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Course; 322 PHL

Pain Pathway Modulators & Narcotic Analgesic

Pain

unwanted events associated with tissue damage caused by injury, inflammation or cancer

Neuronal Mechanisms of Pain

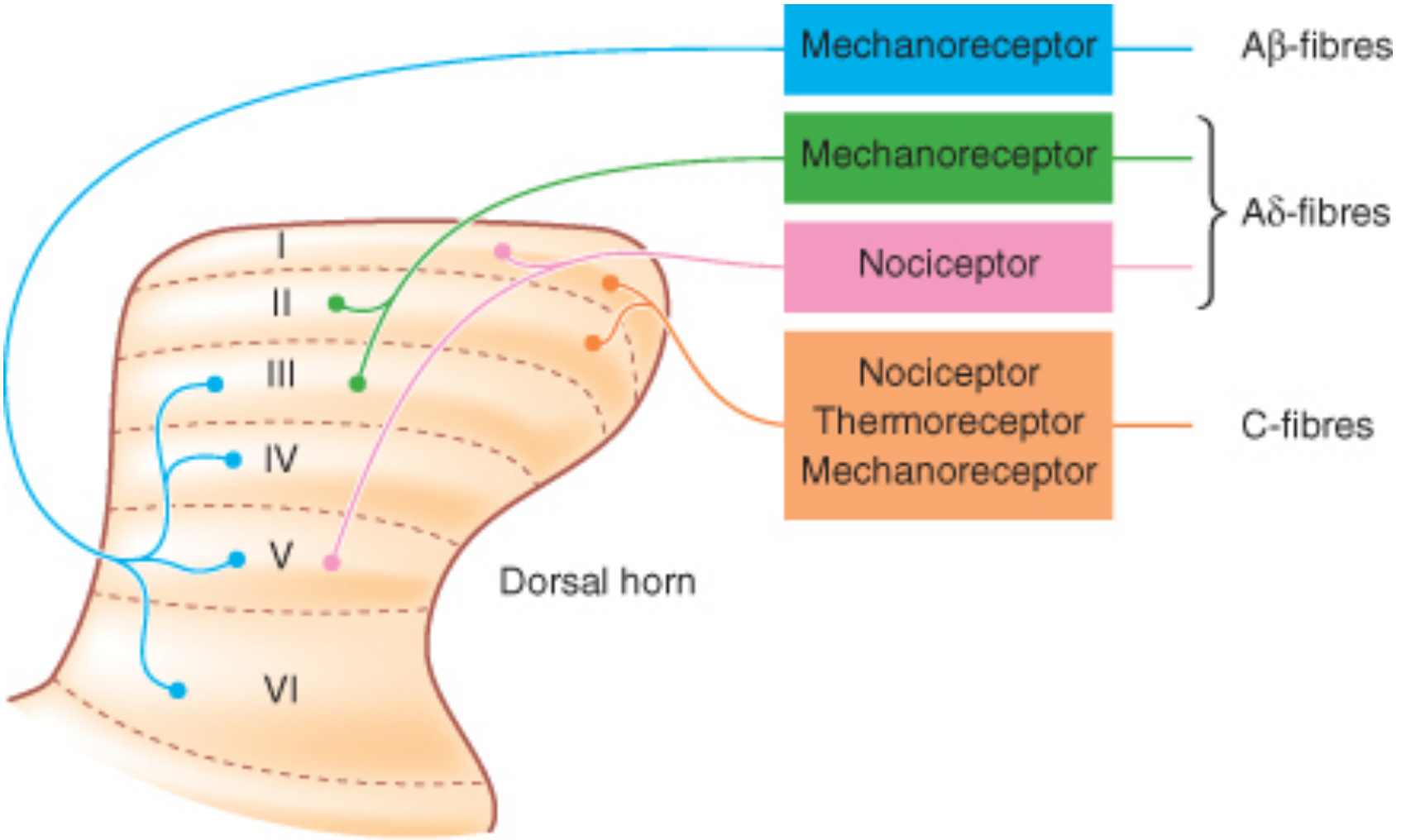
- Components involved in pathological pain states:
  i. the peripheral nociceptive afferent neuron, which is activated by noxious stimuli
  ii. the central mechanisms by which the afferent input generates a pain sensation.

- Noxious = harmful, toxic, poisons, etc

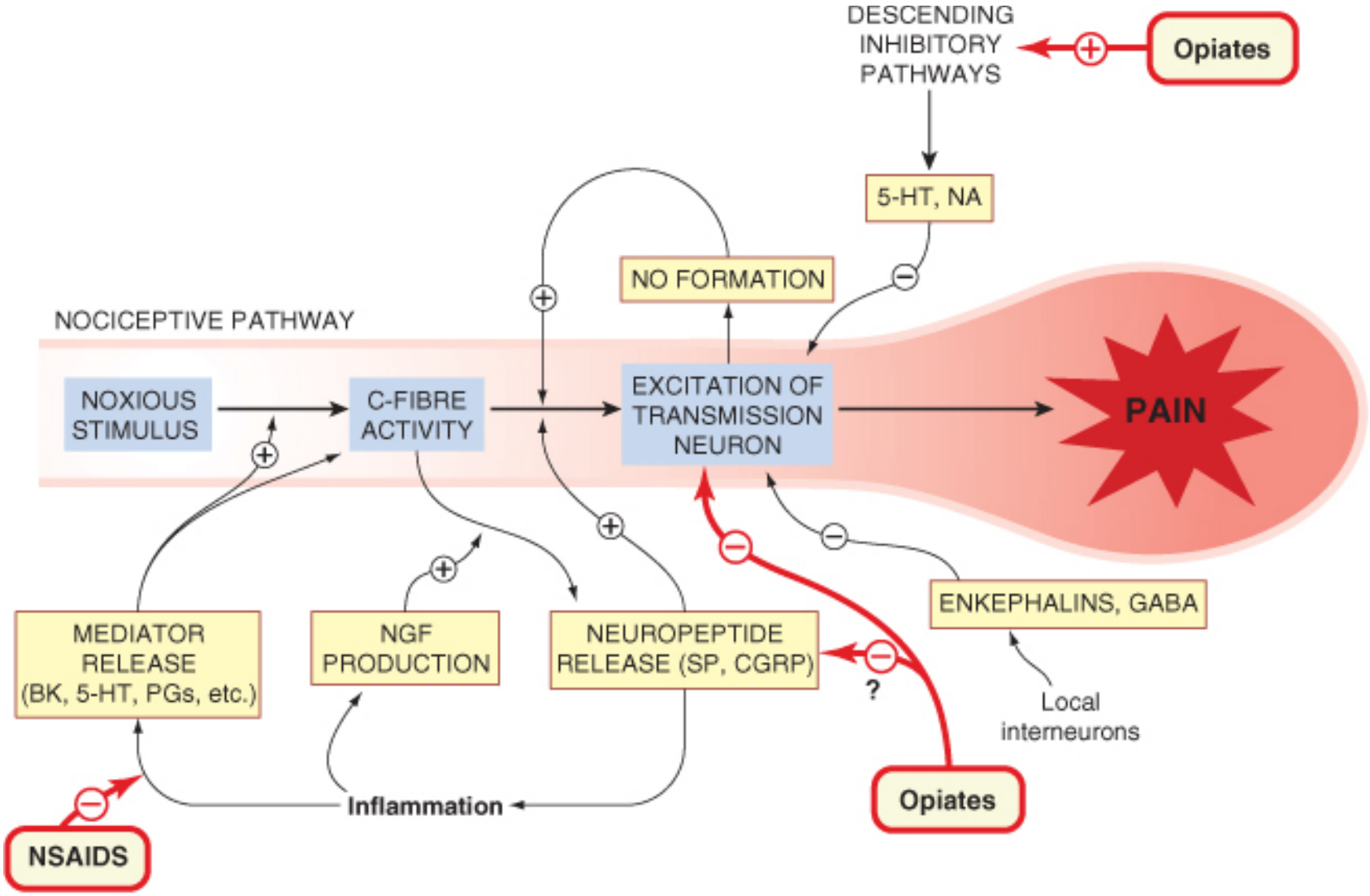
Afferent Fibers

- non-myelinated C-fibers
  - known as ***C-polymodal nociceptors (PMN)***
  - C-fiber activity causes a dull, burning pain
  - contain several neuropeptides, particularly substance P and calcitonin gene-related peptide (CGRP).

- fine myelinated (Aδ) fibers
  - are connected to high-threshold mechanoreceptors
  - a sensation of sharp, well-localized pain



The termination of afferent fibers in the six laminae of the dorsal horn of the spinal cord.



Summary of modulatory mechanisms in the nociceptive pathway.

5-HT; NA; BK, bradykinin; PGs, prostalgandins; NGF, nerve growth factor; SP, substance P; CGRP, calcitonin gene-related peptide; GABA; NSAIDs; NO, nitric oxide.

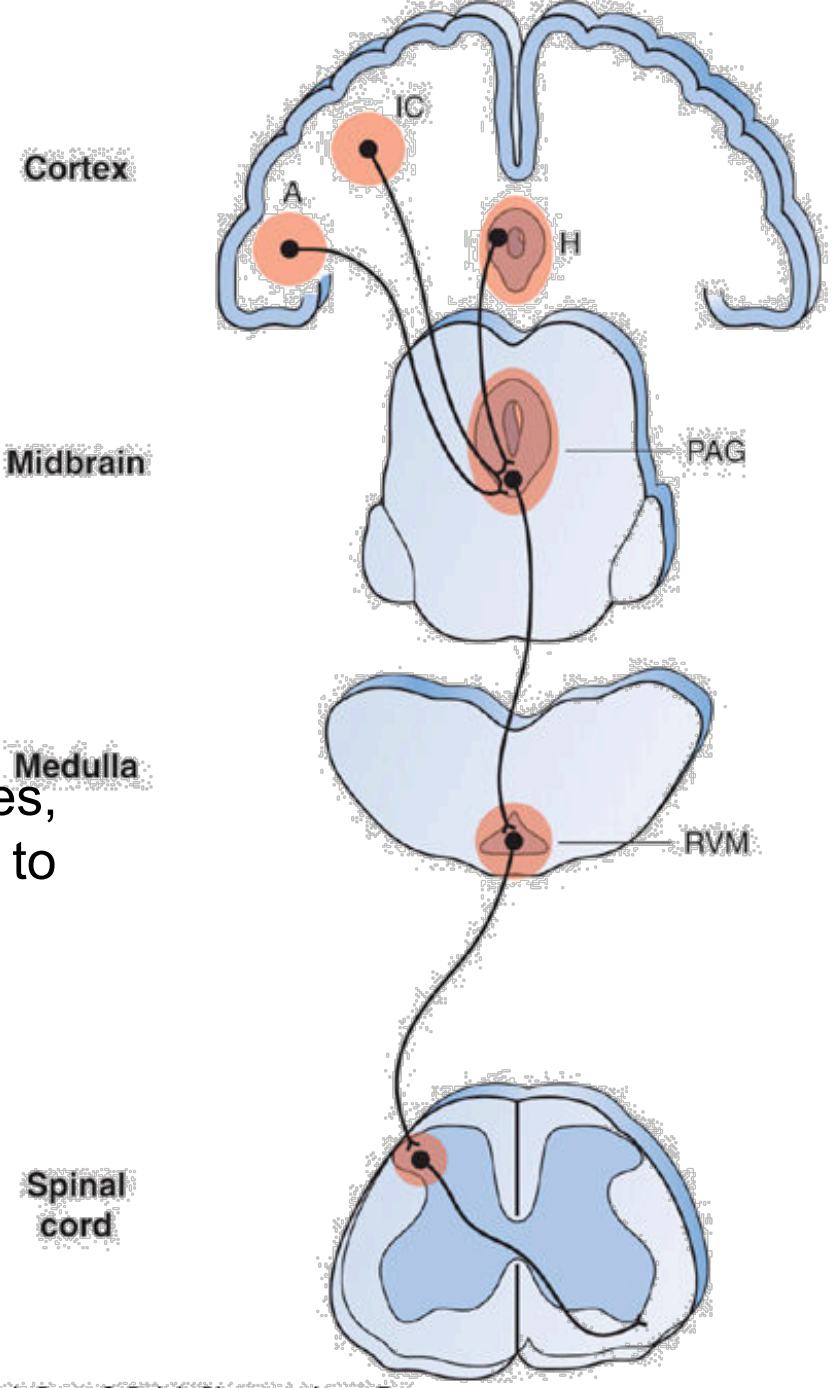
Types of Pain

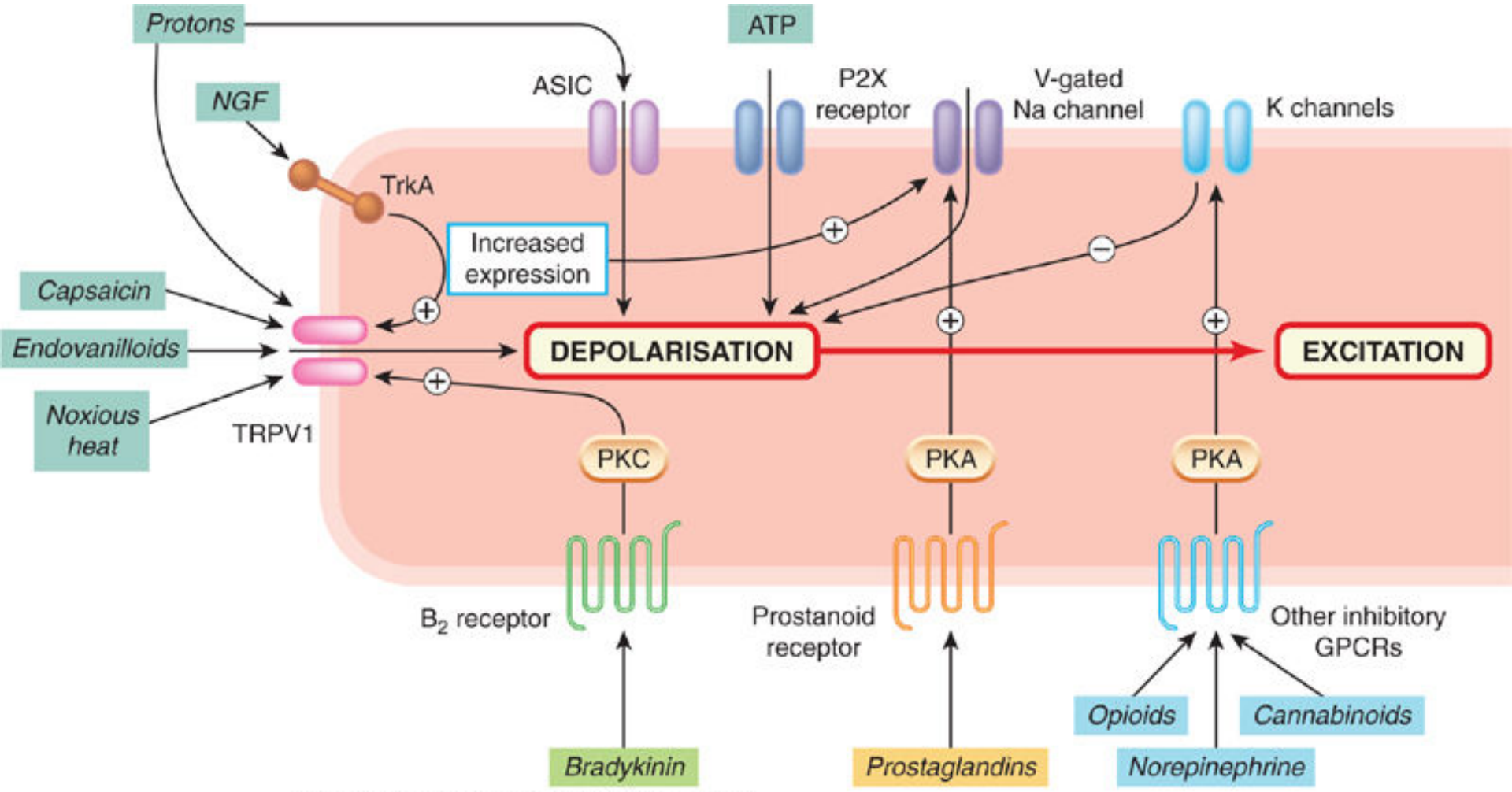
- Acute pain
  - *nociception:* an excessive noxious stimulus giving rise to an intense and unpleasant sensation.
- Chronic pain:
  - *Hyperalgesia:* an increased amount of pain associated with a mild noxious stimulus
  - *Allodynia:* pain evoked by a non-noxious stimulus
  - *Spontaneous pain* without any precipitating stimulus
- Neuropathic pain
  - Damage to neurons of the nociceptive pathway rather than an excessive peripheral stimulus
  - It is frequently a component of chronic pain states and may respond poorly to opioid analgesics.

The descending inhibitory control system

areas rich in opioid receptors;

- Insular cortex (IC),
- Amygdala (A),
- Hypothalamus (H),
- Periaqueductal grey (PAG) region
- Rostroventral medulla (RVM)
- Dorsal horn of the spinal cord
- the RVM, descending inhibitory fibres, contain 5- hydroxytryptamine, project to the dorsal horn of the spinal cord





Rang et al: Rang & Dale's Pharmacology, 7e

Summary

- **Ligand-gated channels** - acid-sensitive channels (ASIC), ATP-sensitive channels (P2X-receptors) and the capsaicin-sensitive channel (TRVP1), which is also sensitive to protons and to temperature.

- **G-protein-coupled receptors** - facilitatory and inhibitory - regulate channel function through various second messenger systems.

- **Growth factor -** nerve growth factor (NGF) act via kinase-linked receptors (TrkA) to control ion channel function and gene expression.

Mechanisms of Pain and Nociception

1. **Chemical stimuli** acting on Polymodal nociceptors (PMN; neurons) - bradykinin, protons, ATP and vanilloids (e.g. capsaicin).

2. PMN are sensitized by prostaglandins, which explains the analgesic effect of aspirin-like drugs, particularly in the presence of inflammation.

3. Nociceptive fibers terminate in the superficial layers of the dorsal horn, forming synaptic connections with transmission neurons running to the thalamus.

4. PMN neurons release glutamate (fast transmitter) and various peptides (especially substance P), which act as slow transmitters.

Transmitters and modulators in the nociception pathway

Tachykinins

- Endogenous tachykinins (CNS and PNS) :
  - substance P
  - neurokinin A (NKA)
  - neurokinin B (NKB)

- Substance P is also released in the periphery when nociceptors are activated contributes to neurogenic inflammation.

- Three tachykinin receptors: NK1, NK2 and NK3

- Nociceptive transmission and neurogenic inflammation are mediated
  mainly through NK1-receptors.

- Selective NK1-receptor antagonists have proved ineffective as analgesic agents.

Transmitters and modulators in the nociception pathway

Opioid peptides

- Old name = endorphine
- **Precursor**: *Preproopiomelanocortin* (POMC), *preproenkephalin* and *preprodynorphin*.
- mostly known as β-endorphin, met-enkephalin, leu-enkephalin and dynorphin.
- dynorphin mainly in the interneurons of the spinal cord,
- enkephalins - descending pathways to the dorsal horn.
- So, they play a regulatory role in many different physiological systems – not only pain

Transmitters and modulators in the nociception pathway

Others

- Glutamate
- GABA
- 5-HT
- Noradrenalin
- Adenosine – have a dual role in regulating nociceptive transmission:
  - activation of A1-receptors causing analgesia
  - activation of A2-receptors does the reverse
  - descending inhibitory purinergic pathways may be acting on pain transmission through A1-receptors

Opioid Analgesics

Opioid

- Endogenous or synthetic
- Produces morphine-like effects
- Blocked by antagonists such as naloxone

Opium

- An extract of the juice of the poppy *Papaver somniferum*
- Produce euphoria, analgesia and sleep
- Prevent diarrhoea
- Addiction (dependence)

Morphine analogues

– Compounds closely related in structure to morphine

– Often synthesized from it

– They may be agonists (e.g. **morphine, diamorphine** (heroin) and **codeine**)

– Partial agonists (e.g. **nalorphine** and **levallorphan**)

– antagonists (e.g. **naloxone**)

Synthetic derivatives

- Structures unrelated to morphine
- Phenylpiperidine series, e.g. **pethidine** and **fentanyl**
- Methadone series, e.g. **methadone** and **dextropropoxyphene**
- Benzomorphan series, e.g. **pentazocine** and **cyclazocine**
- Semisynthetic thebaine derivatives, e.g. **etorphine** and **buprenorphine**.

Opioid receptors

- Three types of opioid receptors (μ, δ and κ)
- G-protein-coupled receptors
- Inhibit adenylate cyclase (AC)
- Activate G protein-coupled inwardly-rectifying potassium channels (GIRKs) → hyperpolarization

μ receptors

- Mediate the major pharmacological effects of morphine, including analgesia
- Most of the analgesic opioids are μ-receptor agonists
- Responsible for some major unwanted effects (e.g. respiratory depression, euphoria, sedation and dependence)

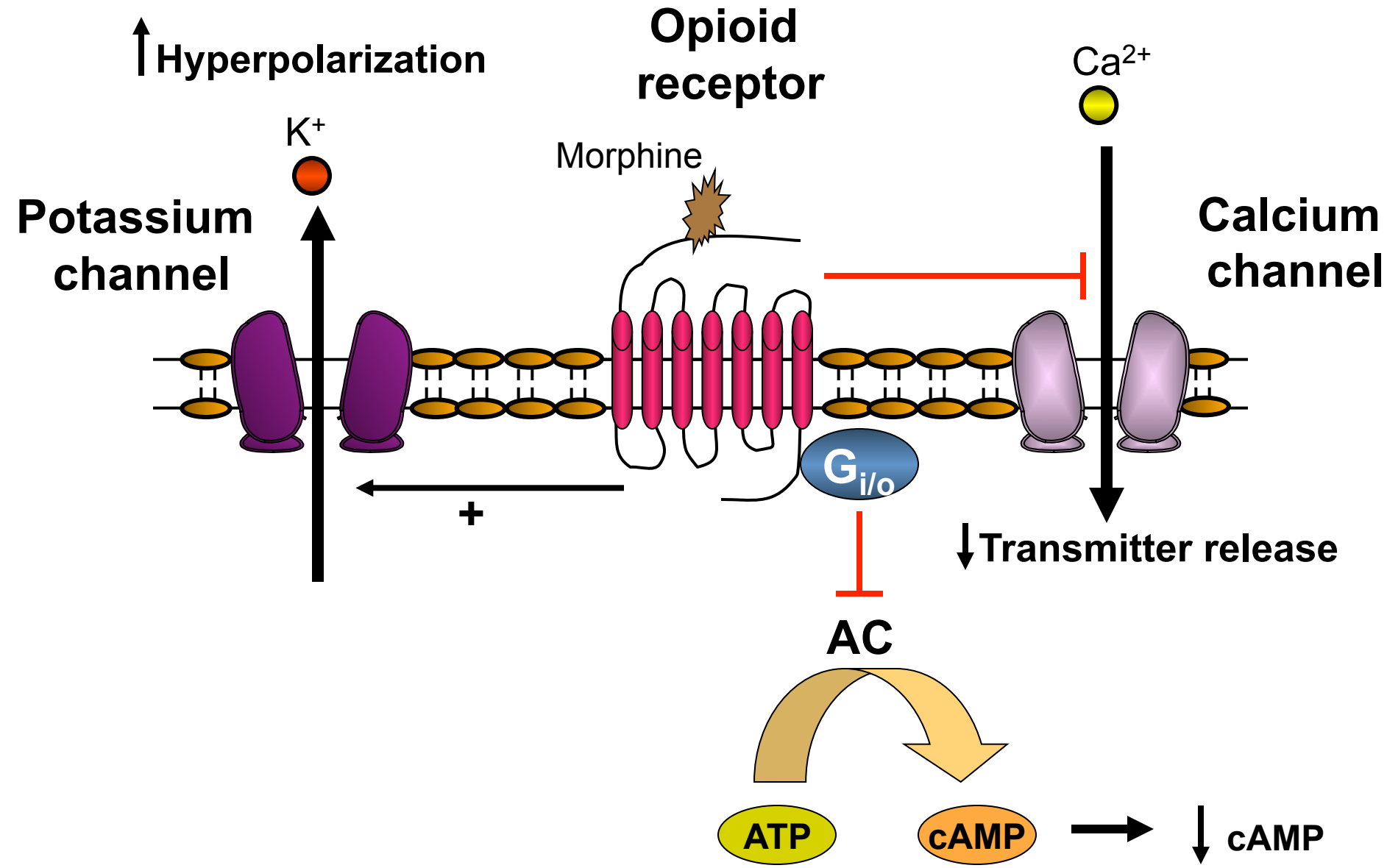
κ receptors

- Contribute to analgesia at the spinal level
- Produce relatively few unwanted effects
- Do not contribute to dependence
- Some analgesics are relatively κ-selective.

δ receptors

- In the periphery
- May also contribute to analgesia

MECHANISM OF ACTION OF OPIOIDS



MECHANISM OF ACTION OF OPIOIDS

- Opioid receptors (GPCR) inhibit adenylate cyclase
- Reduce the intracellular cAMP content
- Exert effects on ion channels through a direct G-protein coupling to the channel
- At the membrane level
  - Opioids promote the opening of potassium channels (reduce neuronal excitability)
  - and inhibit the opening of voltage-gated calcium channels (reduce transmitter release)
- The overall effect is, therefore, inhibitory at the cellular level

Three main categories

- Pure agonists
- Partial agonists and mixed agonist-antagonists
- Antagonists

Pure agonists

- Includes most of the typical morphine-like drugs

- Have high affinity for μ-receptors and generally lower affinity for δ- and κ-sites

Partial agonists and mixed agonist-antagonists

- **Nalorphine** (mixture of agonist and antagonist actions)
  - An agonist
  - It also inhibits competitively the effect of morphine

- **Pentazocine** and cyclazocine
  - Antagonists at μ-receptors
  - Partial agonists on δ- and κ-receptors

- Cause dysphoria, rather than euphoria (mediated by the κ-receptor)

Antagonists

- Produce very little effect when given on their own
- But block the effects of opioids
- Examples: **naloxone** and **naltrexone**.

PHARMACOLOGICAL ACTIONS
Effects on the central nervous system

- **Morphine is taken as the reference compound**

- **The most important effects of morphine are on the CNS and the gastrointestinal**
  1. *Analgesia*
  2. *Euphoria*
  3. *Respiratory depression*
  4. *Nausea and vomiting*
  5. Reduced GI motility
  6. *Pupillary constriction*

Functional effects associated with the main types of opioid receptor

	μ	δ	κ
Analgesia			
Supraspinal	+++	-	-
Spinal	++	++	+
Peripheral	++	-	++
Respiratory depression	+++	++	-
Pupil constriction	++	-	+
Reduced GI motility	++	++	+
Euphoria	+++	-	-
Dysphoria	-	-	+++
Sedation	++	-	++
Physical dependence	+++	-	+

Analgesia

- Effective in most kinds of acute and chronic pain associated with tissue injury, inflammation or tumour growth

- Less useful in neuropathic pain syndromes (such as phantom limb)

Euphoria

- Powerful sense of contentment and well-being
- Agitation and anxiety associated with a painful illness or injury are reduced
- Depends on the circumstances
- Mediated through μ-receptors
- Balanced by the dysphoria associated with κ-receptor activation
- It does not occur with codeine or with pentazocine

Respiratory depression

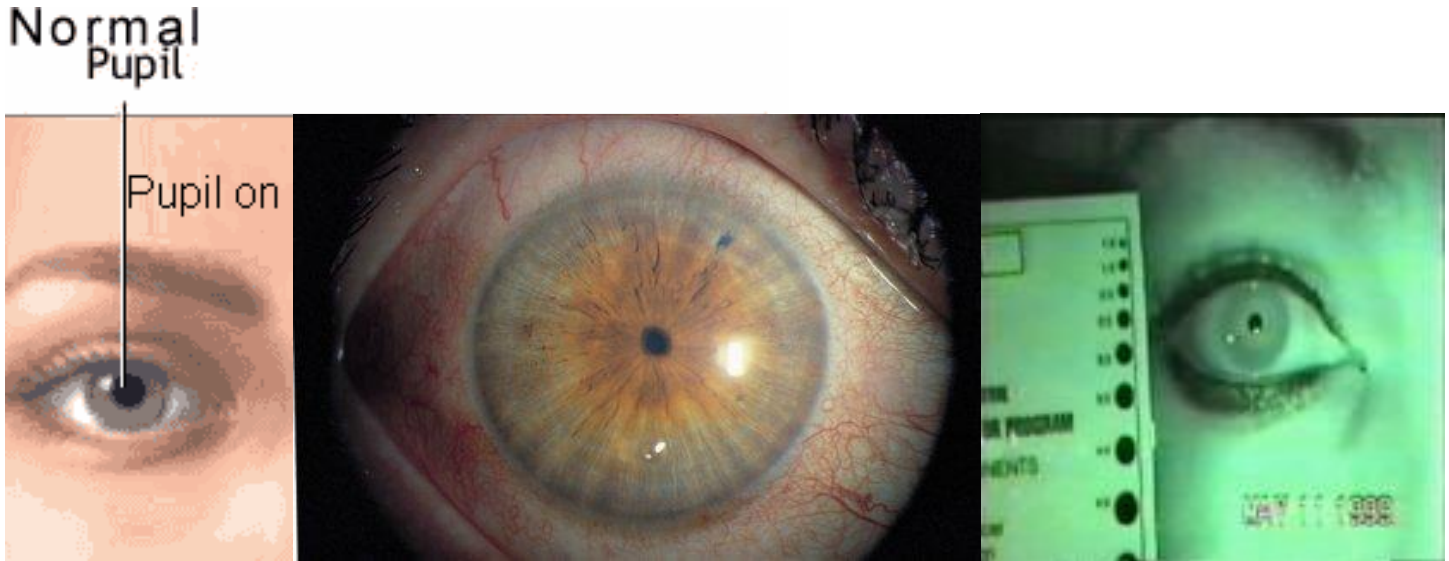
- Mediated by μ-receptors
- The most troublesome unwanted effect
- It occurs at therapeutic doses
- It is the commonest cause of death in acute opioid poisoning.

Depression of cough reflex

- Cough suppression
- Codeine suppresses cough in subanalgesic doses and is often used in cough medicines
- **Pholcodine** is even more selective

Pupillary constriction

- Caused by μ- and κ-receptor-mediated stimulation of the oculomotor nucleus
- Pinpoint pupils are an important diagnostic feature in overdosage with morphine and related drugs



Nausea and vomiting

- Occur in up to 40% of patients when they first take morphine
- The site of action is the area postrema (chemoreceptor trigger zone)
- Disappear with repeated administration.

Effects on the gastrointestinal tract

- Morphine reduces motility of the GIT
- Resulting in constipation
- The receptors involved in these effects are of the μ, κ and δ type

Other actions of opioids

- Morphine releases histamine from mast cells, by an action unrelated to opioid receptors
  - urticaria and itching at the site of the injection
  - or systemic effects, namely bronchoconstriction and hypotension
  - Should not be given to asthmatic patients

- Pethidine does not produce this effect

- Hypotension and bradycardia occur with large doses of most opioids, through an action on the medulla

Other actions of opioids

- Spasm of the ureters, bladder and uterus

- The Straub tail reaction (raising and stiffening of the tail of rats or mice)
  - Caused by spasm of a muscle at the base of the tail

- Immunosuppressant effects (increased susceptibility to infections)

TOLERANCE AND DEPENDENCE

Tolerance

- An increase in the dose needed to produce a given pharmacological effect (develops rapidly)
- Detected within 12-24 hours of morphine administration
- Sensitivity returned to normal within about 3 days of removing the drug
- The mechanism of tolerance is unclear
- It is not pharmacokinetic in origin and receptor downregulation is not a major factor.

DEPENDENCE

- Involves two separate components
  - Physical dependence
  - Psychological dependence

Physical dependence

- Associated with physical withdrawal syndrome (or *abstinence syndrome*)
  - Resembling severe influenza
  - Extreme restlessness and distress
- Lasting for a few days
- Precipitated by μ-receptor antagonists
- Rapidly abolished by re-administration of morphine
- Weak, long-acting μ-receptor agonists, such as methadone, may be used to relieve withdrawal symptoms.

Psychological dependence

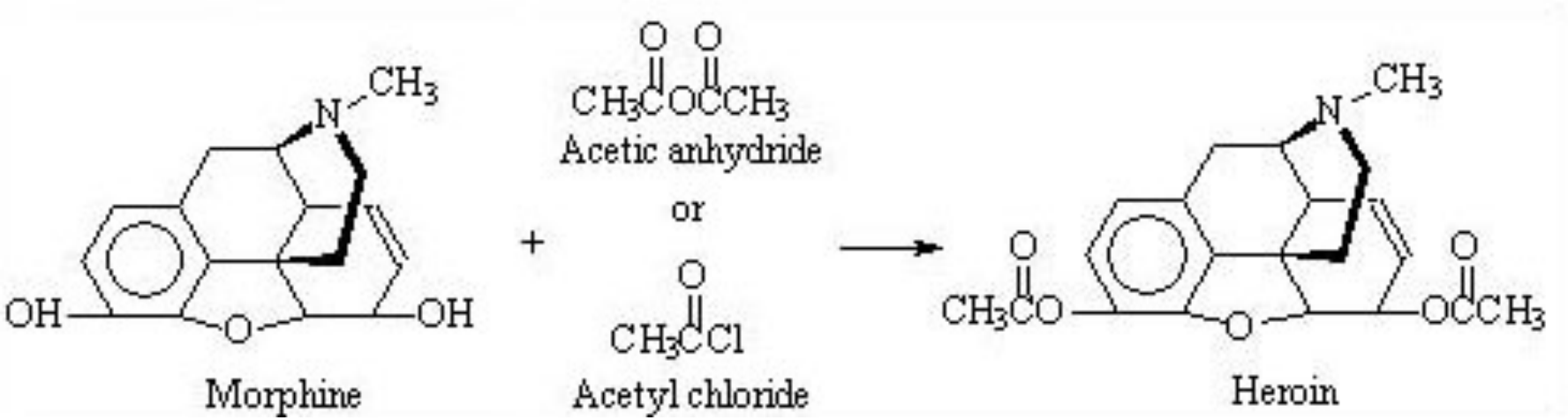
- Associated with craving
- Lasting for months or years
- Rarely occurs in patients being given opioids as analgesics
- Codeine, pentazocine and buprenorphine, are much less likely to cause physical or psychological dependence.

UNWANTED EFFECTS

- Acute overdosage with morphine results in:
  - Coma
  - Respiratory depression
  - Constricted pupils
- Treated by giving naloxone intravenously

Heroin (Diamorphine)

- Diacetyl derivative of morphine



- In the body, it is rapidly deacetylated to morphine

Heroin (Diamorphine)

- It has a greater lipid solubility
- It crosses the blood-brain barrier more rapidly than morphine and gives a greater effect
- Less emetic than morphine
- As morphine, it causes respiratory depressant and dependence
- Its duration of action (about 2 hours) is shorter than that of morphine.

Codeine (3-methoxymorphine)

- Is more reliably absorbed by mouth than morphine
- Has marked antitussive activity
- Used mainly as an oral analgesic for mild types of pain (headache, backache, etc.)
- It is often combined with paracetamol

Codeine (3-methoxymorphine)

- Has only 20% or less of the analgesic potency
- Unlike morphine, it causes little or no euphoria and is rarely addictive
- It produces the same degree of respiratory depression as morphine
- It causes constipation

Codeine (3-methoxymorphine)

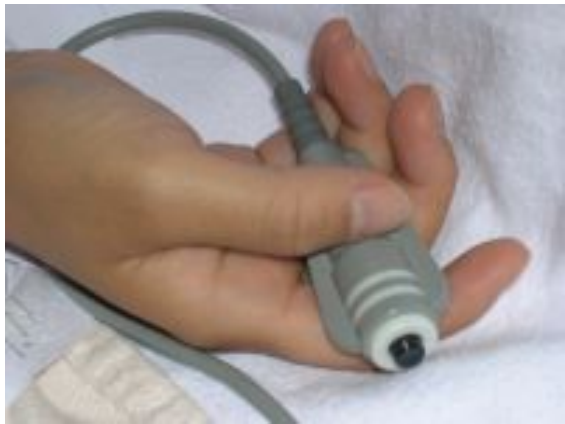
- **Dihydrocodeine** very similar to codeine
- **Dextropropoxyphene** is similar to codeine but has a longer duration of action
- About 10% of the population is resistant to the analgesic effect of codeine, because they lack the demethylating enzyme which converts it to morphine

Pethidine (meperidine)

- Very similar to morphine (pharmacological and euphoric effects and dependence)
- However, it tends to cause restlessness rather than sedation
- Its duration of action is appreciably shorter than that of morphine
- It has an additional antimuscarinic action, which may cause dry mouth and blurring of vision as side-effects

Fentanyl and **sufentanil**

- Their actions are similar to morphine but short lasting, particularly sufentanil
- Their main use is in anaesthesia, and they may be given intrathecally
- They are also used in patient-controlled infusion systems



Etorphine

- 1000 times more potent than morphine (no particular clinical advantage)
- Very similar in its actions to morphine
- It is used to immobilize wild animals for trapping and research purposes

Methadone

- The physical withdrawal syndrome and psychological dependence are less than with morphine
- Widely used to treat morphine and diamorphine addiction
- In the presence of methadone, an injection of morphine does not cause the normal euphoria
- It lacks of a physical abstinence syndrome (wean addicts from morphine or diamorphine)
- Pharmacologically similar to morphine
- It has less sedative action
- Its duration of action is considerably longer (plasma half-life >24 hours)

Pentazocine (mixed agonist-antagonist)

- In low doses, its potency and effects are very similar to those of morphine
- Increasing the dose does not cause a corresponding increase in the effects produced
- Therefore, at high doses, it causes only
  - slight respiratory depression
  - and it causes marked dysphoria, with nightmares and hallucinations, rather than euphoria

Pentazocine

- Given concurrently with morphine, it reduces the analgesic and other actions of morphine
- It can even precipitate the withdrawal syndrome in morphine addicts
- Binding studies show that it has a higher affinity for κ- than for μ-receptors, and also acts on σ-receptors,
- Less tendency to cause dependence
- Its acute toxicity is much less than that of morphine

Buprenorphine

- A partial agonist on μ-receptors
- It is less liable to cause dysphoria than pentazocine
- It is more liable to cause respiratory depression
- It has a long duration of action
- Its abuse liability is probably less than that of morphine

OPIOID ANTAGONISTS

- **Nalorphine**
- Is the first specific antagonist to be discovered
- In low doses, it is a competitive antagonist and blocks most actions of morphine
- Higher doses, however, are analgesic and mimic the effects of morphine

OPIOID ANTAGONISTS (Nalorphine)

- An antagonist action on μ-receptors, coupled with a partial agonist action on δ- and κ-receptors
- It causes dysphoria, which makes it unsuitable for use as an analgesic
- It produces physical dependence
- It precipitates a withdrawal syndrome in morphine or diamorphine addicts
- Nalorphine now has few clinical uses.

OPIOID ANTAGONISTS

- **Naloxone**
- The first pure opioid antagonist, with affinity for all three opioid receptors
- It blocks the actions of endogenous opioid peptides as well as those of morphine-like drugs
- Given on its own, naloxone produces very little effect in normal subjects
- It produces a rapid reversal of the effects of morphine and other opioids, including partial agonists such as pentazocine and nalorphine

OPIOID ANTAGONISTS (Naloxone)

- It is usually given intravenously and its effects are produced immediately
- It is rapidly metabolised by the liver
- Its effect lasts only 2-4 hours (shorter than that of most morphine-like drugs)
- Consequently, it may have to be given repeatedly
- Naloxone has no important unwanted effects of its own but precipitates withdrawal symptoms in addicts.
- It can be used to detect opioid addiction
- The main clinical use of naloxone is
  - to treat respiratory depression caused by opioid overdosage,
  - and occasionally to reverse the effect of opioid analgesics, used during labour

OPIOID ANTAGONISTS

- **Naltrexone**

- very similar to naloxone but with the advantage of a much longer duration of action (half-life about 10 hours).

OTHER ANALGESIC DRUGS

- **Tramadol**
- A metabolite of the antidepressant **trazodone**
- Widely used as an analgesic for postoperative pain
- It is a weak agonist at μ-opioid receptors and also a weak inhibitor of noradrenaline reuptake
- It is effective as an analgesic and appears to have a better side-effect profile than most opioids

NonSteroidal Anti-Inflammatory Drugs

NSAIDs

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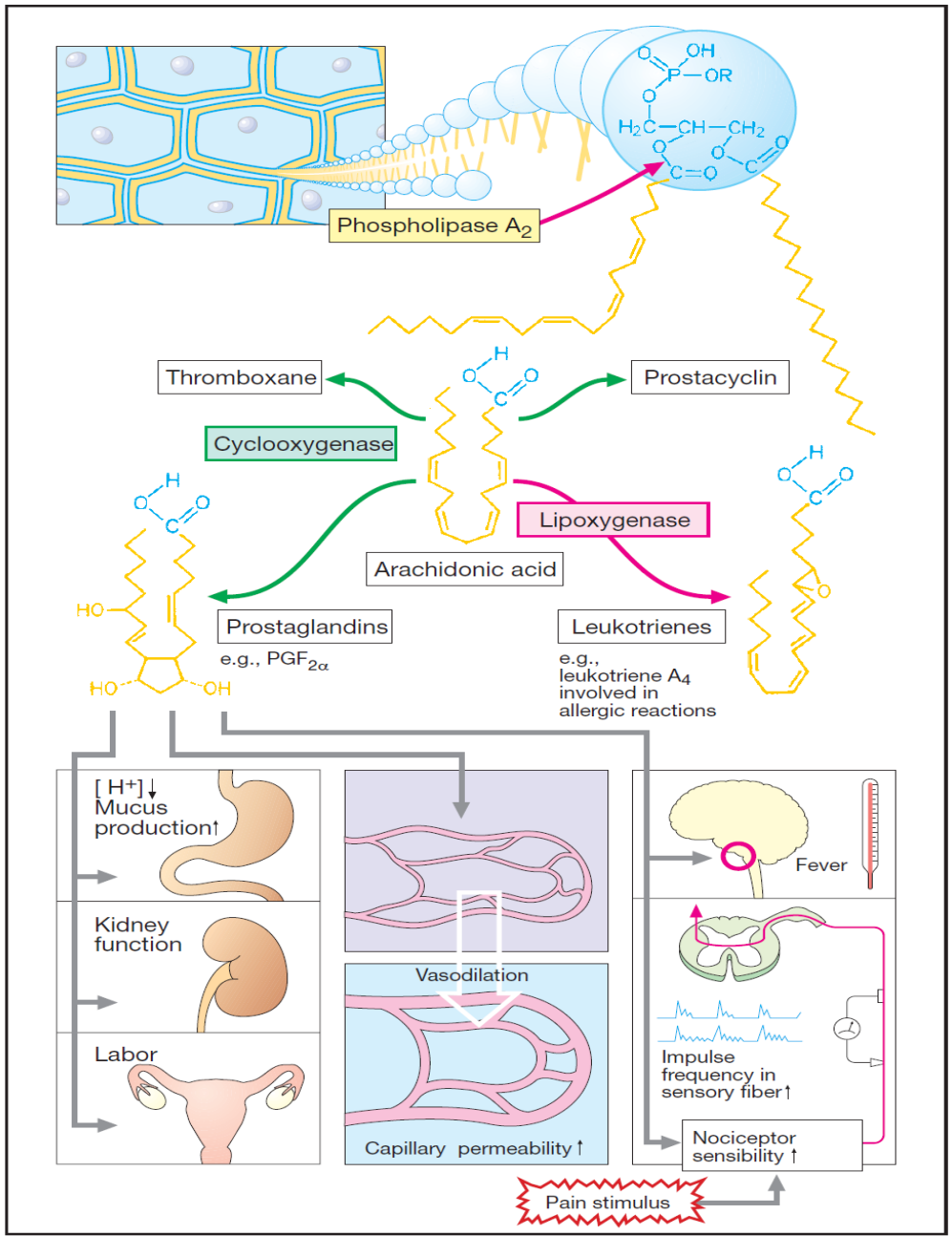
Inflammation

- A response to tissue injury.
- Defense mechanism to inactivate or destroy invading organisms or irritants, and set the stage for tissue repair.
- Triggered by the release of chemical mediators from injured tissues and migrating cells.
- Chemical mediators:
  - amines --- histamine, 5-HT
  - lipids --- prostaglandins
  - small peptides --- bradykinin
  - larger peptides --- interleukin-1.

Origin and effects of eicosanoids

Origin and effects of eicosanoids

- Prostaglandins (D, E, F, G, H, or **I**),
- Thromboxane (Platelet aggregation) — COX
- Prostacyclin (Vascular diameter),
- Leukotrienes (Allergic reactions). — LPs



Inflammatory Mediators/Signaling Molecules

- Histamine --- IgE mediated or complement mediated release from mast cells and basophils; causes vasodilation, permeability, ! gastric acid secretion

- Arachidonic acid derivatives --- (prostaglandins, thromboxanes & leukotrines) increase vasodilation, blood flow, redness, edema, fever, vascular permeability, WBC migration, pain

- Bradykinin --- vasoactive plasma peptides; vasodilator, increase vascular permeability & pain

- Cytokines --- IL-1 and TNFα released from tissue macrophages and increase vascular permeability and increase adhesion molecule expression

- Chemokines --- chemoattractants, IL-8, RANTES, MCP-1

PROSTAGLANDINS (PGs)

- All Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit the synthesis of PGs.
- Role of PGs as local mediators
  - Produced by virtually all tissues;
  - Act locally on the tissues where they are synthesized.
  - Rapidly metabolized.
  - PGs do not circulate in the blood in significant concentrations.

Synthesis of PGS (Cyclooxygenase pathway)

- Two related isoforms of the cyclooxygenase:
  - **COX-1:**

➢ Constitutive form present in stomach, intestine, platelet and kidney.

➢ Responsible for the physiologic production of prostanoids.

➢ Regulates normal cellular processes (e.g. gastric cytoprotection, vascular homeostasis, platelet aggregation, and kidney function).

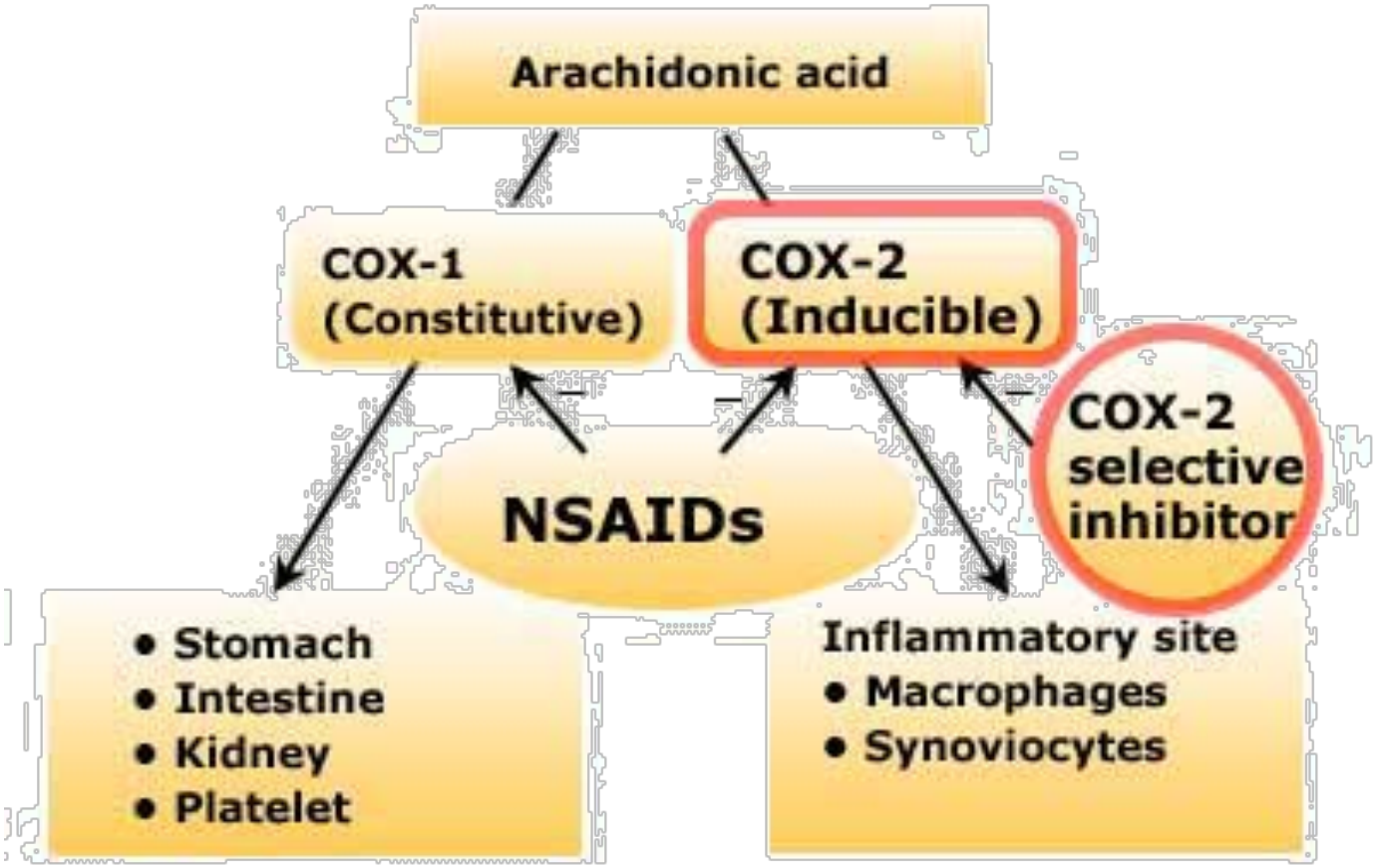
  - **COX-2:**

➢ Inducible = increased during states of inflammation.

➢ Elevated production of prostanoids that occurs in sites of disease and inflammation.

➢ Expressed in some tissues (brain, kidney, bone).

➢ COX-2 is inhibited by glucocorticoids (anti-inflammatory effect).


Arachidonic acid
COX-1
(Constitutive)
COX-2
(Inducible)
COX-2
selective
inhibitor
NSAIDs
• Stomach
• Intestine
• Kidney
• Platelet
Inflammatory site
• Macrophages
• Synoviocytes

- Actions of PGS
  - GPCR, Gs, Gi, or Gq = subsequently activate or inhibit adenylyl cyclase or stimulate phospholipase C. This causes an enhanced formation of diacylglycerol (DAG) and IP_3.
  - $PGF_{2\alpha}$, leukotrienes and thromboxane A_2 - mediate actions by activating phosphatidylinositol metabolism and causing an increase of intracellular Ca^{2+}.
- Functions in the body
  - PGs act as local signals.
  - TXA_2 in platelets --- triggers platelet aggregation (the first step in clot formation).
  - PGs - released in allergic and inflammatory processes.

Role of prostanoids in inflammation

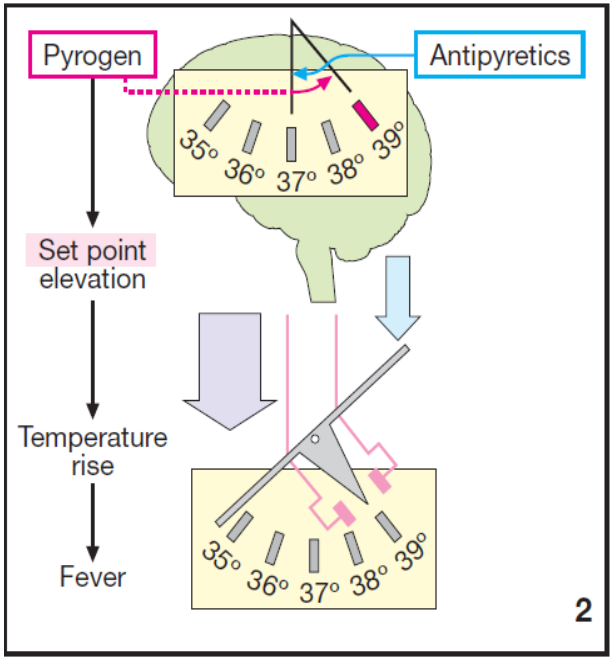
- PGI_2 (prostacyclin) released by endothelial cells; increase vasodilatation and decrease platelet aggregation
- PGD_2 released by mast cells; increase vasodilatation and decrease platelet aggregation
- TXA_2 released by platelets; increase platelet aggregation and promote vasoconstriction
- PGE_2 released by several inflammatory cells; increase temperature, contraction and relaxation of GI tract and bronchial smooth muscles, inhibit GI secretion
- PGF_2 causes myometrial contractions
- All will synergize with histamine and bradykinin to increase vascular permeability, fever and pain

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)

- Does not have the same chemical structure
- Differ in their antipyretic, analgesic, anti-inflammatory activities, and severity of side effects.
- MOA: inhibition of COX enzymes (COX-1 AND COX-2)
- COX-2 inhibitors:
  - Advantage --- less GI ulcers
  - Disadvantage --- increase risks of myocardial infarctions and strokes with long-term use
  - *See COX-2 slide*

Pharmacological effects of NSAID

- **Antipyretic**
  - Infection, hypersensitivity, malignancy, or inflammation --- activate white cells to release endogenous fever-producing proteins (pyrogen), such as a cytokine, IL-1 → stimulate release of PGE_2
  - Pyrogens (induce fever by ↑ the controller prostaglandins and interleukin-1).
  - PGE_2 – elevate the hypothalamic set-point for temperature control
  - Antipyretics such as acetaminophen and acetylsalicylic acid return the set point to its normal level.
  - Lowering the raised in temperature
  - Via decrease in PGE_2,



- Analgesic
  - Decrease certain types of pain
  - Via decrease PGs overproduction, and relief of headache due to decreased PGs-mediated vasodilatation
  - PGE_2 – it sensitizes nerve endings to bradykinin, histamine, and other mediators released by the inflammatory process.
  - Salicylates - used mainly for the management of pain of low to moderate intensity.

- Anti-inflammatory
  - Via decrease in PGE_2 and PGI_2 i.e. less vasodilatation and less oedema
  - NSAIDs are superior to opioids for the management of pain in when inflammation is involved.

- Effect on platelets
  - TXA_2 enhances aggregation (the first step in thrombus formation) - PGI_2 decreases aggregation (vasodilation)
  - Low doses (60-80 mg daily) of aspirin can irreversibly inhibit thromboxane production in platelets without markedly affecting TXA_2 production in the endothelial cells of the blood vessel.
  - The acetylation of COX is irreversible. Because platelets lack nuclei, they cannot synthesize new enzyme, and the lack of thromboxane persists for the lifetime of the platelet (3 to 7 days).
  - This contrasts with the endothelial cells (with nuclei) – therefore they can produce new COX --- PGI_2.
  - Because of the decrease in TXA_2 and no change in PGI_2, the platelet aggregation is reduced --- anticoagulant effect with a prolonged bleeding time.

- GIT effects:
  - PGI_2 inhibits gastric acid secretion while PGE_2 and PGF_{2a} stimulate synthesis of protective mucus in both the stomach and small intestine.
  - In the presence of aspirin --- increased gastric acid secretion and diminished mucus protection --- epigastric distress, ulceration, hemorrhage.
  - At ordinary aspirin doses - as much as 3 to 8 ml of blood may be lost in the feces per day.
  - Antiulcers: The PGE_1 derivative misoprostol, the proton pump inhibitor omeprazol, and H_2-antihistamines reduce the risk of gastric ulcer.

- Actions on the kidney:
  - PGE_2 and PGI_2 are responsible for maintaining renal blood flow
  - COX inhibitors prevent the synthesis of PGE_2 and PGI_2 --- retention of sodium and water and edema and hyperkalemia may occur.
  - Interstitial nephritis may occur with all NSAIDs except aspirin.

Some pharmacokinetic aspects of NSAID

- Well absorbed orally
- Rectal absorption is a useful route in vomiting children.
- Salicylates (except for diflunisal) cross the placenta.
- Salicylates, especially methyl salicylate, are absorbed through intact skin.
- High plasma protein binding
- Salicylate is converted by the liver to water-soluble conjugates that are rapidly excreted by the kidney
- At higher doses, the hepatic enzymes saturated - a half-life of 15 hours or more. Saturation of the hepatic enzymes requires treatment for several days to one week.

NSAIDS: Chemistry and Pharmacokinetics

- Grouped into several chemical classes
- Weak organic acids that are well absorbed

- Utilize CYP3A or CYP2C family of cytochrome P450 enzymes in the liver

- Final renal excretion but also biliary excretion and reabsorption (excreted unchanged or as H_20 soluble metabolites

- Protein bound, usually to albumin (drug interactions?)

- All can be found in synovial fluid after repeated dosing

ASPIRIN and other salicylates

- aspirin (acetylsalicylic acid)
- sodium salicylate
- methylsalicylate (topically used)
- Diflunisal (dolobid)

Mechanism of action:

- Irreversibly acetylates (and thus inactivates) COX - unique among other NSAIDs
- Other NSAIDs - including salicylate - are all reversible inhibitors of COX.
- Aspirin - rapidly deacetylated by esterases, producing salicylate, which has anti-inflammatory, antipyretic, and analgesic effects.

✧ DIFLUNISAL

- Derivative of salicylic acid, it is not metabolized to salicylate → it cannot cause salicylate intoxication.
- Diflunisal is 3-4 times more potent than aspirin as an analgesic and an anti-inflammatory agent
- Does not enter the central nervous system (CNS) and therefore cannot relieve fever (does not have antipyretic properties)

Toxicity and overdose

- Salicylism = the mild form: nausea, vomiting, hyperventilation, headache, mental confusion, dizziness, and tinnitus.
- Severe intoxication = large doses: The above symptoms + restlessness, delirium, hallucinations, convulsions, coma, respiratory and metabolic acidosis, and death from respiratory failure.
- Children are particularly prone to salicylate intoxication.
- Treatment of salicylism: measurement of serum concentrations and pH. Mild cases - symptomatic treatment. Increasing the urinary pH enhances the elimination of salicylate.
- Seriouse cases - i.v. fluid, hemodialysis or peritoneal dialysis, correction of acid-base and electrolyte balances.
- Note: Diflunisal does not cause salicylism.

Propionic acid derivatives

- Ibuprofen, naproxen, fenoprofen, ketoprofen, flurbiprofen, oxaprozin
- Reversible inhibitors of COX.
- Anti-inflammatory, analgesic, and antipyretic activity.
- Chronic treatment of rheumatoid arthritis and osteoarthritis – because of lower frequency of GIT adverse affects.
- Oxaprozin has the longe st half-life, and is administered once daily.
- Hepatic metabolism, excreted by the kidney.
- The most common adverse effects are GI (dyspepsia, bleeding).

Acetic acid derivatives

- INDOMETHACIN, SULINDAC, ETODOLAC, DICLOFENAC AND KETEROLAC
- Anti-inflammatory, analgesic, and antipyretic activity.
- Reversible inhibition of COX.
- Very potent. Not used to lower fever.
- Toxicity of indomethacin limits its use
- Interactions: may decrease antihypertensive effect of furosemide, thiazide diuretics, beta-blockers, ACE-inhibitors.
- Used for
  - treatment of acute gouty arthritis, ankylosing spondylitis, osteoarthritis of the hip
  - beneficial in postoperative ophthalmic pain.
  - antipyretic for Hodgkins disease when the fever is refractory to other agents.

Acetic acid derivatives *continued*

- Sulindac
  - a prodrug, related to indomethacin
  - Useful in rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, and acute gout.
  - The adverse reactions are less severe than in indomethacin.

- Etodolac - effects similar to other NSAIDs. GIT problems may be less common.

Acetic acid derivatives *continued*

✧ DICLOFENAC

- Diclofenac accumulates in synovial fluid
- long-term use in the treatment of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis.
- Side effects: GIT problems and elevation of hepatic enzymes.

✧ KETOROLAC

- Can be administered I.M. in the treatment of postoperative pain and topically for allergic conjunctivitis.

Enolic acid (Oxicam) derivatives

- PIROXICAM (Feldene) and MELOXICAM (Mobic)
  - For rheumatoid arthritis, ankylosing spondylitis, and osteoarthritis.
  - They have long half-lives
  - Meloxicam is relatively COX-2 selective and at low to moderate doses shows less GI irritation than piroxicam. However, at high doses, meloxicam is a nonselective NSAID (inhibition COX-1 and COX-2).
  - Excreted in the urine, interference with the excretion of lithium.

• Fenamic acid derivatives (Fenamates)

- MEFENAMIC ACID, MECLOFENAMATE
- No advantages over other NSAIDs.
- Side effects: e.g., diarrhea (even severe with inflammation of the bowel), hemolytic anemia.

COX-2 INHIBITORS

- The structural difference between COX-1 and COX-2 allowed the development of COX-2-selective agents.
- Some traditional NSAIDs (etodolac, meloxicam, and nimesulide) display some level of COX-2 selectivity.
- Advantages:
  - lower risk for the development of GI bleeding. They also have
  - no significant effects on platelets.
- disadvantages
  - like the traditional NSAIDs, may cause renal insufficiency and increase the risk of hypertension.
  - increase the risks of myocardial infarctions and strokes
- CELECOXIB: Approved for treatment of osteoarthritis and rheumatoid arthritis.
  - Contraindicated in patients who are allergic to sulfonamides. If there is a history of sulfonamide allergy, the use of a nonselective NSAID is recommended.

ACETAMINOPHEN “PARACETAMOL”

A. inhibits PGS synthesis in the CNS - it explains its antipyretic and analgesic properties.

B. less effect on COX in peripheral tissues --- weak anti-inflammatory activity.

C. does not affect platelet function or increase blood clotting time.

Therapeutic uses:

- Suitable for the analgesic and antipyretic effects for patients with gastric complaints.
- Analgesic/antipyretic of choice for children with viral infections or chickenpox (aspirin increases the risk of Reye syndrome; *sudden (acute) brain damage and liver function problems of unknown cause and occurred in children who have been given aspirin when they have chicken pox or the flu).*

Pharmacokinetics of Paracetamol:

- Rapidly absorbed from the GIT.
- A significant first-pass metabolism
- Under normal circumstances is conjugated in the liver to form inactive glucuronidated or sulfated metabolites.
- A portion of paracetamol hydroxylated to form N-acetylbenzoimino- quinone - a highly reactive and dangerous metabolite that reacts with sulfhydryl groups.
- At normal doses, the N-acetylbenzoiminoquinone reacts with the sulfhydryl group of glutathione, forming a nontoxic substance.
- Excreted in urine.

Adverse effects of Paracetamol:

- Skin rash and minor allergic reactions occur infrequently.
- Large doses of paracetamol (about 10 g or more in adult) - the available glutathione in the liver becomes depleted → N-acetylbenzoiminoquinone reacts with the sulfhydryl groups of hepatic proteins, forming covalent bonds.
- Hepatic necrosis can result. Renal tubular necrosis may also occur.
- Possibly dangerous in alcoholics.
- ANTIDOTE: N-acetylcysteine (containing sulfhydryl groups to which the toxic metabolite can bind) can be lifesaving if administered within ten hours of the overdose.