PAIN

PAIN

- Worldwide chronic pain afflicts more than 1.5 billion individuals
- The economic burden associated with persistent pain, which includes healthcare utilization, quality of life and impact on productivity, absenteeism and risk of leaving the labor market, is comparatively greater than most other health conditions
- In the USA the estimated financial cost of treatment and loss of productivity as a consequence of chronic pain is USD 560–635 billion per year

PAIN

- Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage
  - Pain constitutes the body's mechanism of self preservation but has the potential to evolve into a debilitating disease under certain pathological condition such as inflammation, cancer, viral infection, diabetes and other acute and chronic disease

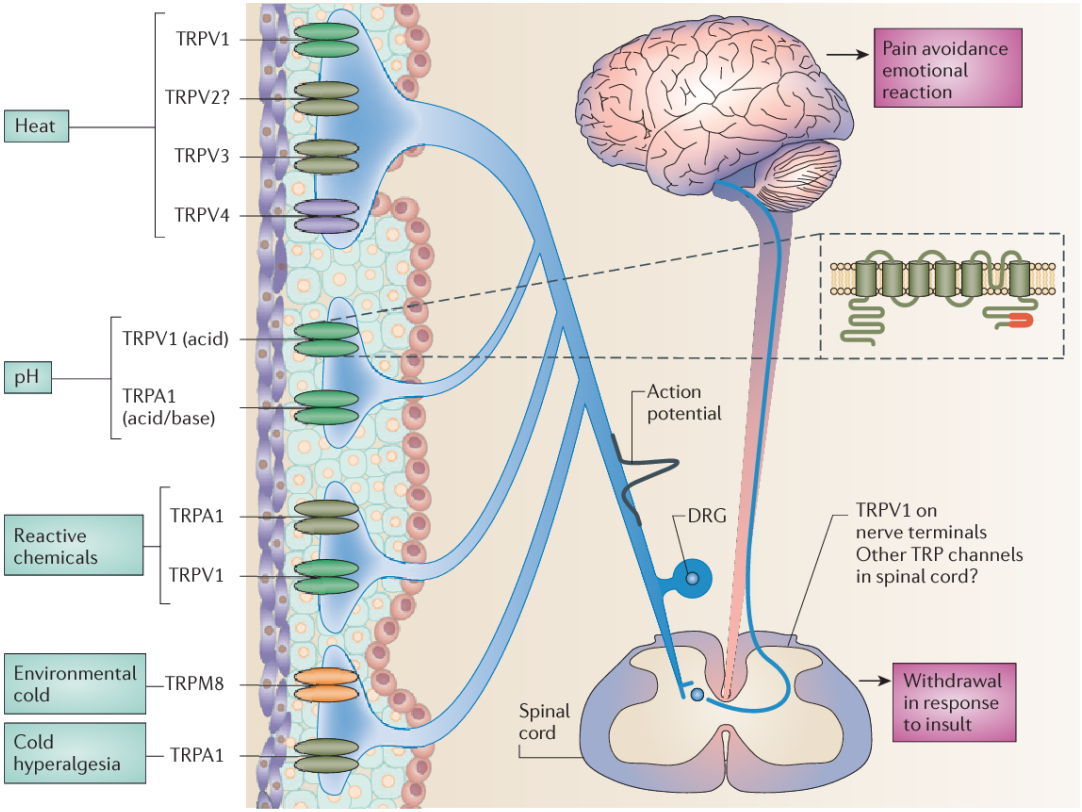
PAIN

- Classification of pain types
  - Acute
    - When it occurs as a normal, predictable response to trauma or an acute illness. Moreover, acute pain is generally associated with identifiable cause, resolves after the removal of the cause, responds to treatment and lasts less than 1-3 months
      - Chemical
      - Thermal
      - Mechanical
  - Chronic
    - When it does not have a clear cause, or that last longer than 1-3 months after the initial injury heals

PAIN

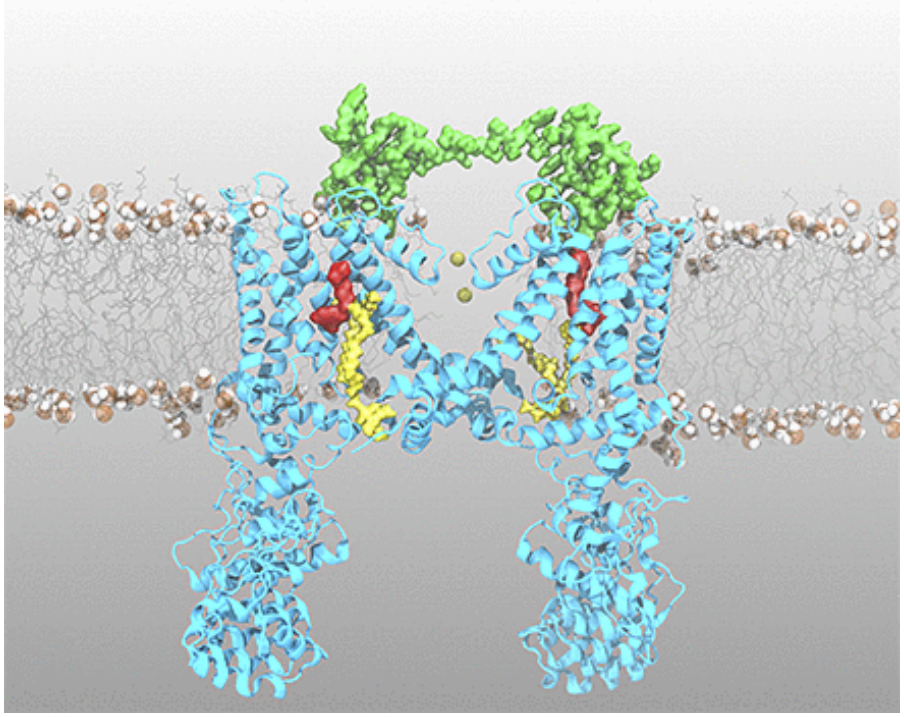
- Nociceptive pain
  - Resulting from a tissue damage (e.g. cancer, osteoarthritis) and it is the normal physiological response to a noxious stimulus (e.g. injury, inflammation)
- Neuropathic pain
  - It is abnormal form of pain that continues to persist long after the resolution of tissue damage or even in the absence of a causative illness
    - Allodynia
      - It is a perception of pain following a stimulus that would not normally be painful
    - Hyperalgesia
      - It is an enhanced response to a mildly noxious stimulus
    - Causalgia
      - It is a chronic burning pain that persists in the absence of a obvious noxious stimulus

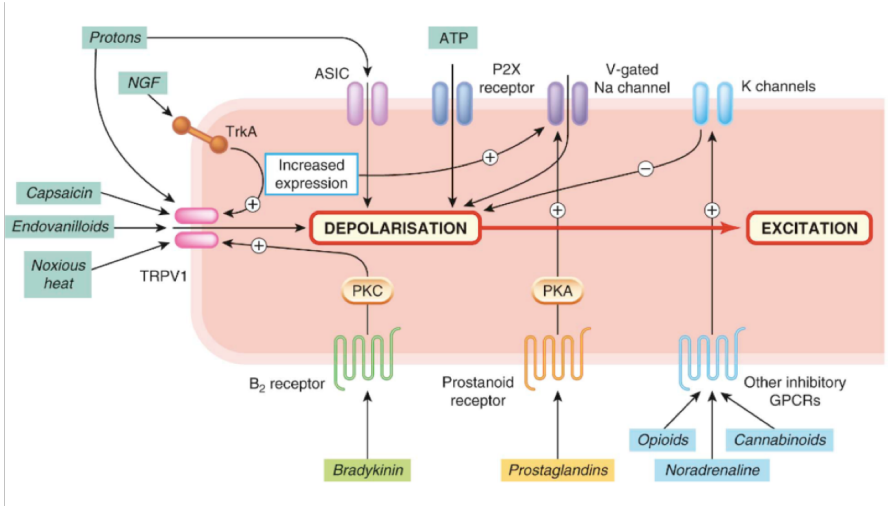
NOCICEPTIVE PAIN



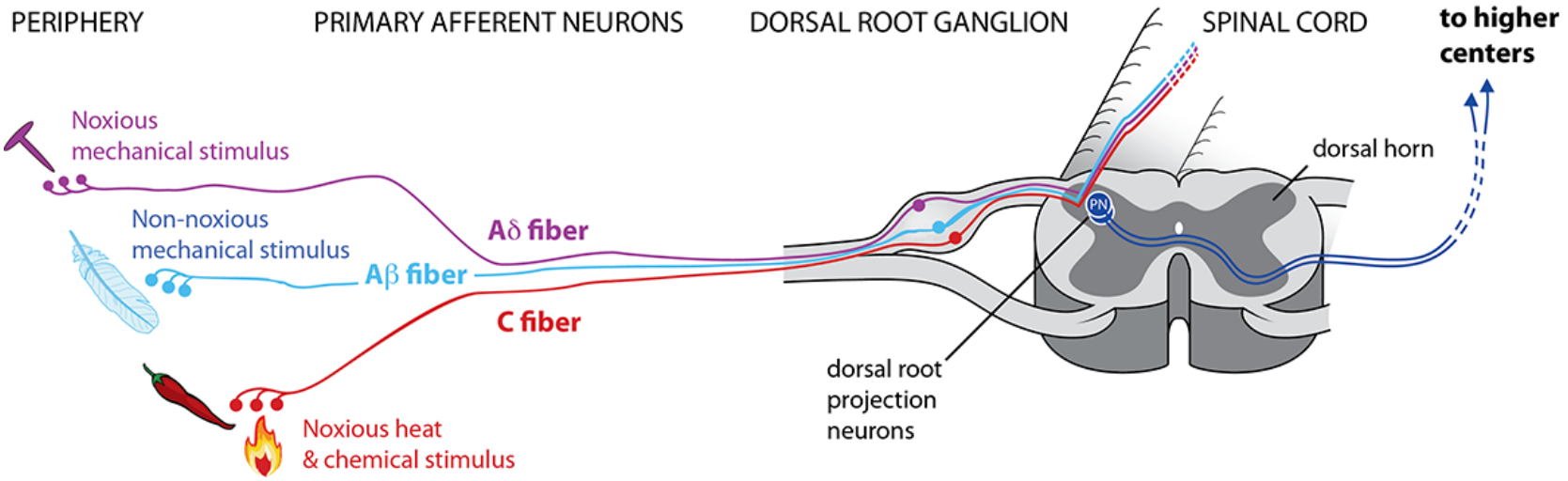
The transient receptor potential (TRP) cation channels

NOCICEPTIVE PAIN

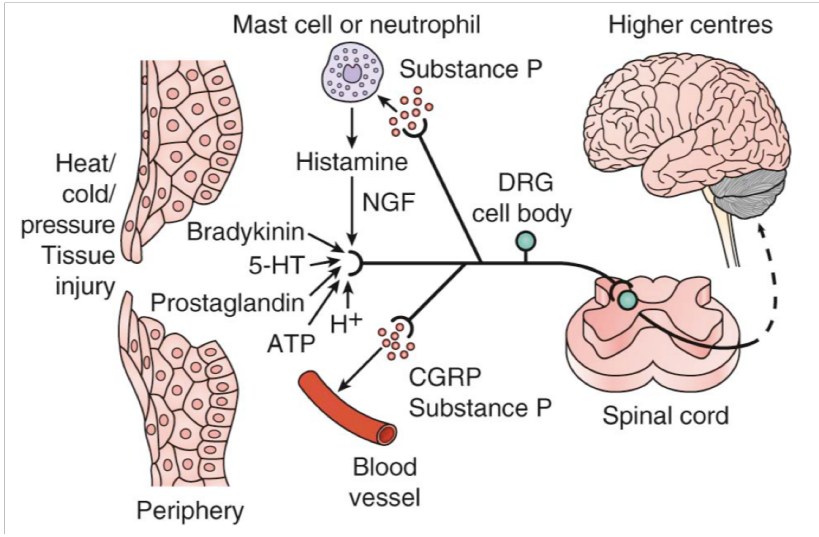


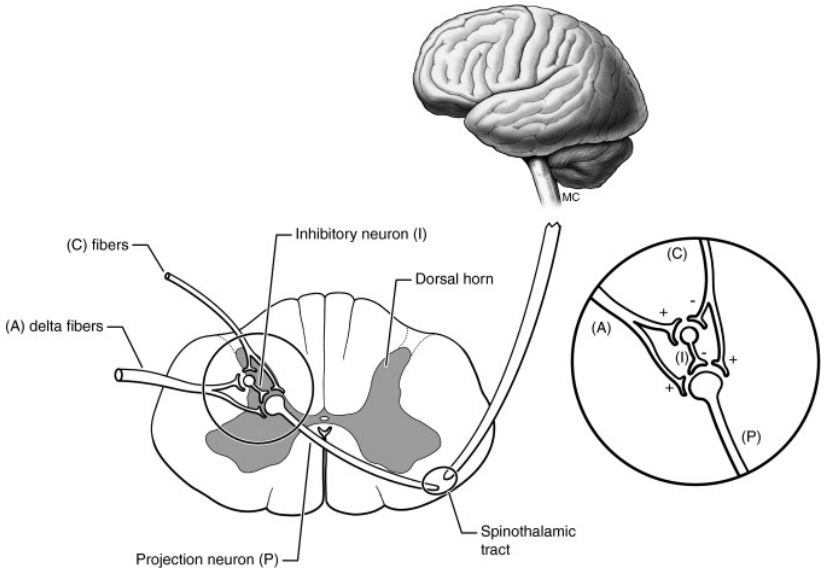


NOCICEPTIVE PAIN



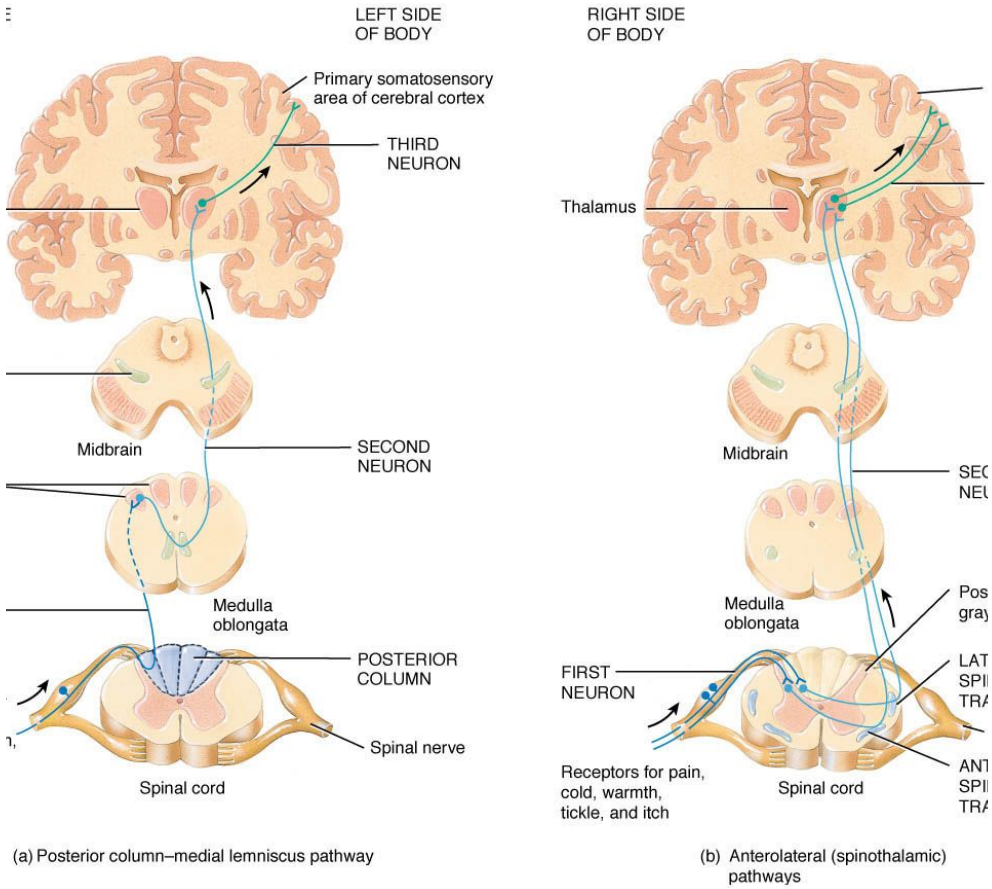
NOCICEPTIVE PAIN





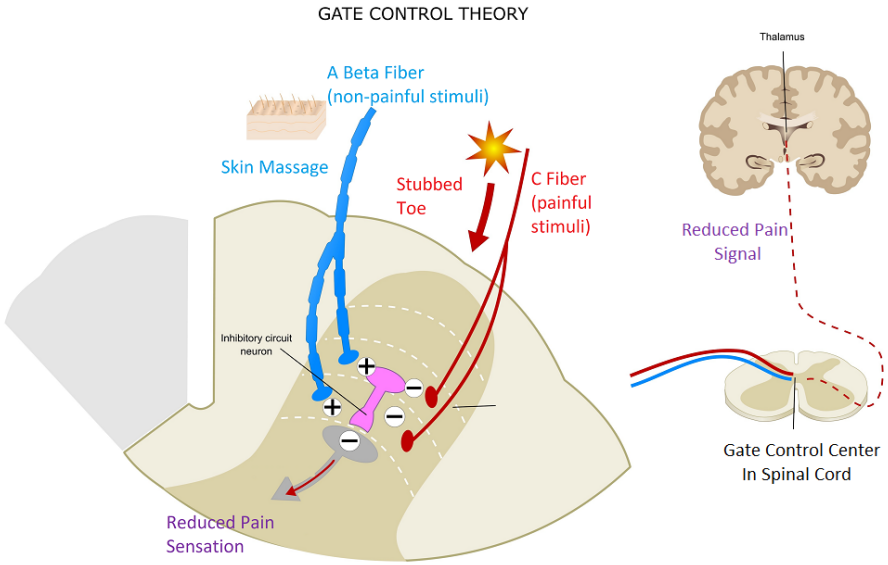
NOCICEPTIVE PAIN

- Transmitters
  - Glutamate
  - Substance P
  - ATP
  - Potassium
  - Bradykinin
  - Prostaglandins
  - Cytokines
  - Histamine

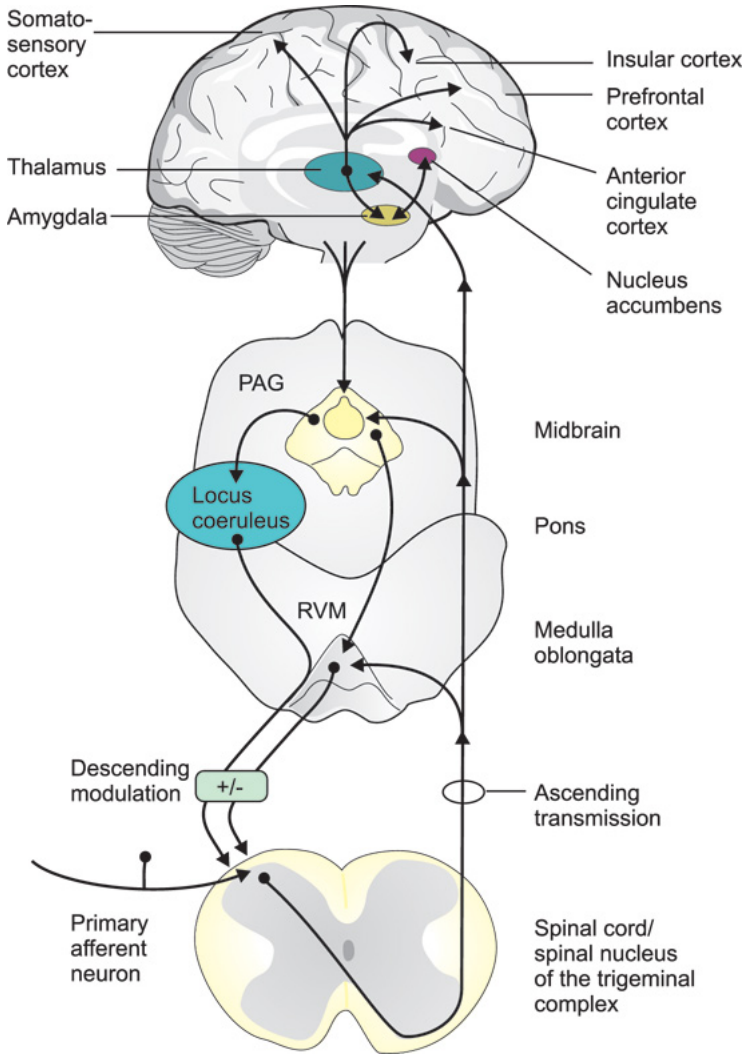


NOCICEPTIVE PAIN

- Pain Gate Theory
  - According to the gate control theory, interneurons in the dorsal horn release GABA and glycine, which mediate inhibitory postsynaptic potential to reduce nociceptive impulse



NOCICEPTIVE PAIN



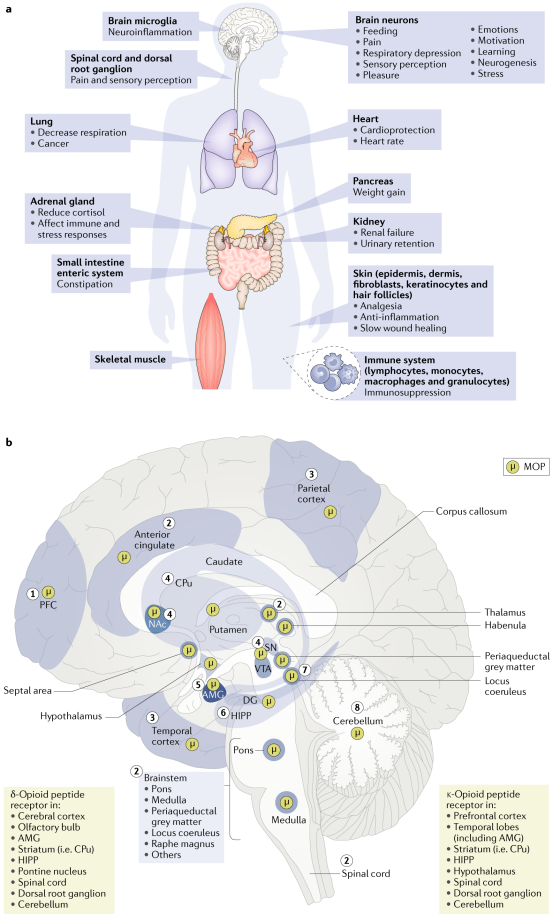
A, Amygdala; IC, Insular Cortex; H, hypothalamus; PAG, Periaqueductal Grey Region; RVM, Rostroventral Medulla

- Descending pathway
  - Descending pathway from the midbrain and brain stem exert a strong inhibitory effect on dorsal horn transmission
  - The descending inhibition is mediated mainly by 5-HT, NA and A
  - Opioids cause analgesia partly by activating these descending pathways, partly by inhibiting transmission in the dorsal horn and partly by inhibiting excitation of sensory nerve terminals in the periphery

THE OPIOID SYSTEM

THE OPIOID SYSTEM

- The opioid system represents one of the endogenous systems involved in neurotransmission and/or neuromodulation and consists of specific pepdidergic ligands and their corresponding receptors
- The system is present in the Central and Peripheral nervous system and is also involved in the regulation of gastrointestinal tract, endocrine and autonomic function, in reward and dependence mechanisms as well as in memory and learning process

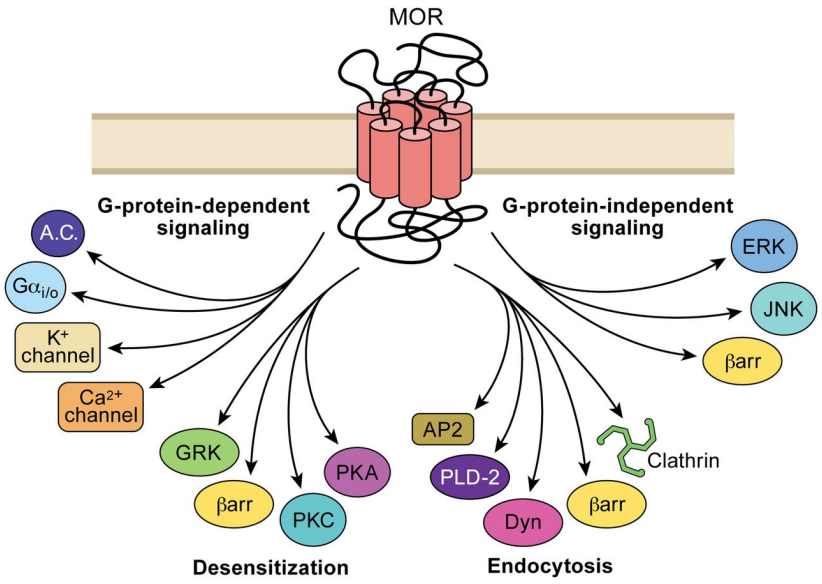


THE OPIOID SYSTEM

- Endogenous opioid peptides
  - Opioid neuropeptides are short amino acid sequences serving as natural endogenous ligands for opioid receptors. All classical opioid peptides may be classified into four families
    - Enkephalins
    - Endorphins
    - Dynorphins
    - Nociceptin

THE OPIOID SYSTEM

- The four opioid receptors
  - μ (MOR)
    - Endorphin
  - δ (DOR)
    - Enkephalin
  - κ (KOR)
    - Dynorphin
  - ORL_1 (NOP)
    - Nociceptin
      - All are G protein-coupled receptors interacting with different G proteins (GPCRs)

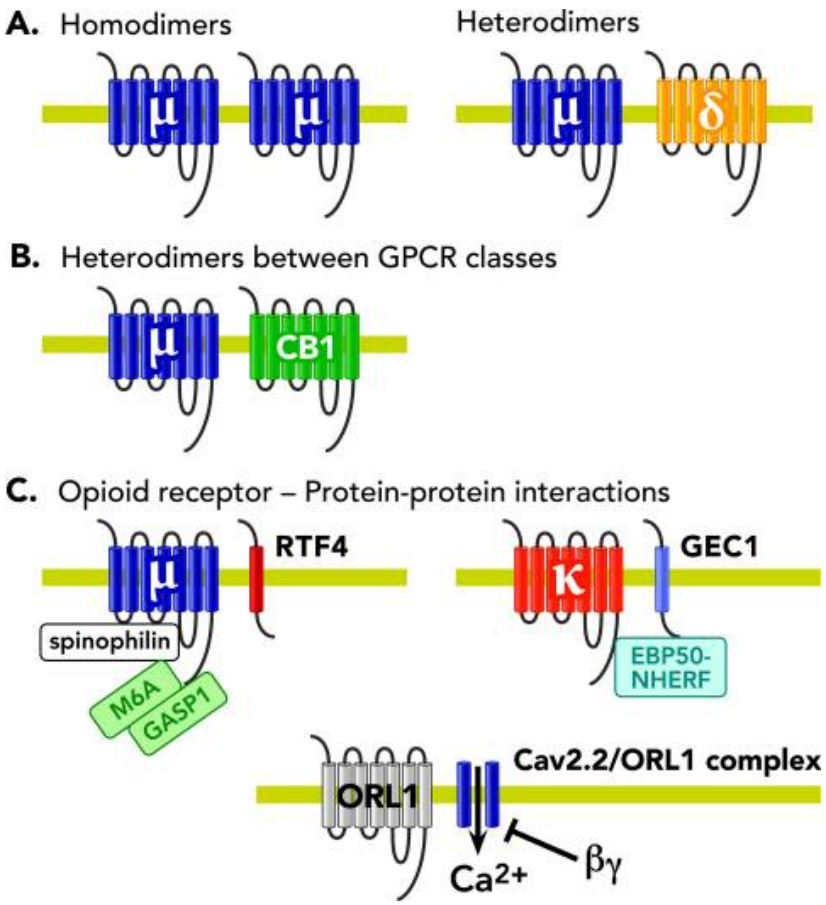


THE OPIOID SYSTEM

	μ (MOR)	δ (DOR)	κ (KOR)	ORL_1 (NOP)
Analgesia supraspinal spinal peripheral	 +++ ++ ++	 ++	 + ++	 anti-opioid ++
Respiratory depression	+++	++		
Pupil constriction	++		+	
Reduced GI motility	++	++	+	
Euphoria	+++			
Dysphoria and hallucinations			+++	
Sedation	++		++	
Catatonia				++
Physical dependence	+++			

THE OPIOID SYSTEM

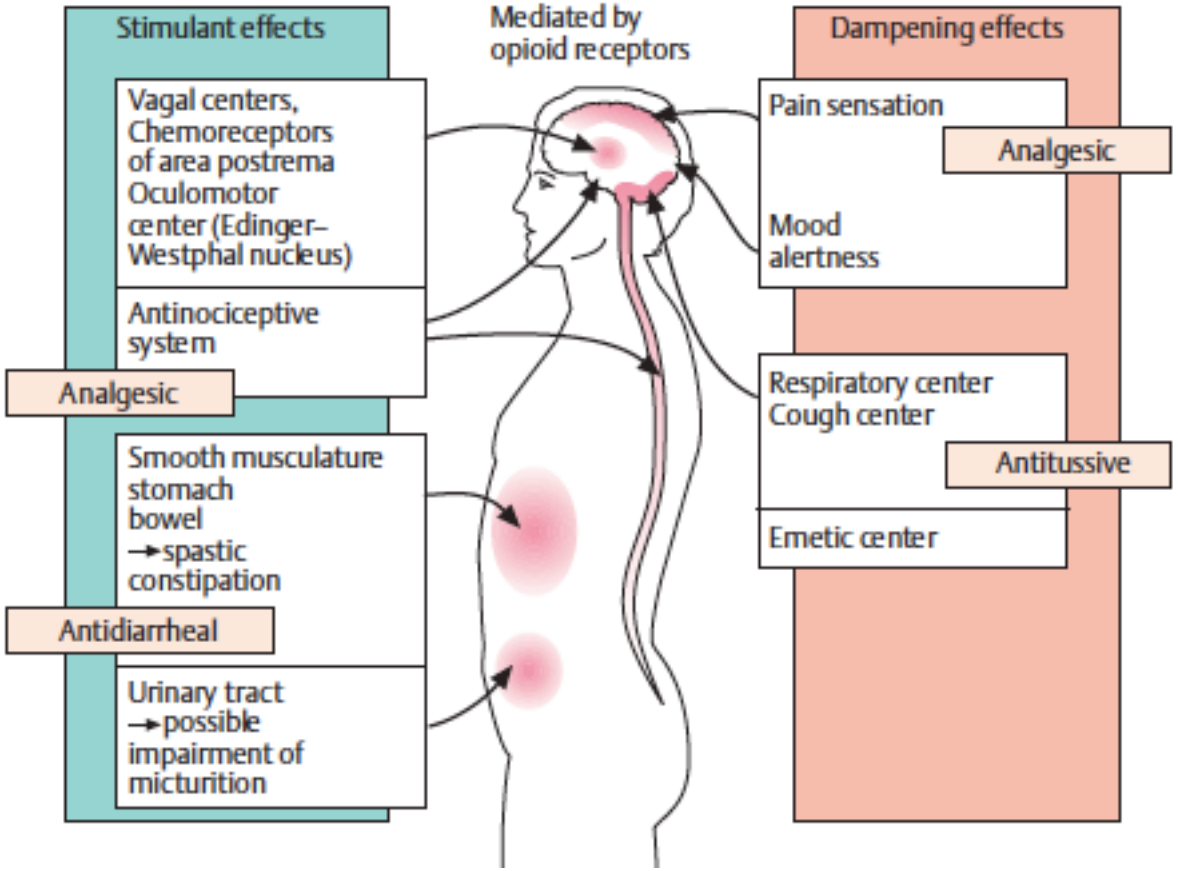
- Evidence indicate that opioid receptors interact with five different isoforms of $G_{\alpha i}/G_o$-coupled receptors, thereby regulate signal transduction through different effectors, such as inhibition of adenylate cyclase, activation the mitogen protein kinases (MAPK) opening K^+ channels (causing hyperpolarisation) and inhibiting the opening of Ca^{2+} channels (inhibiting transmitter release)
- It has been also suggested that opioids exert some o their actions, such as analgesia, tolerance and dependence through $G_{\alpha s}$ protein
- Functional heteromeres, formed by combination of different types of opioid receptor or with other types of G protein-coupled receptor, may occur and give rise to further pharmacological diversity



THE OPIOID SYSTEM

- The DOR-KOR heterodimer displays distinct pharmacological properties when compared to DOR and KOR homodimers
- The DOR-MOR heterodimer creates a novel binding site with reduced affinity for selective synthetic agonists (including morphine), but increased affinity for endogenous opioid peptides (endomorphin-1 and Leu-enkephalin)
- A major problem associated with morphine treatment for pain relief is the development of opioid tolerance following chronic use; a large body of evidence indicates that the DOR is involved in the development of morphine tolerance and that blocking the DOR enhances MOR analgesia

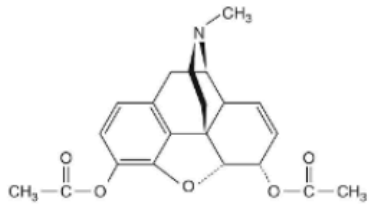
THE OPIOID SYSTEM



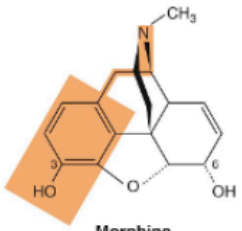
THE OPIOID SYSTEM

- Opium is an extract of the juice of the poppy Papaver somniferum that contains morphine and other related alkaloids
  - Opiates – Both natural (compounds that are found in the opium poppy e.g. morphine, codeine) and synthetic substances related to morphine
  - Opioids – The endogenous substances that are natural ligands of opioid receptor

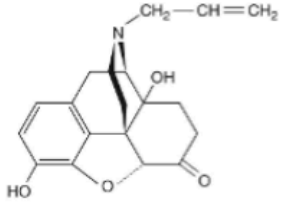
THE OPIOID SYSTEM



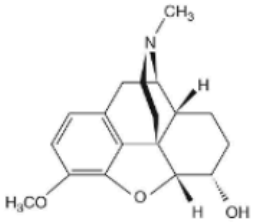
Heroin



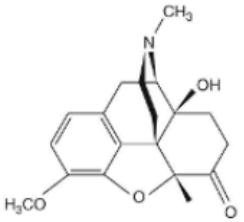
Morphine



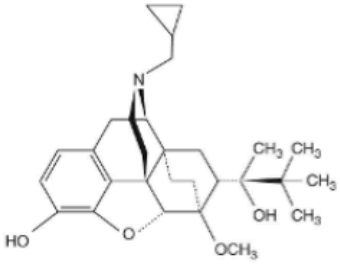
Naloxone



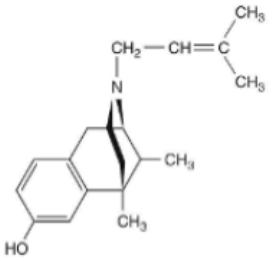
Codeine



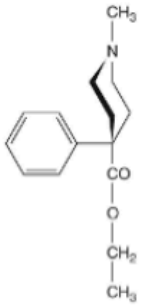
Oxycodone



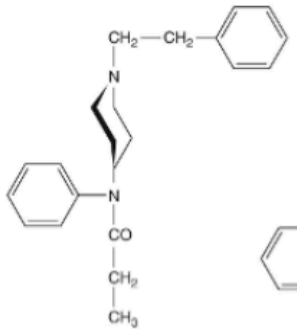
Buprenorphine



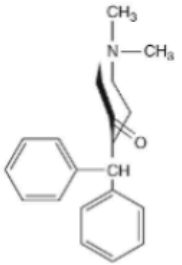
Pentazocine



Pethidine



Fentanyl



Methadone

THE OPIOID SYSTEMP

- Opiate and opioid drugs vary not only in their receptor specificity but also in their efficacy at the different types of receptor
  - Morphine - μ partial agonist
  - Buprenorphine - μ partial agonist
  - Codeine - μ low agonist
  - Pentazocine - k agonist μ antagonist
  - Naloxone and naltrexone - μ antagonist

THE OPIOID SYSTEM

- Morphine-like opioids
  - Mechanism of action
    - Biochemical level
      - Inhibition of Adenylate Cyclase. Inhibition of calcium entry, by enhancing outward movement of potassium ions
    - Cellular level:
      - Presynaptic
        - Reducing transmitter release
      - Postsynaptic
        - Decreasing neuronal excitability

THE OPIOID SYSTEM

- Morphine-like opioids
  - Analgesia
    - Supraspinal opioid analgesia involves endogenous opioid peptide release both at supraspinal and spinal sites (at the spinal level is also due to the release of 5-HT from descending inhibitory fibres)
    - Spinal opioid analgesia involves inhibition of the transmission of nociceptive impulses through the dorsal horn and suppression of nociceptive spinal reflex
    - A combination of effects at supraspinal and spinal sites contribute to the analgesic response

THE OPIOID SYSTEM

- Morphine-like opioids
  - Respiratory depression (decrease in the sensitivity of the respiratory centres to arterial PCO_2 and inhibition of respiratory rhythm generation, occurring at therapeutic doses)
  - Depression of cough reflex (antitussive effect – codeine)
  - Nausea and vomiting (40% patients - area postrema/ CRTZ)
  - Pupillary constriction (pinpoint pupils- stimulation of the oculomotor nucleus)

THE OPIOIOD SYSTEM

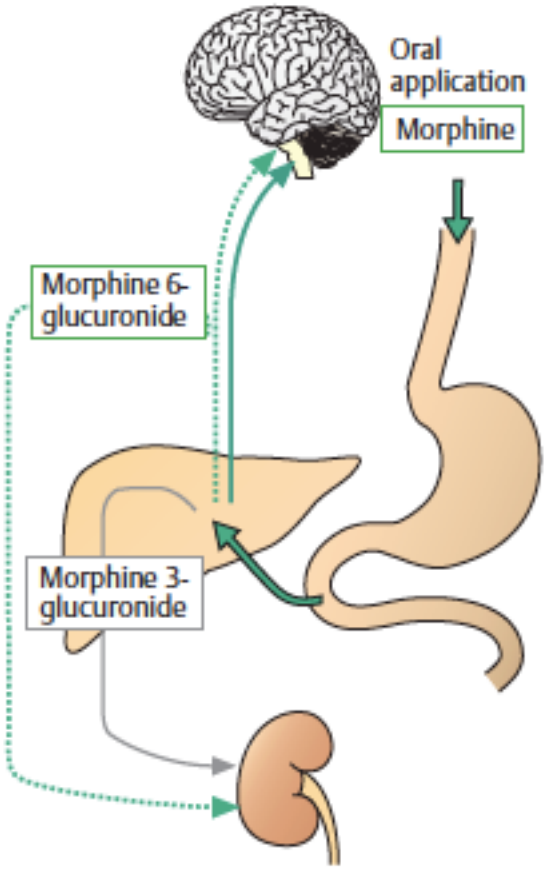
- Morphine-like opioids
  - Constipation (increasing tone and reduced motility) and contraction of the gall bladder and constriction of the biliary sphincter (rise in intrabiliary pressure)
  - Release of histamine (urticaria, itching, bronchoconstriction)
  - Hypotension and bradycardia
  - Immunosuppressant effects

THE OPIOID SYSTEM

- Pharmacokinetic features
  - Morphine-like opioids may be given orally, by injection or intrathecally to produce analgesia (patient-controlled analgesia by infusion pump or touch-sensitive transdermal patches)
  - Most morphine-like opioids undergo considerable first-pass metabolism
  - The plasma half-life of the most morphine analogues is 3-6 h

THE OPIOID SYSTEM

- Pharmacokinetic features
  - Morphine hepatic metabolism is the main mode of inactivation, usually by conjugation with glucuronide (3- and 6- OH groups); diamorphine and codeine are converted to morphine



THE OPIOID SYSTEM

- Unwanted effects
  - Morphine-like opioids
    - Coma and respiratory depression with characteristically constricted pupils
    - Individual variability (10-fold) due to altered metabolism or sensitivity of the receptors

THE OPIOID SYSTEM

- Morphine-like opioids
  - Tolerance
  - Physical dependence
  - Withdrawal syndrome
  - Addictions

THE OPIOID SYSTEM

- Morphine-like opioids
  - Tolerance and physical dependence are two pharmacological phenomena that develop after chronic exposure to morphine-like opioids
  - Tolerance is the decrease of the pharmacological effects occurring after repeated administration of opioid receptor agonist, which cause the need to increase the dose to achieve the same effect
  - Once doses much higher that the starting ones are reached, the body loses its homeostasis and physical dependence take place
  - Tolerance and drug dependence are therefore related to each other and independent of psychic dependence

THE OPIOID SYSTEM

- Morphine-like opioids
  - The most studied cellular adaptation downstream of receptor signalling consists in the superactivation of cAMP pathway, with an increase in cyclic AMP response element DNA binding protein (CREB) and Fos protein. That represents the molecular mechanism underlying the homeostatic response to long-term inhibition of adenylate cyclase

THE OPIOID SYSTEM

- Morphine-like opioids
  - Diamorphine (heroin) is 3,6-diacetylmorphine, it can be considered a pro-drug, its effects are indistinguishable from those of morphine following oral administration, however due to its greater lipid solubility, it crosses the BBB rapidly and gives greater “buzz” when injected iv
  - Oxycodone – slow release oral preparation (“hillbilly heroin”)

THE OPIOID SYSTEM

- Morphine-like opioids
  - Codeine (3-methoxymorphine) is more reliably absorbed by mouth than morphine, but has only 20% of the analgesic potency (mild types of pain). It is metabolised to morphine and 10% of the population is resistant to its analgesic effect because they lack the demethylating enzyme. It has marked antitussive activity and is often used in cough mixtures

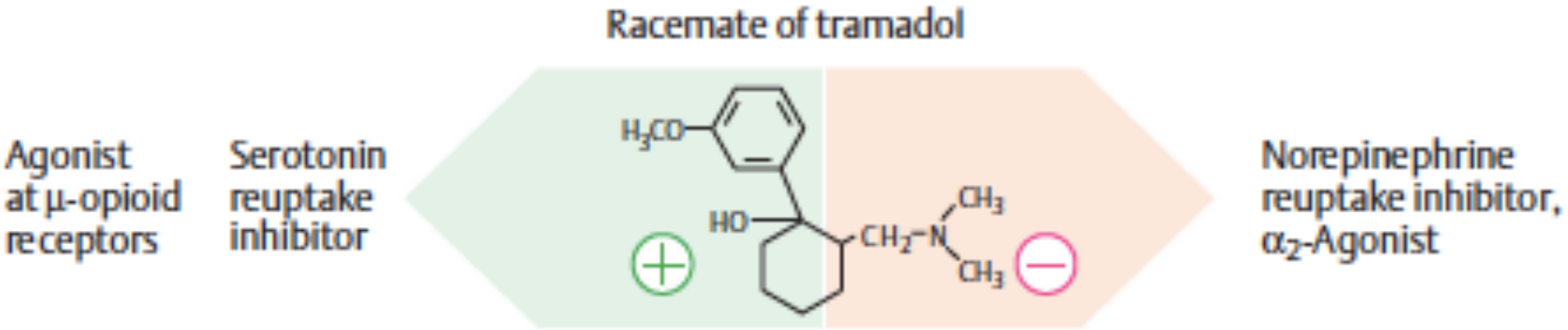
THE OPIOID SYSTEM

- Morphine-like opioids
  - Fentanyl, alfentanil, sulfentanil and remifentanil (phenylpiperidine derivatives) with a more rapid onset and shorter duration of action compared to morphine (anaesthesia, patient-controlled infusion and patches)

THE OPIOID SYSTEM

- Morphine-like opioids
  - Buprenorphine is a partial agonist on m receptors that produces strong analgesia; it has abuse liability but like methadone it is also used in the treatment of heroin addiction
  - Loperamide is extruded from the brain by P-gp and therefore lacks analgesic activity; it inhibits peristalsis and is used to control diarrhoea
  - Tramadol is a weak μ receptor agonist and a weak inhibitor of monoamine reuptake (postoperative pain)

THE OPIOID SYSTEM



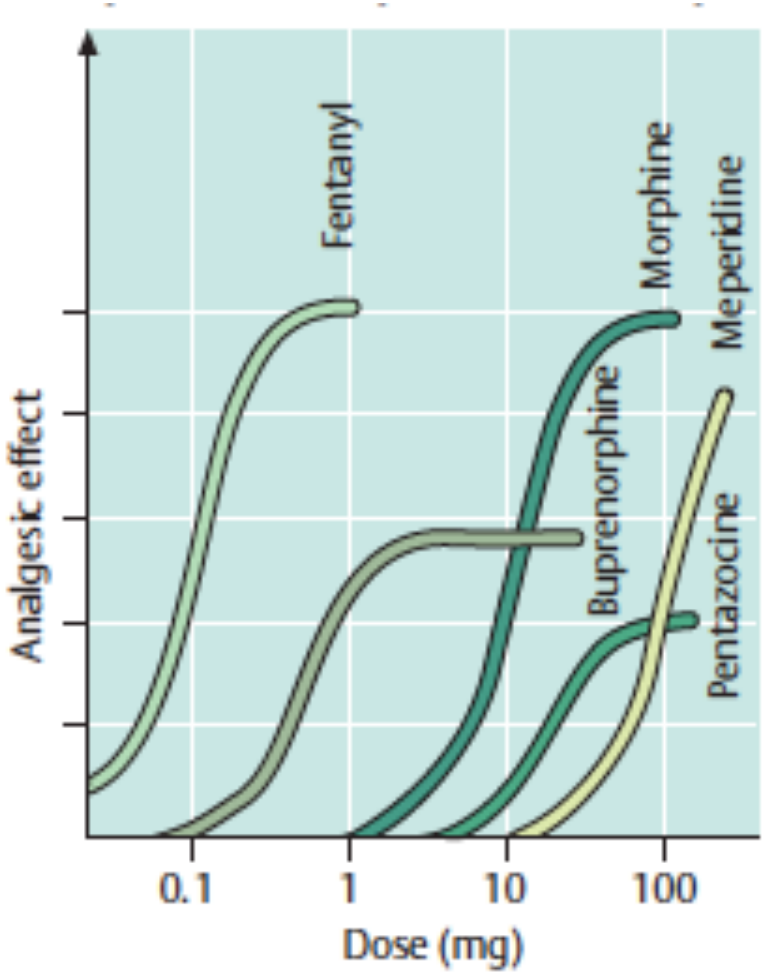
THE OPIOID SYSTEM

- Morphine-like opioids
  - Pethidine (meperidine) is very similar to morphine in its pharmacological effects, except that it tends to cause restlessness rather than sedation; its route of metabolic degradation is different (it is partly N-demethylated to norpethidine, which as hallucinogenic and convulsant effects). It is preferred to morphine for analgesia during labour, because it does not reduce the force of uterine contraction

THE OPIOID SYSTEM

- Morphine-like opioids
  - Methadone is orally active and pharmacologically similar to morphine but with a longer plasma half-life (> 24h); on withdrawal the physical abstinence syndrome is less acute than with morphine, although the psychological dependence is no less pronounced; it is widely used for treating heroin addiction (interindividual variation in the response)

THE OPIOID SYSTEM



THE OPIOID SYSTEM

- Opiate antagonists
  - Naloxone was the first pure opioid antagonist, with affinity for all three classic opioid receptors ($\mu > \kappa \geq \delta$); it blocks the actions of endogenous opioid peptides as well as those of morphine-like drugs. The main clinical uses of naloxone are to treat respiratory depression caused by opioid overdosage, and occasionally to reverse the effect of opioid analgesics, used during labour, on the respiration of the new born baby

THE OPIOID SYSTEM

- Opiate antagonists
  - Naltrexone is very similar to naloxone but with the advantage of a much longer duration of action (half-life about 10 h) it may be of value in addicts who have been "detoxified" (slow-release subcutaneous implant formulation). It is also effective in reducing alcohol consumption in heavy drinker and in treating chronic itching (pruritus)
  - Methylnaltrexone bromide and alvimopan are μ opioid-receptor antagonists that do not cross the BBB, they can be used in combination with opioid agonists to block unwanted effects (reduced GI motility, nausea and vomiting)

THE OPIOID SYSTEM

Drugs	Targets	Mechanisms	Functional consequences	Side effects
Opioids	G-protein coupled μ-, δ-, κ-receptors	↓ cAMP ↓ Ca^{2+} currents ↑ K^+ currents	↓ Excitability of peripheral and central neurons ↓ Release of excitatory neurotransmitters	μ, δ: sedation, nausea, euphoria/reward, respiratory depression, constipation κ: dysphoria/aversion, diuresis, sedation
NSAIDs	Cyclooxygenases (COX-1, COX-2)	↓ Prostaglandins ↓ Thromboxanes	↓ Sensitization of sensory neurons ↑ Inhibition of spinal neurons	Nonselective: gastrointestinal ulcers, perforation, bleeding, renal impairment COX-2: thrombosis, myocardial infarction, stroke
Serotonin agonists	G-protein coupled 5-HT receptors 5-HT_3: ion channels	↓ cAMP (5-HT_1) ↑ cAMP ($5\text{-HT}_{4–7}$) ↑ PLC (5-HT_2)	↓ Release of excitatory neuropeptides ↓ Neurogenic inflammation ↑ vasoconstriction	Myocardial infarction, stroke, peripheral vascular occlusion
Antiepileptics	Na^+, Ca^{2+} channels GABA receptors	↓ Na^+currents ↓ Ca^{2+} currents ↑ GABA receptor activity	↓ Excitability of peripheral and central neurons ↓ Release of excitatory neurotransmitters	Sedation, dizziness, cognitive impairment, ataxia, hepatotoxicity, thrombocytopenia
Antidepressants	Noradrenaline/5-HT transporters Na^+, K^+ channels	↓ Noradrenaline/5-HT reuptake ↓ Na^+ currents ↑ K^+ currents	↓ Excitability of peripheral and central neurons	Cardiac arrhythmia, myocardial infarction, sedation, nausea, dry mouth, constipation, dizziness, sleep disturbance, blurred vision

NEUROPATHIC PAIN

- Neuropathic pain
  - The pathophysiological mechanisms underlying this kind of pain are poorly understood, although spontaneous activity in damaged sensory neurons, due to overexpression or redistribution of voltage-gated sodium channels, is thought to be a factor. In addition, central sensitisation occurs. The sympathetic nervous system also plays a part, because damaged sensory neurons can express α adrenoceptors and develop a sensitivity to noradrenaline that they do not possess under normal conditions. Thus, physiological stimuli that evoke sympathetic responses can produce severe pain, a phenomenon described clinically as sympathetically mediated pain

NEUROPATHIC PAIN

- Neuropathic pain
  - It responds poorly to conventional analgesic drugs but can be relieved by some antidepressant and antiepileptic agents
    - Amitriptyline, nortriptyline and desipramine - tricyclic antidepressants that act centrally by inhibiting NA reuptake
    - Duloxetine and venlafaxine - antidepressants that inhibit 5-HT and NA reuptake
    - Gabapentin and pregabalin - antiepilectic drugs that reduce the expression of $\alpha 2\delta$ subunits of voltage-activated Ca^{2+} channels on the nerve membrane reducing the release
    - Carbamazepine – an antiepilectic drug that blocks voltage-gated Na^{+} channels such as Nav1.8 that are thought to be upregulated by nerve damage
    - Lidocaine – a local anaesthetic drug that can be used topically and probably acts by blocking spontaneous discharges from damaged sensory nerve terminals

NEUROPATHIC PAIN

- Neuropathic pain
  - Nefopam - an inhibitor of amine uptake with some Na^+ channel blocking properties, is used in the treatment of persistent pain unresponsive to non-opioid drugs (AR sympathomimetic and antimuscarinic side effects)
  - Ketamine – is an anaesthetic that works by blocking NMDA receptor channels and probably reduce the "wind-up" phenomenon in the dorsal horn
  - Cannabinoids acting on CB1 receptors such as sativex are effective for central neuropathic pain in multiple sclerosis