Pharmacology of Opioids

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- Effects of opioids
- Mechanism of action
- Actions and selectivities of some opioids
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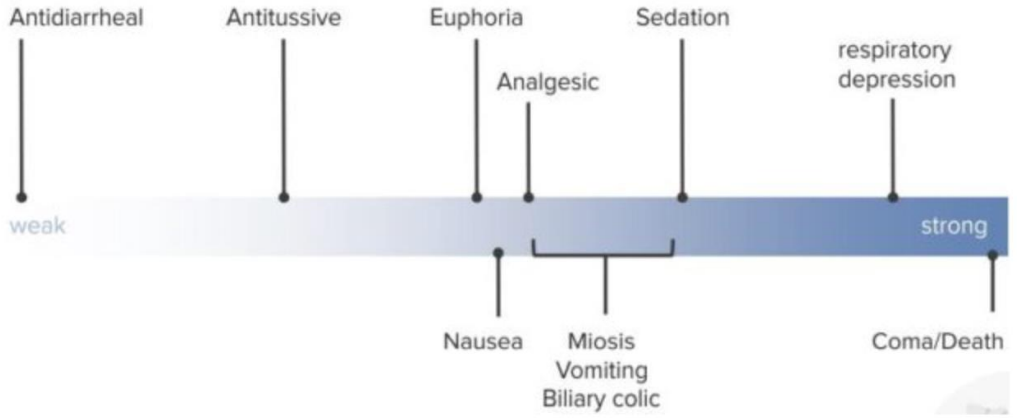
Definition

- Opiates = compounds structurally related to products found in opium.
  - E.g. morphine, codeine
- Opioids = agents with functional and pharmacological properties (regardless of their structure) of opiates.
  - E.g. endogenous opioids (endorphins), fentanyl

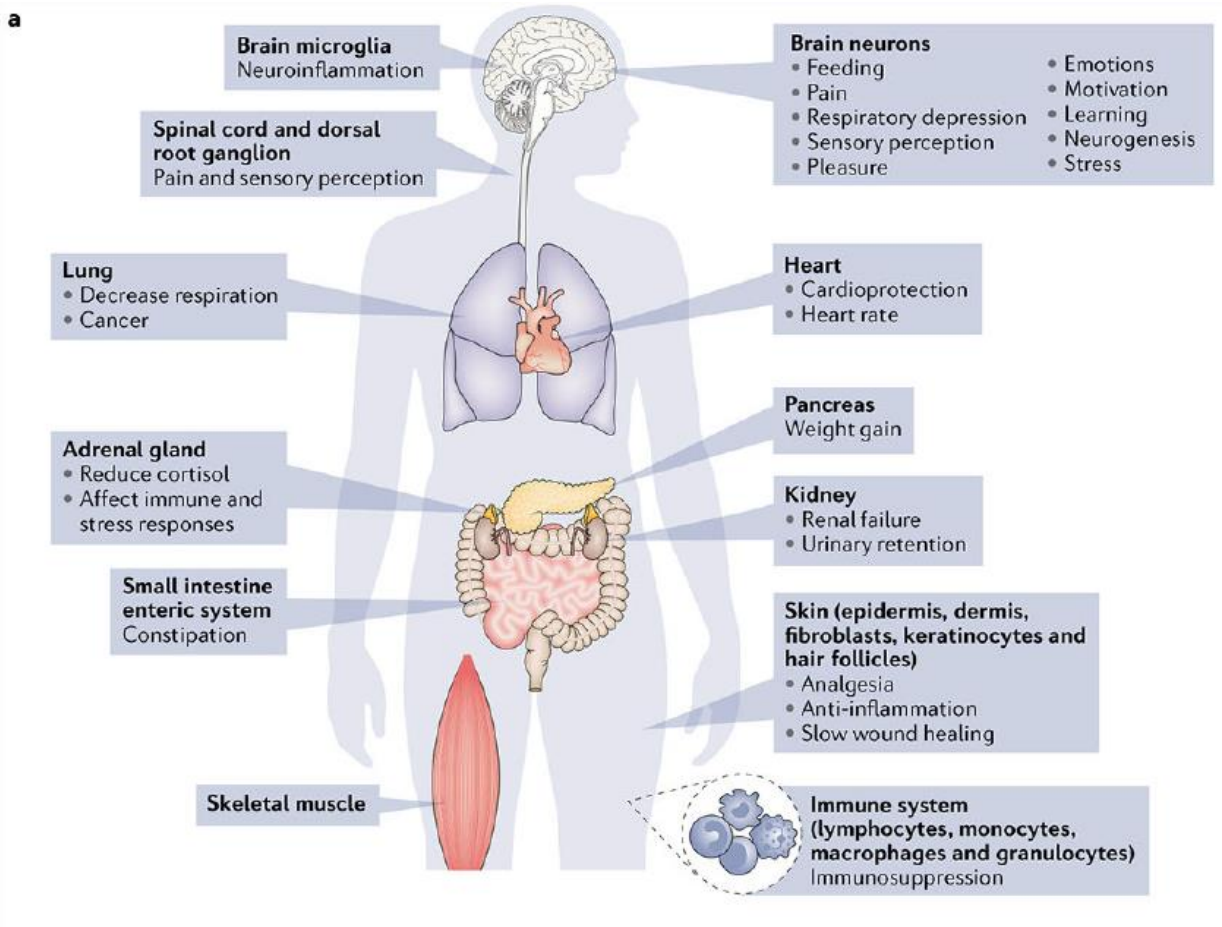
Effects of opioids

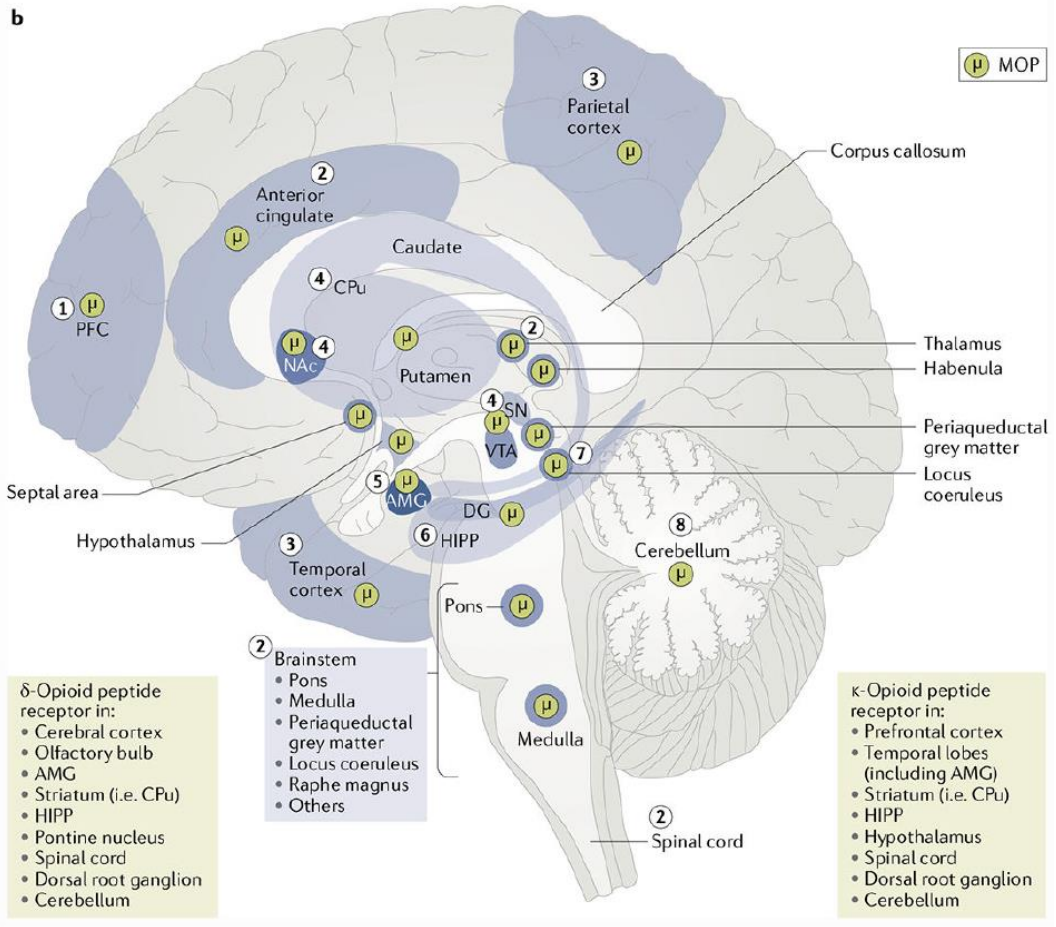
- Analgesia
- Mood alterations and rewarding properties
- Sedation
- Miosis
- Pruritis
- Pulmonary oedema
- Respiratory depression
- Reduced bowel motility → constipation
- Smooth muscle contraction → gastroparesis
- Nausea and vomiting
- Dry mouth → dental decay



https://www.lecturio.com/magazine/opioids/

Opioid actions throughout the body



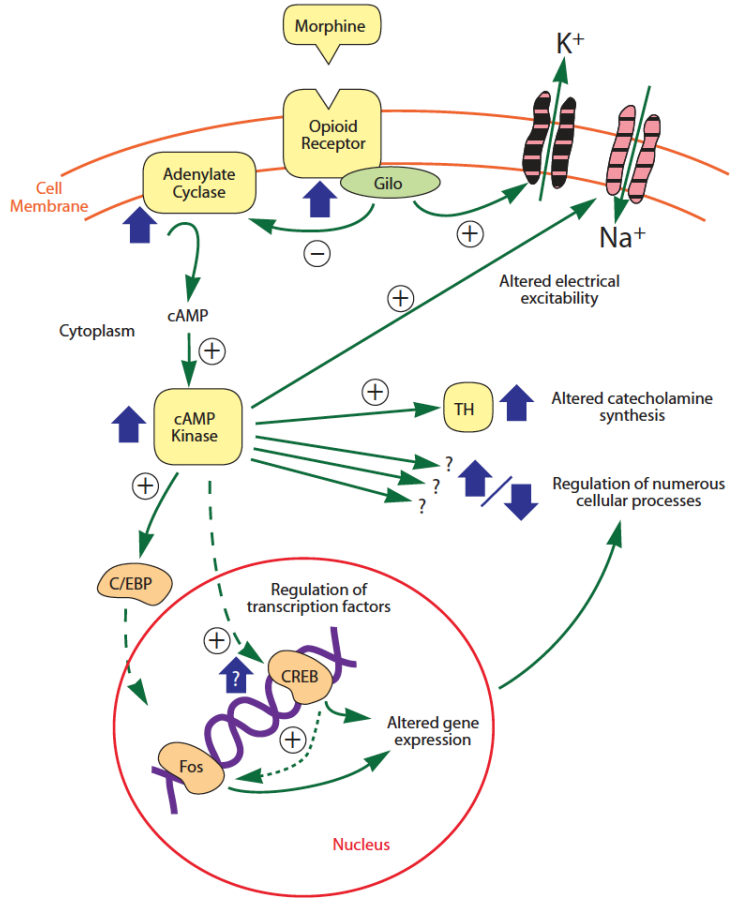


(Kibaly et al. 2019)

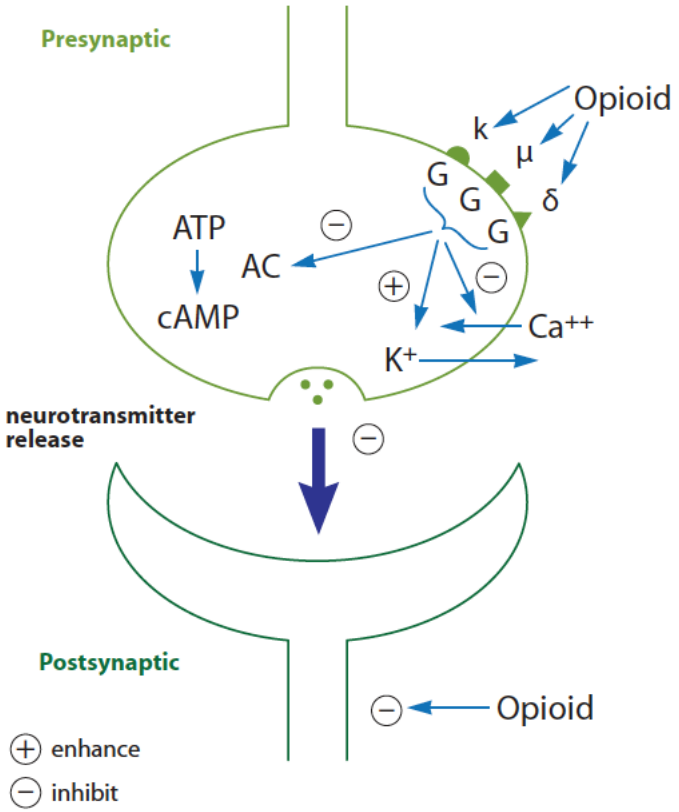
Mechanism of action

- Opioids act on opioid receptors in the brain to produce analgesia, and varying amounts of euphoria and sedation.
  - Mu receptors → located primarily in the brainstem and medial thalamus → euphoria, sedation, analgesia, miosis, reduced GI motility, respiratory depression, physical dependence
  - Kappa receptors → located principally in the spinal cord, basal ganglia and temporal lobes → drowsiness and dysphoria
  - Delta receptors → mediate analgesia and also have cardiovascular effects (hypotension, bradycardia)
- Stimulation of mu (and possibly delta) opioid receptors is involved in reward systems.

Mechanism of action



(Trescot et al., 2008)

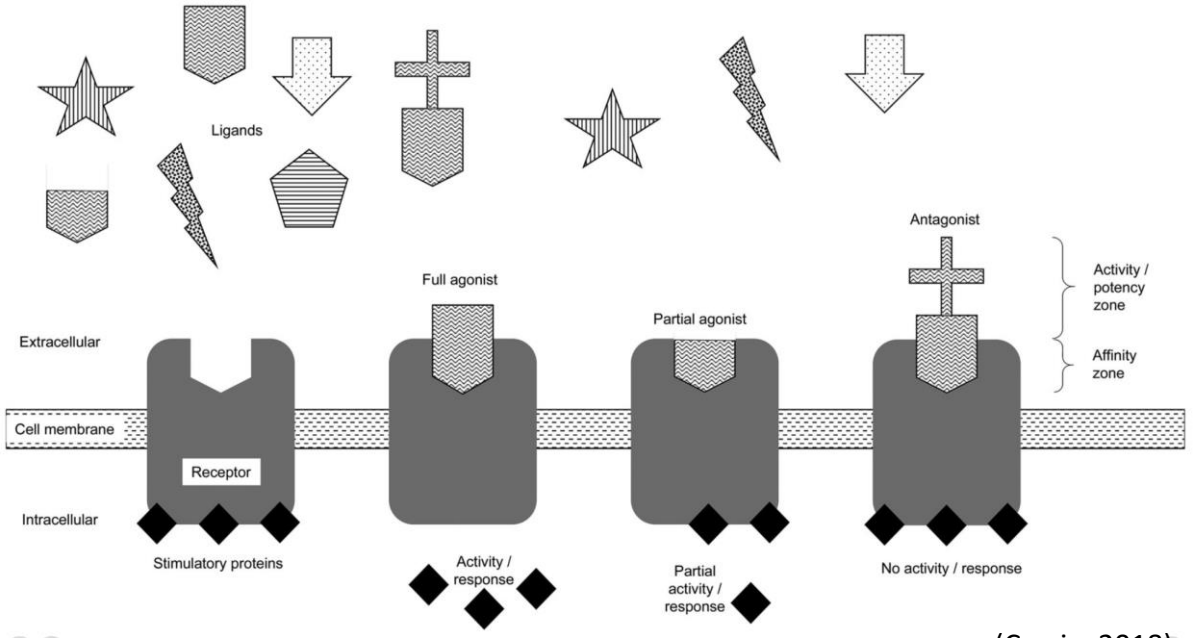


(Trescot et al., 2008)

Classification by actions

- Affinity = strength of interaction between a compound binding to its receptor (“fit the lock”)
- Efficacy = strength of activity or effect from this binding at the receptor (“turn the key”)

- Agonist: affinity and efficacy
- Antagonist: affinity, no efficacy
- Partial agonist: affinity, partial efficacy

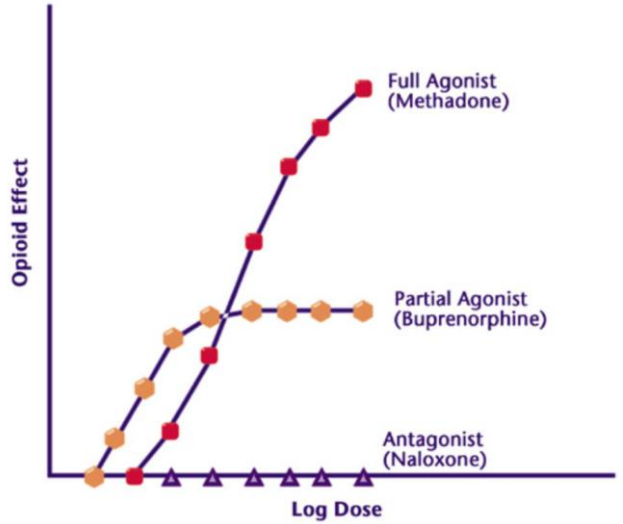


(Currie, 2018)

Actions and selectivities of some opioids

Opioid ligands	μ receptors	δ receptors	κ receptors
Morphine	+++		+
Fentanyl	+++		
Methadone	+++		
Buprenorphine	P		--
β-endorphin	+++	+++	
Naloxone	---	-	--

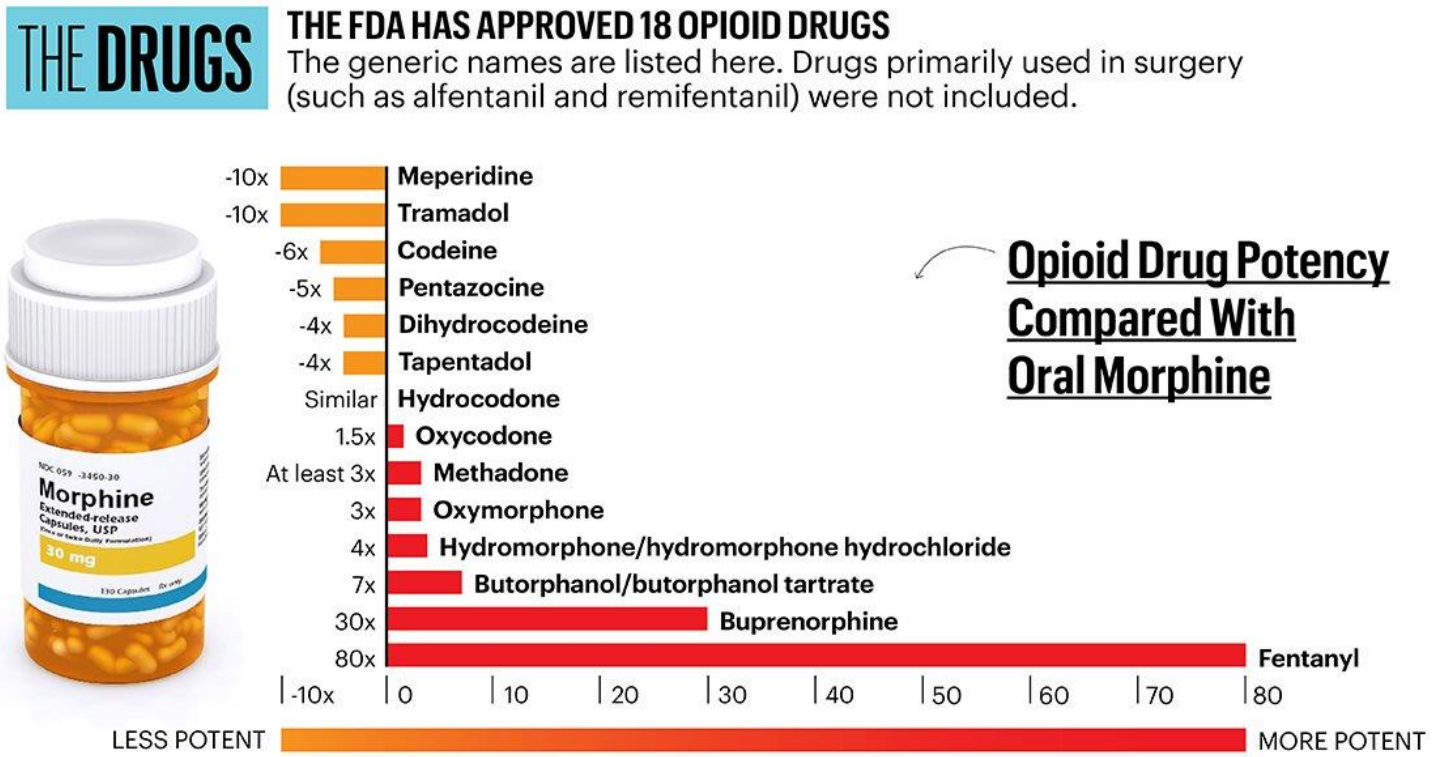
+ : agonist
- : antagonist
P : partial agonist



http://www.naabt.org/education/technical_explanation_buprenorphine.cfm

Potency

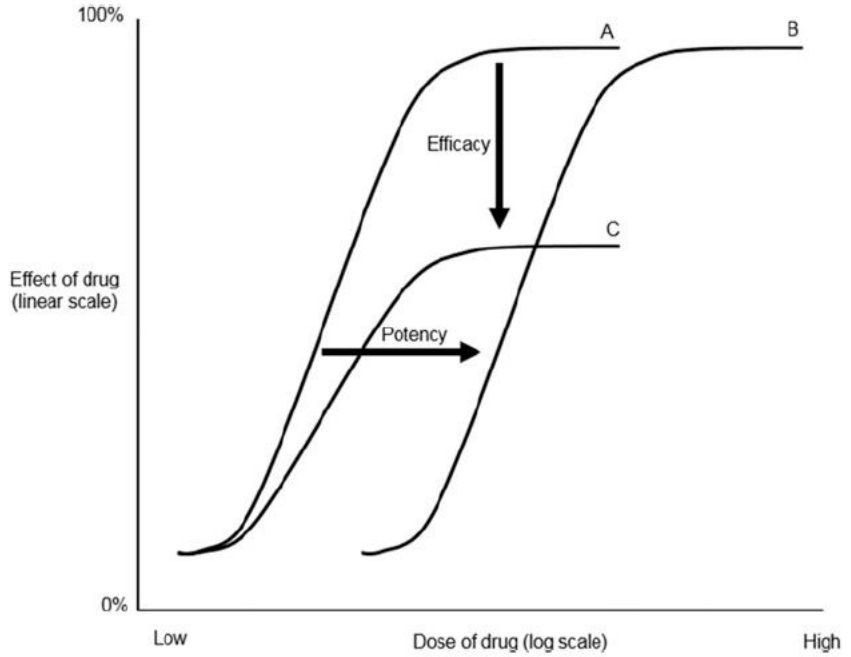
- Potency = the amount of drug required to produce an effect of given intensity.



(AARP, 2017)

Functional consequences of acute and chronic receptor activation

- Desensitization / ‘acute tolerance’ = due to uncoupling of opioid receptors from G-proteins (minutes to hours); specific to the receptor and disappear with a time course parallel to the clearance of the agonist.
- Tolerance = sustained administration of an opiate agonist (days to weeks) leading to progressive loss of drug effect.



(Currie, 2018)

Functional consequences of acute and chronic receptor activation

- Dependence = a state of adaptation manifested by receptor/drug class-specific withdrawal syndrome produced by cessation of drug exposure (e.g. drug abstinence) or administration of an antagonist.
- Addiction = a behavioural pattern characterised by compulsive use of a drug and overwhelming involvement with its procurement and use.

Comparison of the pharmacology of some opioids

	Heroin	Methadone	Buprenorphine
Receptor	Mu agonist	Mu agonist	Partial mu agonist Kappa antagonist
Administration	IV	Oral usually. May be given in reduced dose, IM or SC if NBM	Sublingual
Peak plasma levels	1-2 minutes	2-4 hours	1-2 hours
Plasma half life	2 hours	22 hours	~36 hours
Onset of effects	Minutes	30-60 minutes	30-60 minutes
Peak effect	1-2 minutes	3-6 hours	1-4 hours
Duration of effect	4-5 hours	16-30 hours dose dependent	12 hours low dose 72 hours high dose

Take home message

- Central and peripheral effects of opioids are based on their binding to different receptor types.
- Understanding the concept of efficacy, affinity and potency is helpful in learning about pharmacology of opioids.
- Understanding the association between acute and chronic opioid receptor activation with desensitisation and tolerance is important.

References

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