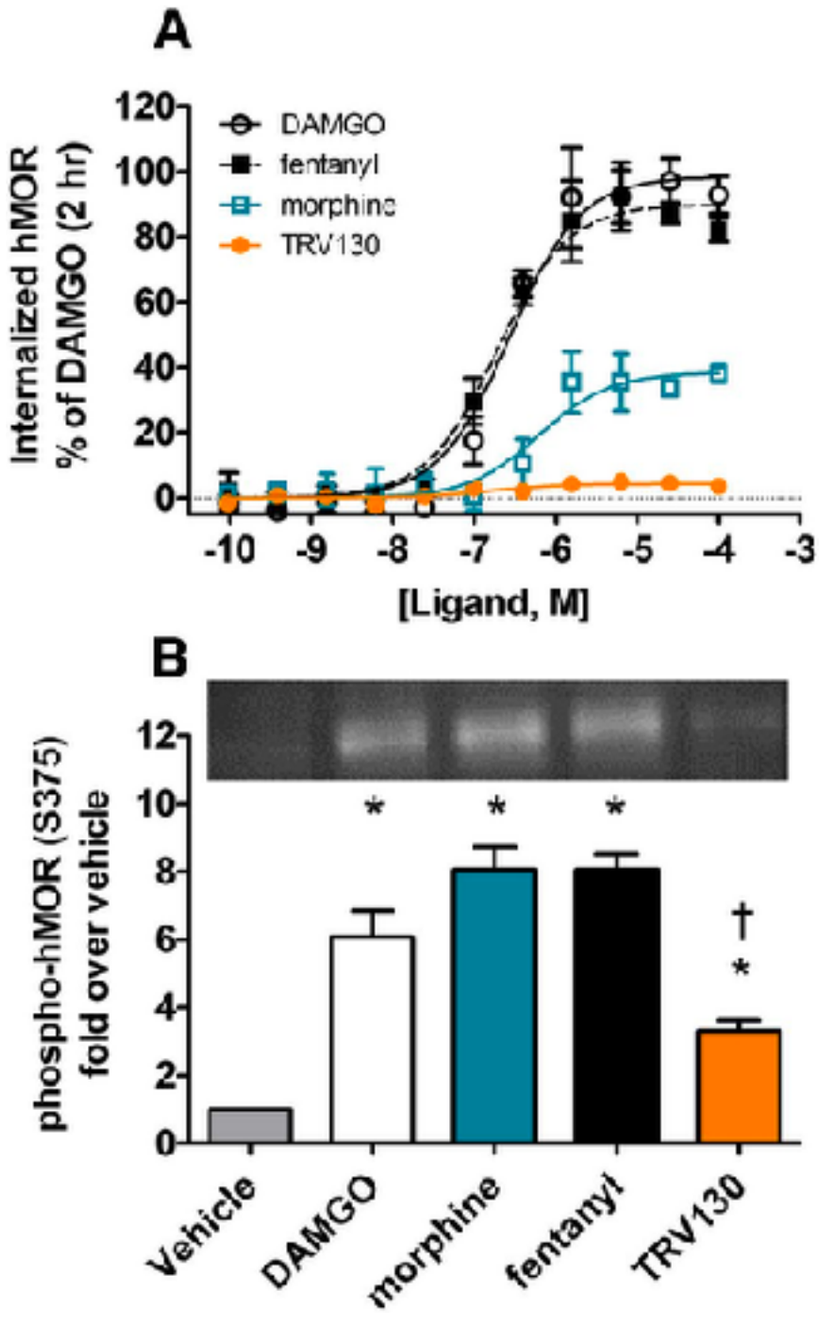
TRV130

Relative to morphine:

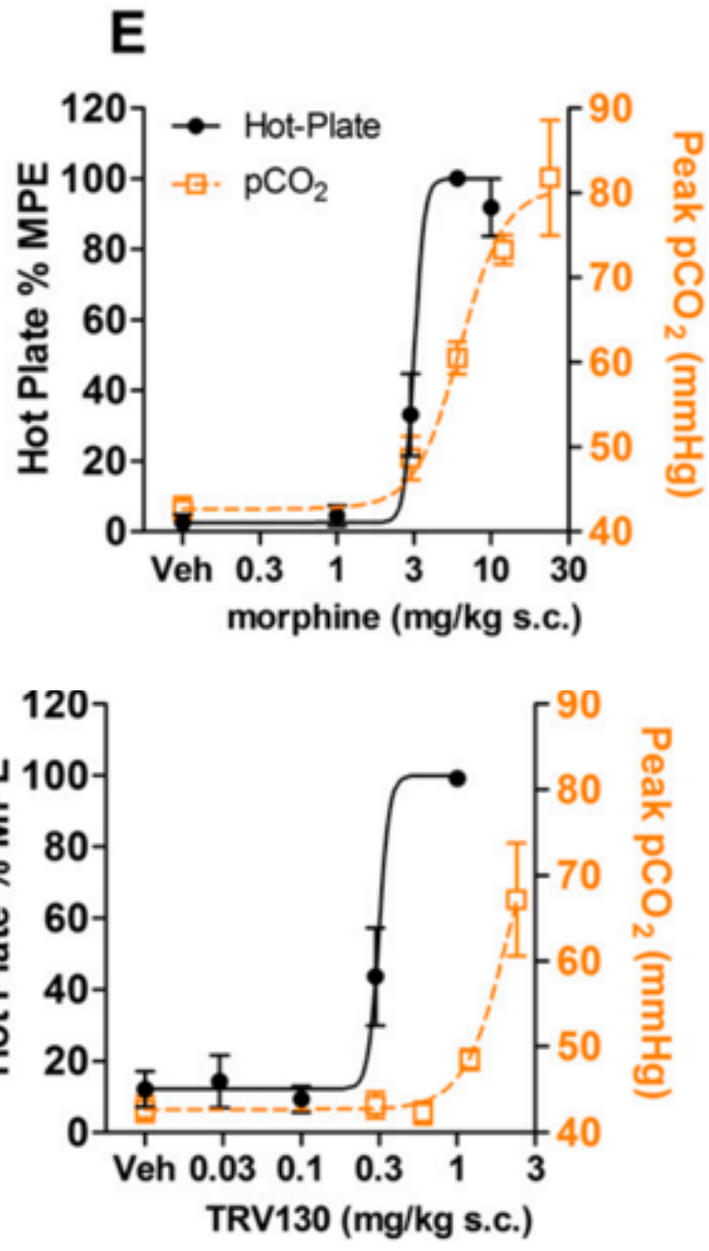
- More potent
- Comparable levels of G-coupling efficiency
- Highly reduced β-arrestin recruitment

DeWire SM, Yamashita DS, Rominger DH, Liu G, Cowan CL, Graczyk TM, et al. A G protein-biased ligand at the μ-opioid receptor is potently analgesic with reduced gastrointestinal and respiratory dysfunction compared with morphine". *The Journal of Pharmacology and Experimental Therapeutics*. **2013**, *344,* 708–17.

Mice studies show reduced adverse effects



Reduced receptor phosphorylation and internalization



Reduced respiratory depression

DeWire SM, Yamashita DS, Rominger DH, Liu G, Cowan CL, Graczyk TM, et al. A G protein-biased ligand at the μ-opioid receptor is potently analgesic with reduced gastrointestinal and respiratory dysfunction compared with morphine". *The Journal of Pharmacology and Experimental Therapeutics*. **2013**, *344,* 708–17.

Development and approval of oliceridine

Oct. 2018

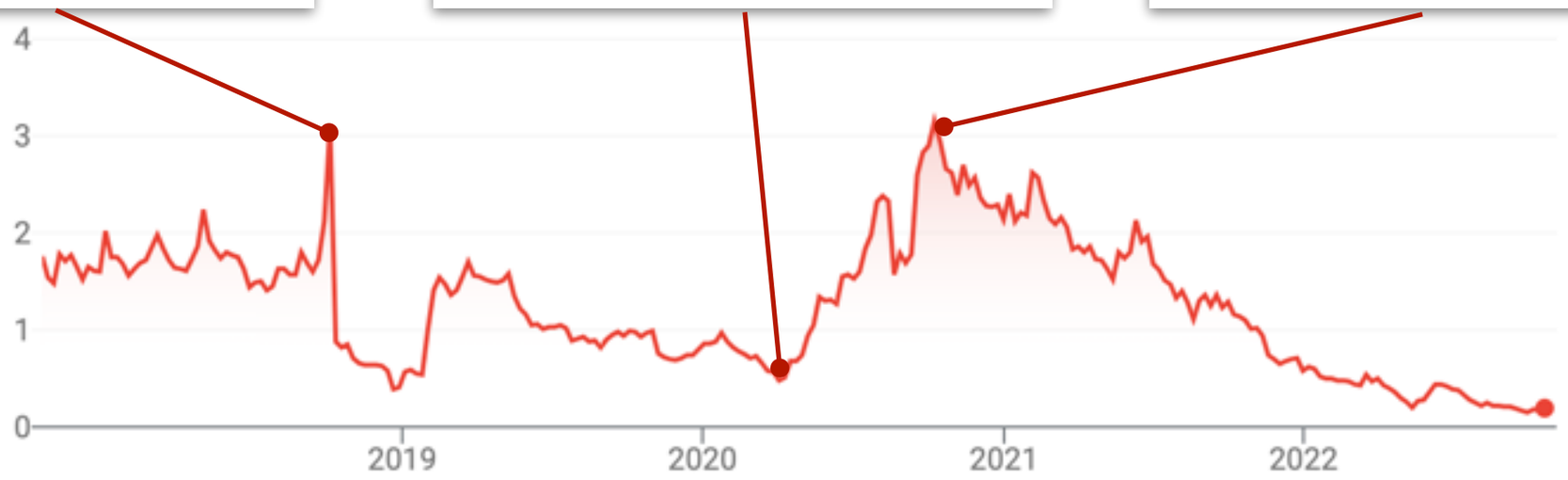
Oliceridine rejected by FDA in a 7-8 vote for inadequate safety profile

Feb. 2020

After obtaining further data, Trevena resubmits application for approval

Aug. 2020

Oliceridine approved by FDA in a 8-7 vote



Development and approval of oliceridine

ADVERSE EVENTS (AEs) IN ≥5% OF PATIENTS	PLACEBO (n=162)	OLINVYK ≤27% mg (n=316)	IV MORPHINE (n=158)
Patients with any TEAE	**73**	**86**	**96**
Nausea (%)	35	52	70
Vomiting (%)	10	26	52
Headache (%)	30	26	30
Dizziness (%)	11	18	25
Constipation (%)	9	14	14
Hypoxia (%)	3	12	17
Pruritus (%)	6	9	19
Sedation (%)	5	7	13
Somnolence (%)	4	6	10
Back pain (%)	4	6	6
Hot flush (%)	4	4	8
Pruritus generalized (%)	1	2	10

Doubts of β-arrestin mechanism

How much can the adverse effects of opioids be attributed to β-arrestin-dependent signaling pathways?

- Re-examining the original mice knockout studies
- New studies on the relationship between G-proteins, b-arrestin, and adverse effects

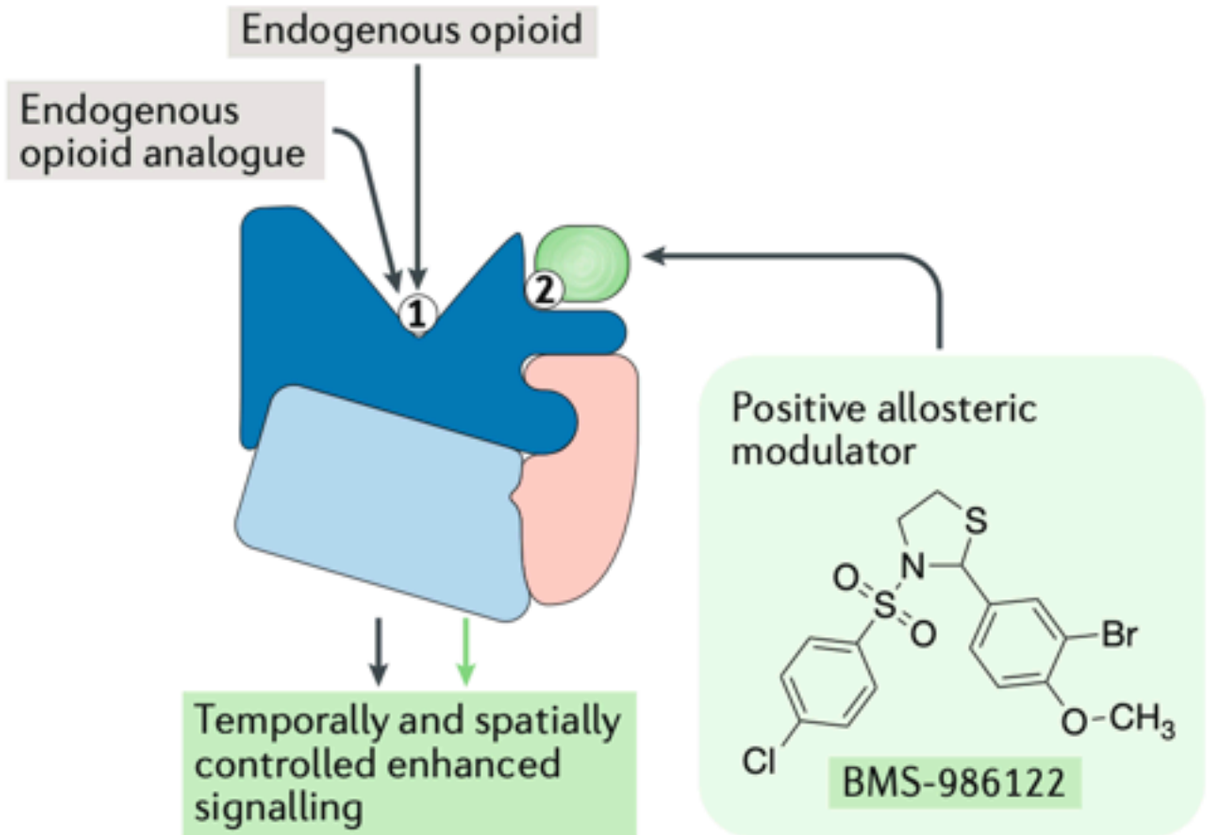
Do biased opioid receptor ligands selectively activate G-protein-dependent signaling pathways?

- Re-examining the assays used to study biased opioid receptor ligands
- Re-examining the proposed mechanism of action of biased opioid receptor ligands

Gillis, A.; Kliewer, A.; Kelly, E.; Henderson, G.; Christie, M. J.; Schulz, S.; Canals, M. Critical assessment of G protein-biased agonism at the μ-opioid receptor. Trends Pharmacol. Sci. 2020, 41, 947–959.

Approaches for designing safer opioids

Allosteric opioid receptor modulators:
Positive allosteric modulators enhance binding affinity

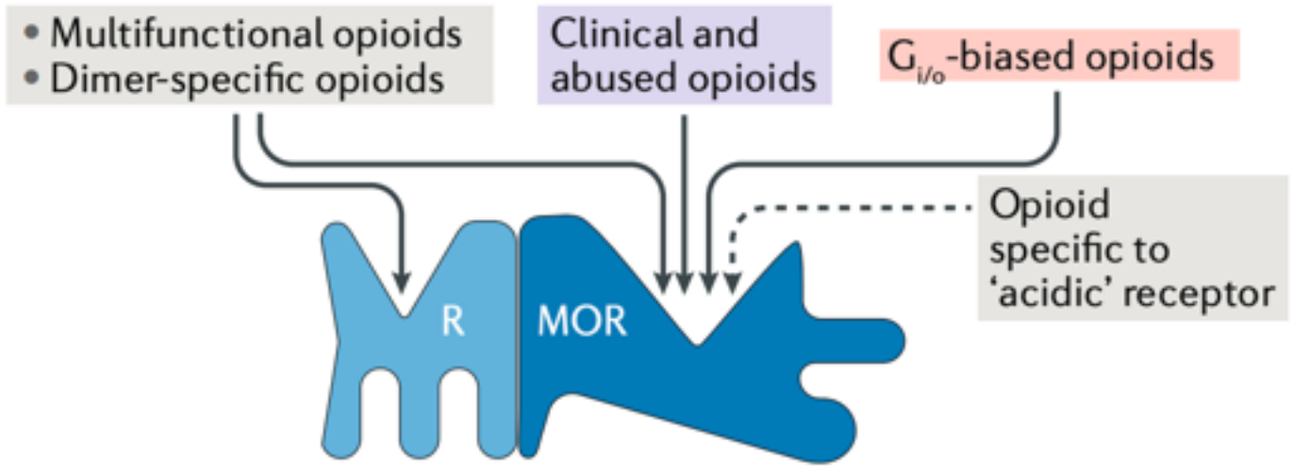


Darcq, E., Kieffer, B.L. Opioid receptors: drivers to addiction?. *Nat Rev Neurosci.* **2018,** *19*, 499–514.

Approaches for designing safer opioids

Multifunctional opioid ligands:

- Target multiple opioid receptors
- Target opioid and nonopioid receptors



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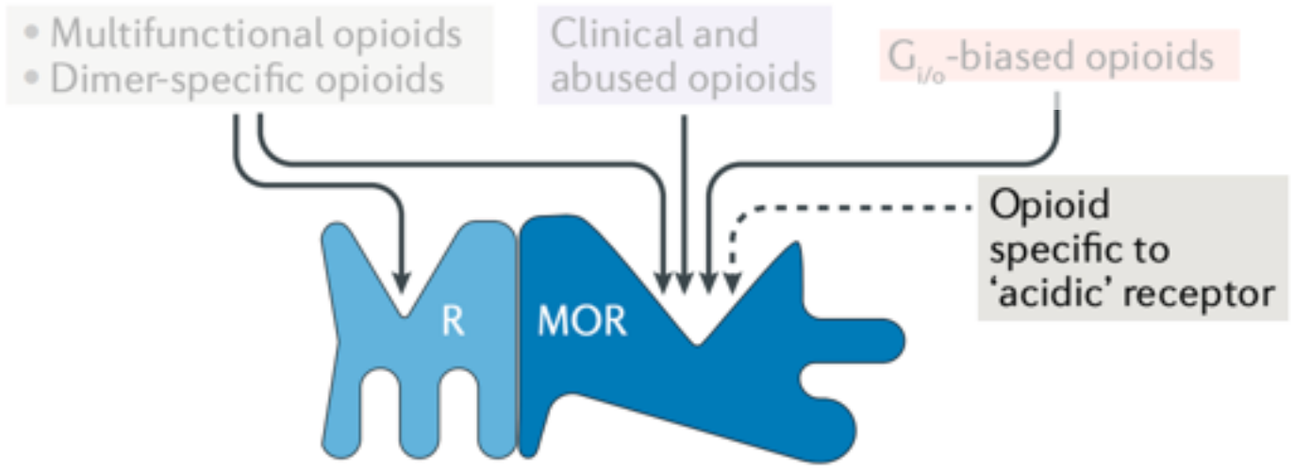

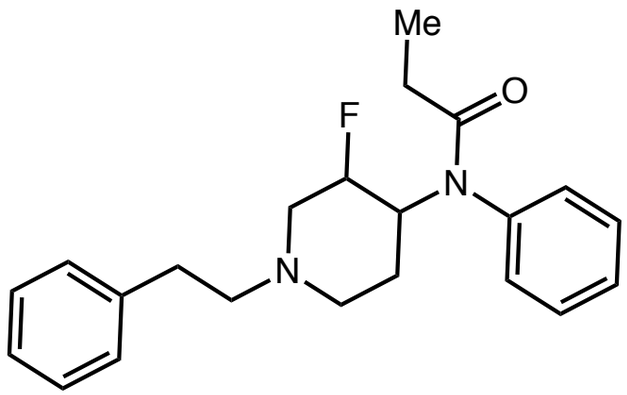

NFEPP:
pH-sensitive
fentanyl derivative

Darcq, E., Kieffer, B.L. Opioid receptors: drivers to addiction?. *Nat Rev Neurosci.* **2018,** *19*, 499–514.

Approaches for designing safer opioids

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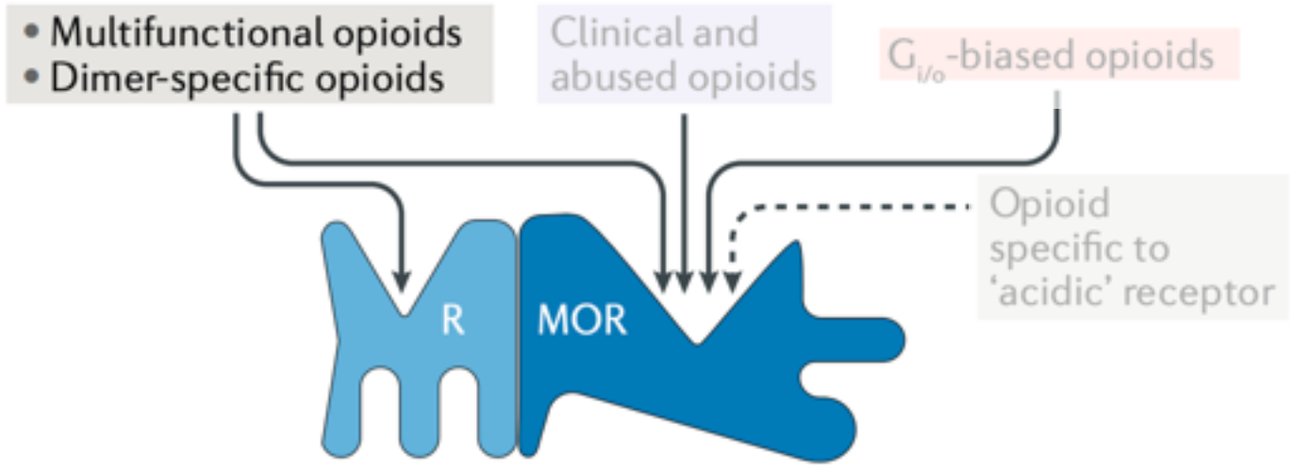

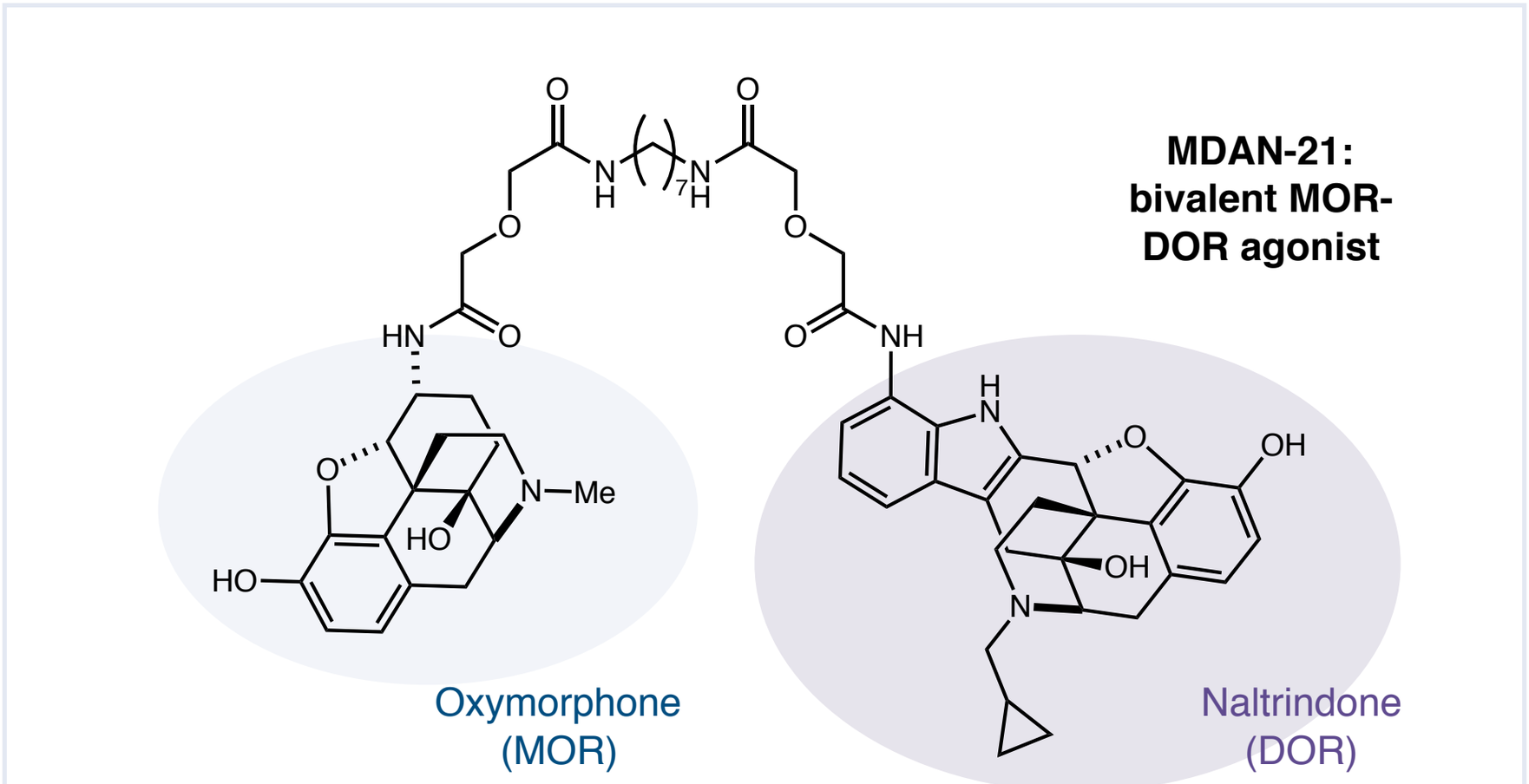

Darcq, E., Kieffer, B.L. Opioid receptors: drivers to addiction?. *Nat Rev Neurosci.* **2018,** *19*, 499–514.

Conclusion

Table 2. NIH Expenditures per Affected Person in the United States for 6 Major Chronic Conditions

Chronic Condition	*Dollars Per Affected Person**
Heart disease	48
Diabetes	41
HIV/AIDS	2,562
Alzheimer's disease	97
Cancer	431
Chronic pain	4

Challenges:

- Difficulties in translating preclinical models to humans
- Insufficient understanding of mechanisms behind pain