Physiology & Pharmacology of Pregnancy

Objectives

- Definition of pain
- Nociceptors : Location, types
- Types of pain
- Pathway of Pain
- Opioid analgesics
  - Mechanism of action
  - Morphine
  - Other opioid analgesics

Pain

- Unpleasant sensory and emotional experience associated with actual or potential damage
- Pain is redefined as a perception instead of a sensation because it is always a psychological state.
  - Latin word "peona " meaning punishment
- Pain is always subjective
- It is differently experienced by each individual.

Nociception

- Coined by Sherrington
- Latin: noxa means injury
- it means the ´perception of noxious stimuli´

- Mechanism by which noxious peripheral stimuli are transmitted to the central nervous system to elicit a mechanical response .

Pain - Receptors

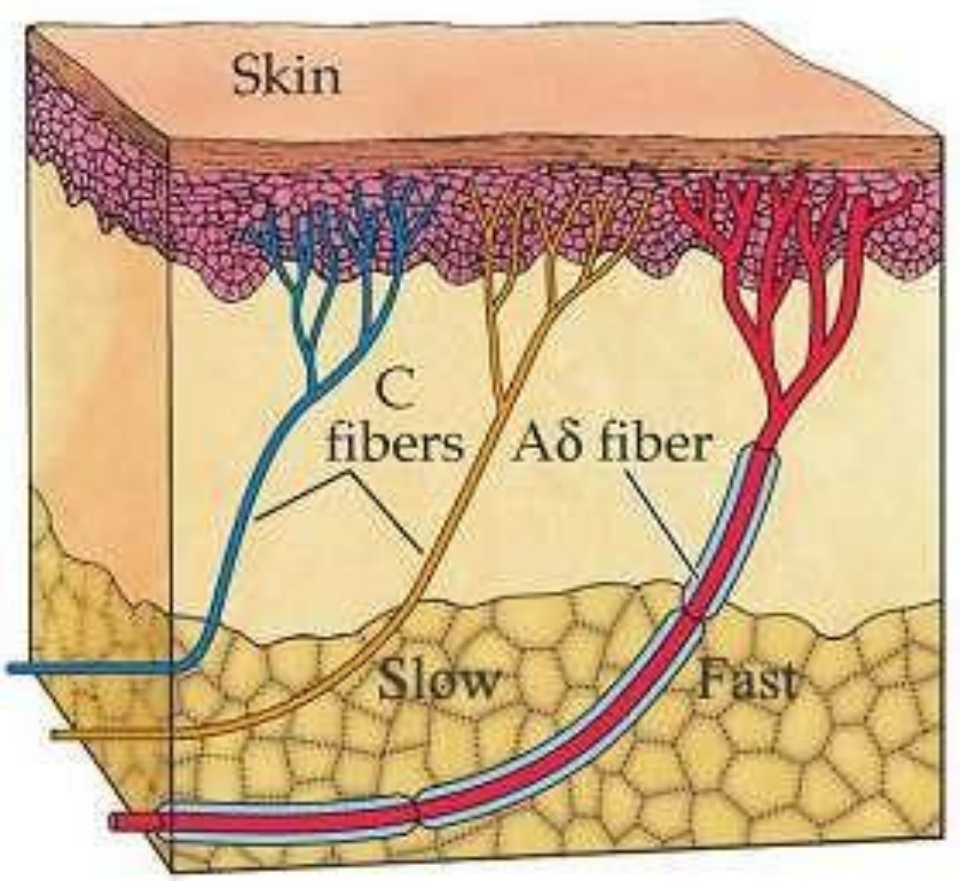
- Specialized naked nerve endings found in almost every tissue of the body.
- Activated by stimuli (mechanical, thermal, chemical)
- Distinguished from other receptors by
  - their higher threshold, and
  - they are normally activated only by stimuli of noxious intensity-sufficient to cause some degree of tissue damage.
- Aδ: Myelinated
- C: Unmyelinated

Characteristic features of Aδ & C fibres

Feature	Aδ fibre	C fibre
Number	Less	More
Myelination	Myelinated	Unmyelinated
Diameter	2-5 µm	0.4-1.2 µm
Conduction velocity	12-30 m/s	0.5 -2 m/s
Specific stimulus	Most sensitive to pressure	Most sensitive for chemical agents
Impulse conduction	Fast component of pain	Slow component of pain

Location of nociceptors

- Superficial skin layers
- Deeper tissues
  - Periosteum, joints, arterial wall, liver capsule, pleura
- Other deeper tissues
  - Sparse pain nerve endings
  - But wide spread tissue damage results in pain



Types of Nociceptors

- Somatic
  - Free nerve endings of Aδ & C fibres
  - Unimodal, polymodal, silent
- Visceral
  - Wide spread inflammation, ischemia, mesentric streching , spasm or dilation of hollow viscera produces pain
  - Probably strech receptors

Pain stimuli

- Mechanical / thermal stimuli
  - Fast pain: Sharp well localized , pricking type
- Chemical stimuli
  - Slow pain: poorly localized, dull, throbbing
  - K+, ADP, ATP
  - Bradykinin, histamine
  - Serotonin, Prostaglandins
  - Substance P, CGRP

Clinical types of pain

- Somatic
- Visceral
- Referred pain
  - Convergence & facilitation theory
- Projected pain
- Radiating Pain
- Hyperalgesia

Pathway of pain sensation

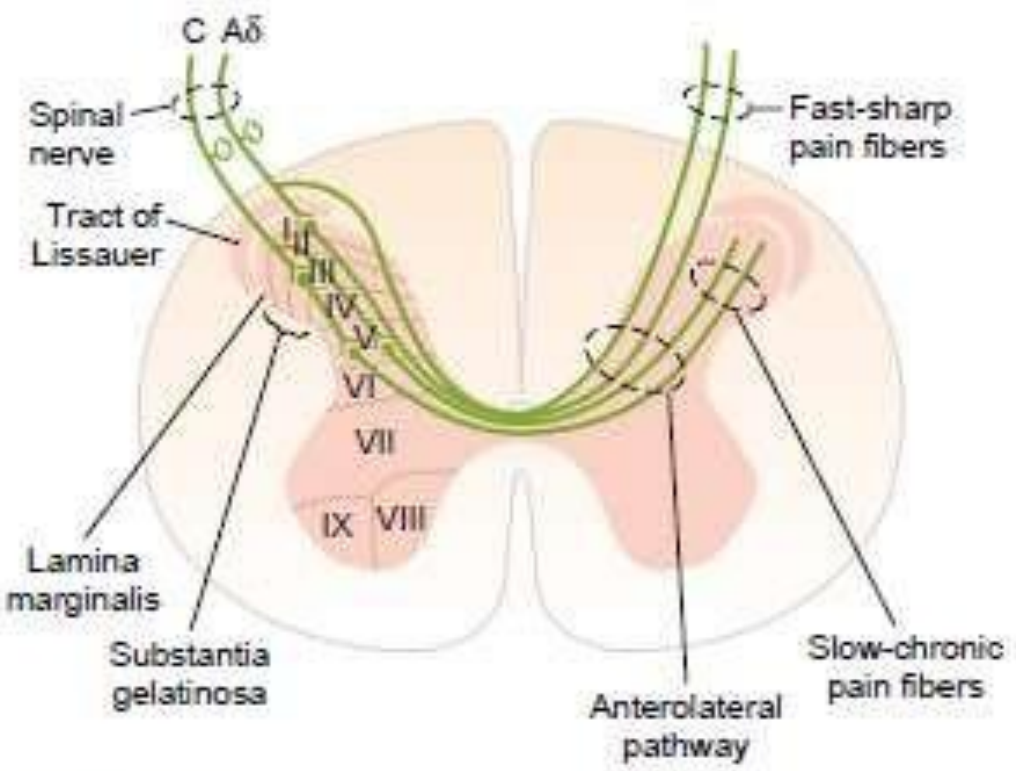
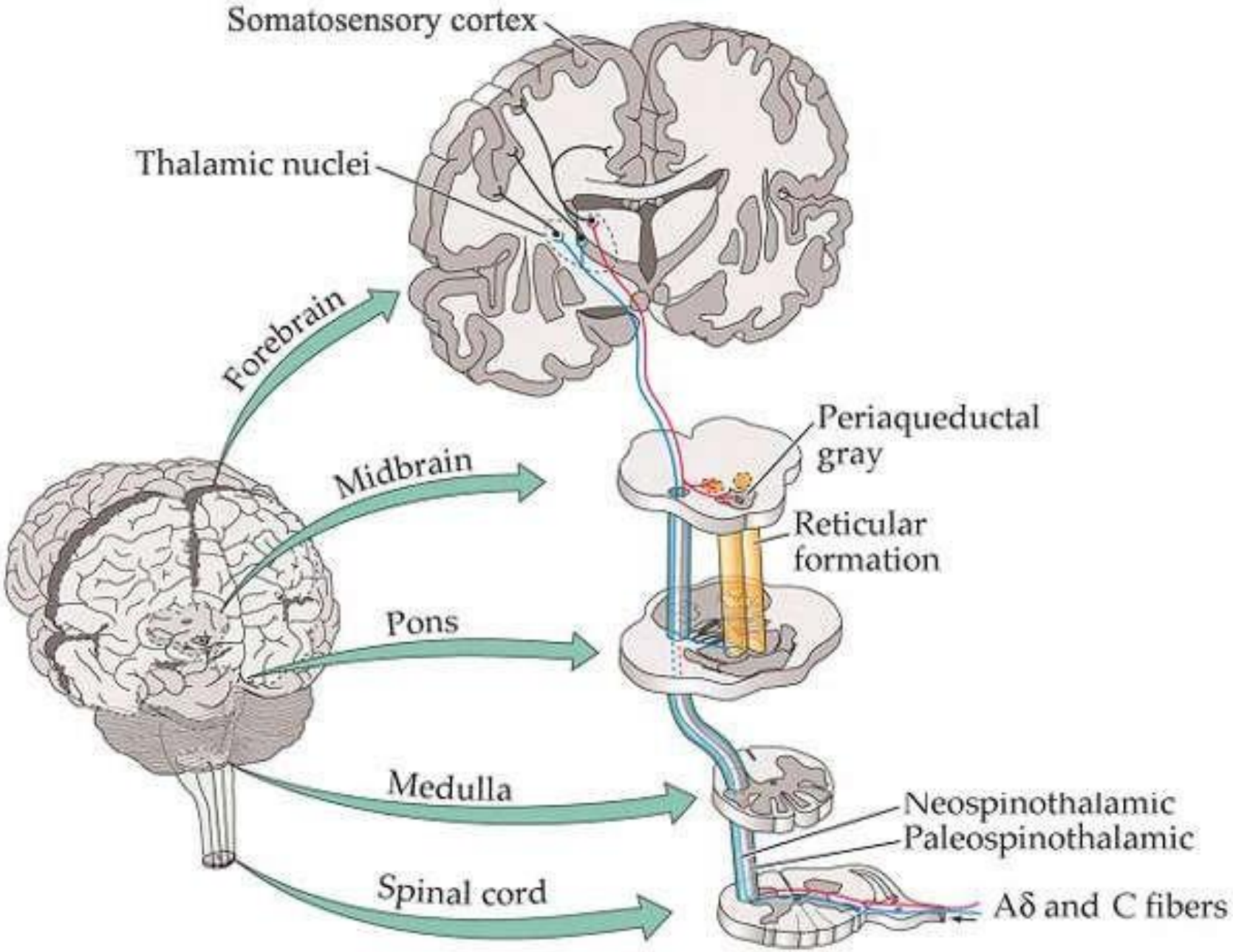
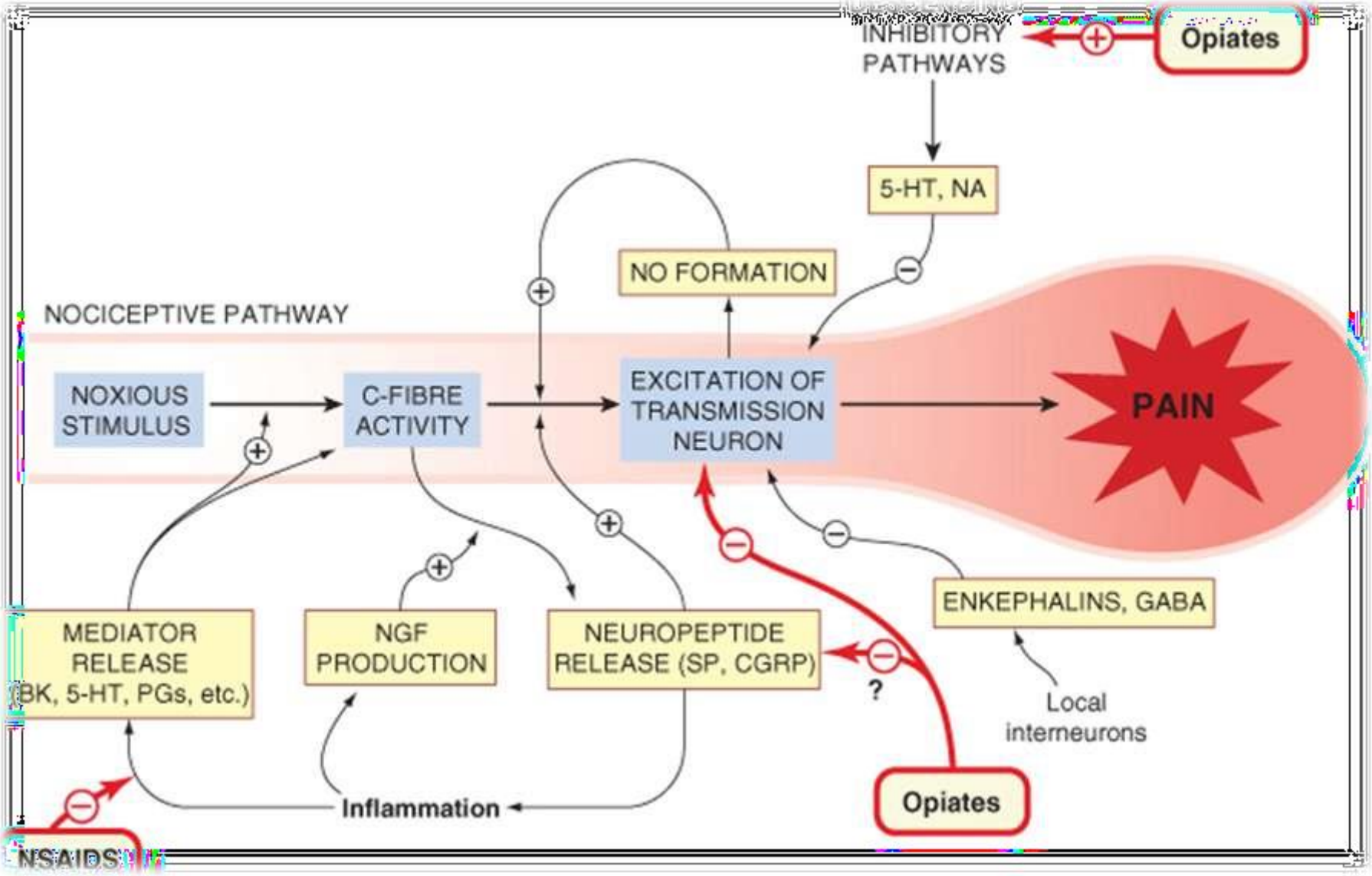


Figure 48–2

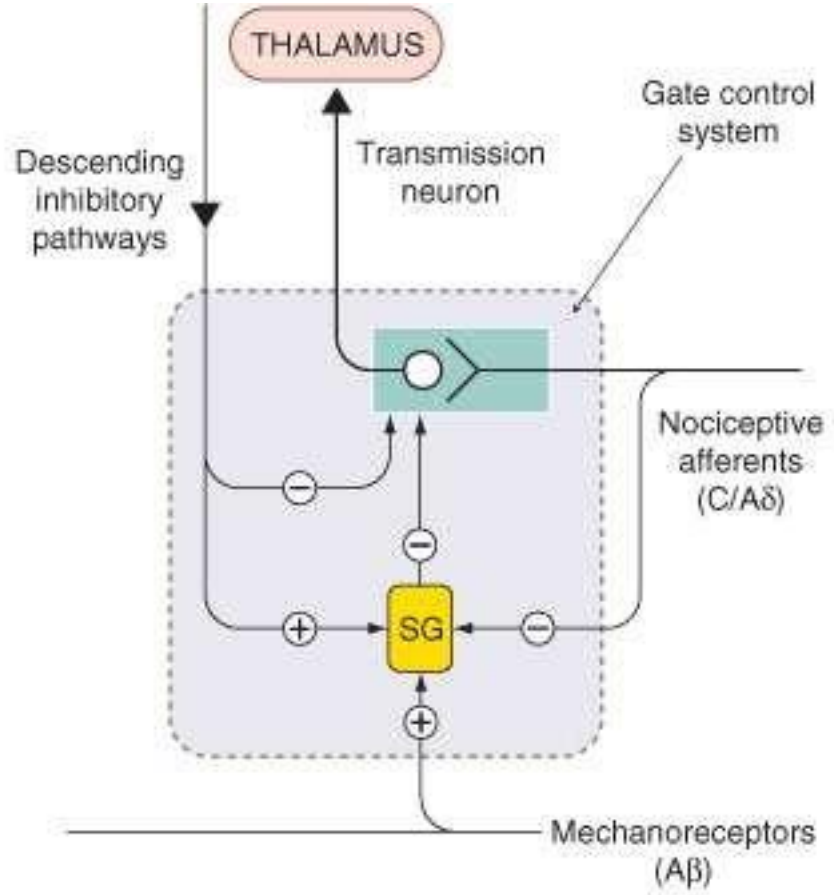
Transmission of both "fast-sharp" and "slow-chronic" pain signals into and through the spinal cord on their way to the brain.


Somatosensory cortex
Thalamic nuclei
Forebrain
Midbrain
Pons
Medulla
Spinal cord
Periaqueductal gray
Reticular formation
Neospinothalamic
Paleospinothalamic
Aδ and C fibers

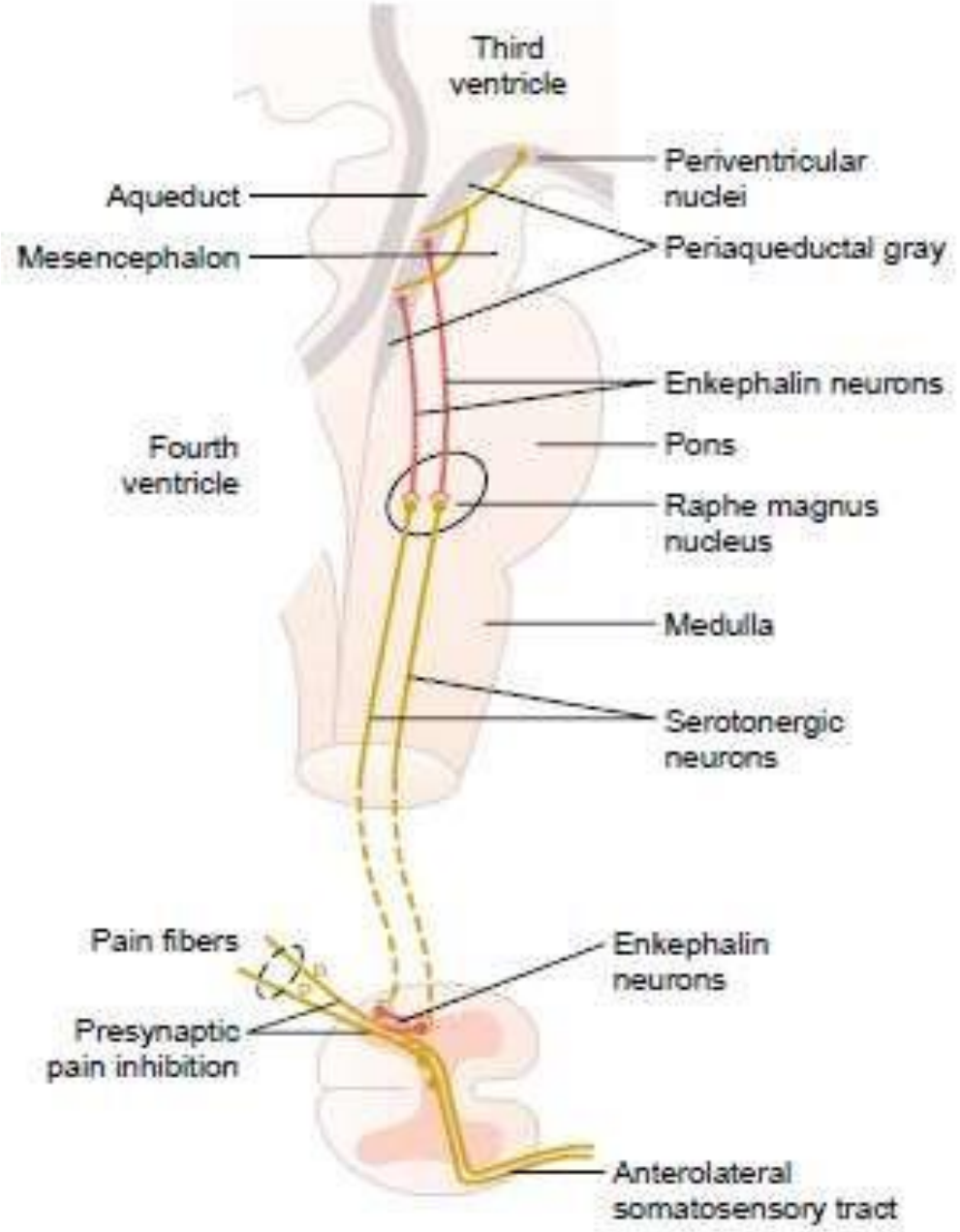
Modulation of pain



Gate control system



Supra spinal pain supression system



Analgesics

- Drugs which relieve pain due to multiple causes with out causing loss of consciousness
- Drugs which relieve pain due to single causes or specific pain syndromes (ergotamine, carbamazepine, nitrates) are not classified as analgesics
- Corticosterroids also not classified as analgesics

Analgesics

- Opioid analgesics
  - Morphine and morphine like drugs
- Non steroidal anti-inflammatory drugs
  - Paracetamol, diclofenac, ibuprofen etc

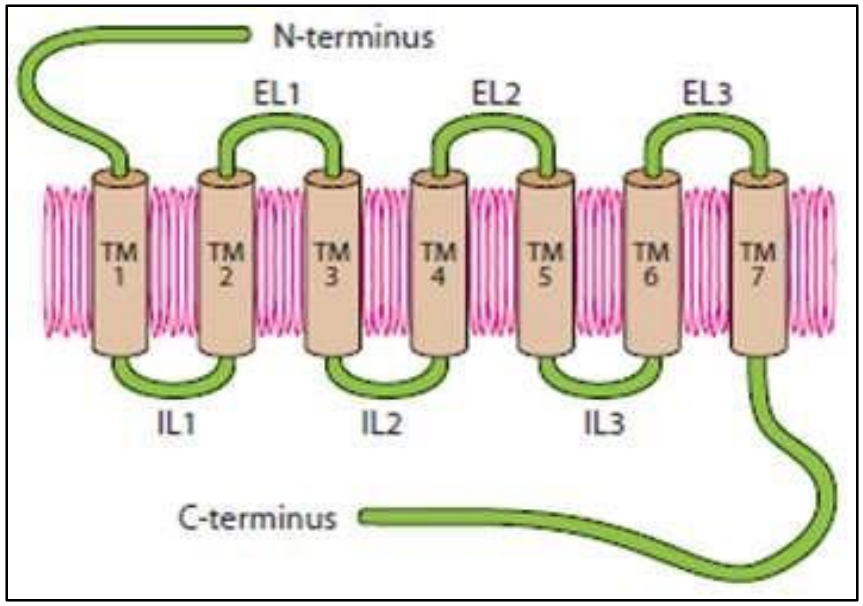
Mechanism of action of Opioids

Opioid Receptors

- Opioid receptors found in the brain, spinal cord and peripheral nervous system
- Mu (μ_1 and μ_2)
- Kappa (k1 & k3)
- Delta (δ)
- Nociceptin/Orphanin (N/OFQ)

Opioid Receptors

- Inhibitory action; coupled to G_o & G_i



Structure of the opioid receptor

Mu-Receptor: Two Types

μ_1

- Located outside spinal cord
- Higher affinity for morphine
- Supraspinal analgesia
- Selectively blocked by naloxone

μ_2

- Located throughout CNS
- Responsible for
  - spinal analgesia,
  - Respiratory depression,
  - constipation
  - physical dependence, and euphoria

Kappa Receptor

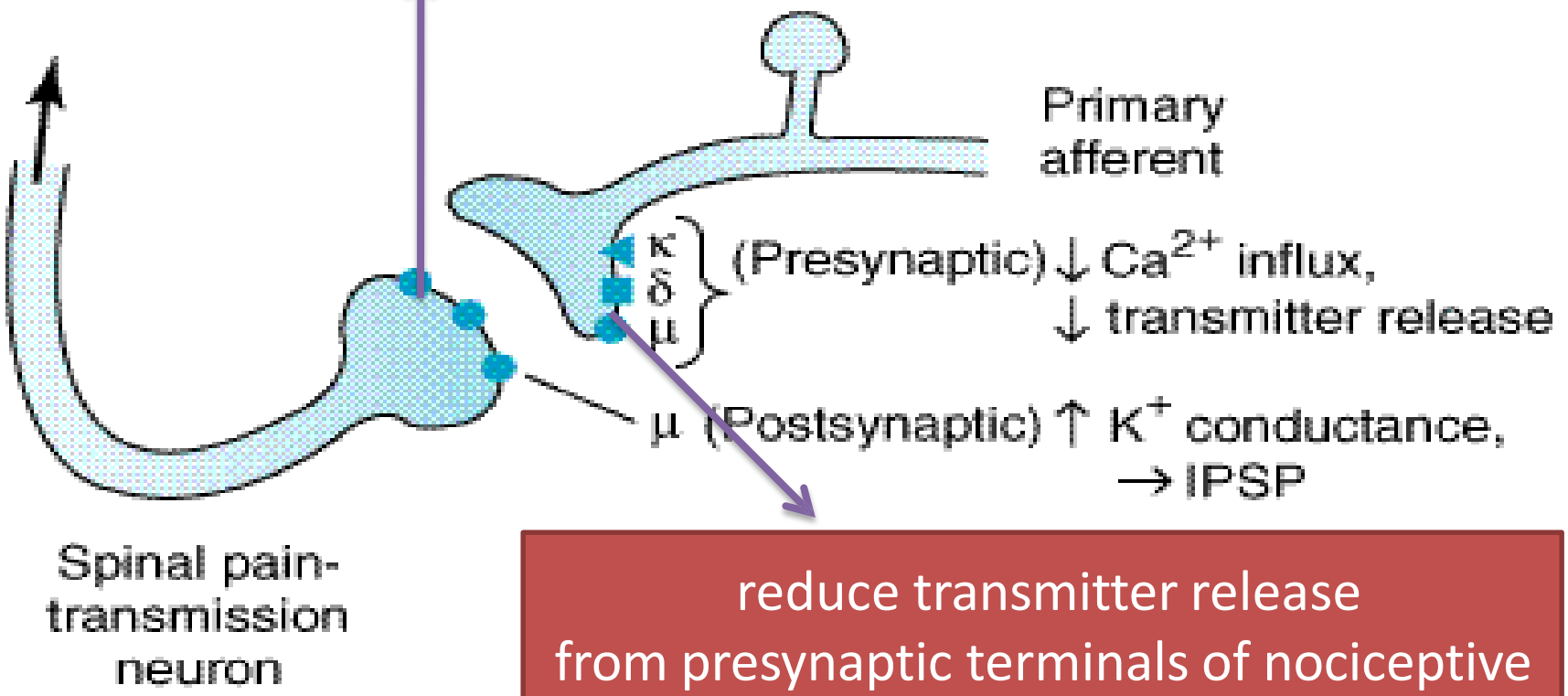
- Only modest analgesia(spinal κ_1 and supraspinal κ_3)
- Little or no respiratory depression
- Little or no dependence
- Dysphoric effects
- Miosis
- Reduced GI motility

Delta Receptor

- High affinity for Leu/Met enkephalins endogenous ligands.
- The δ mediated analgesia is mainly spinal
- Affective component of supraspinal analgesia appears to involve δ receptors as these receptors are present in limbic areas—also responsible for dependence and reinforcing actions.
- The proconvulsant action is more prominent in δ agonists.

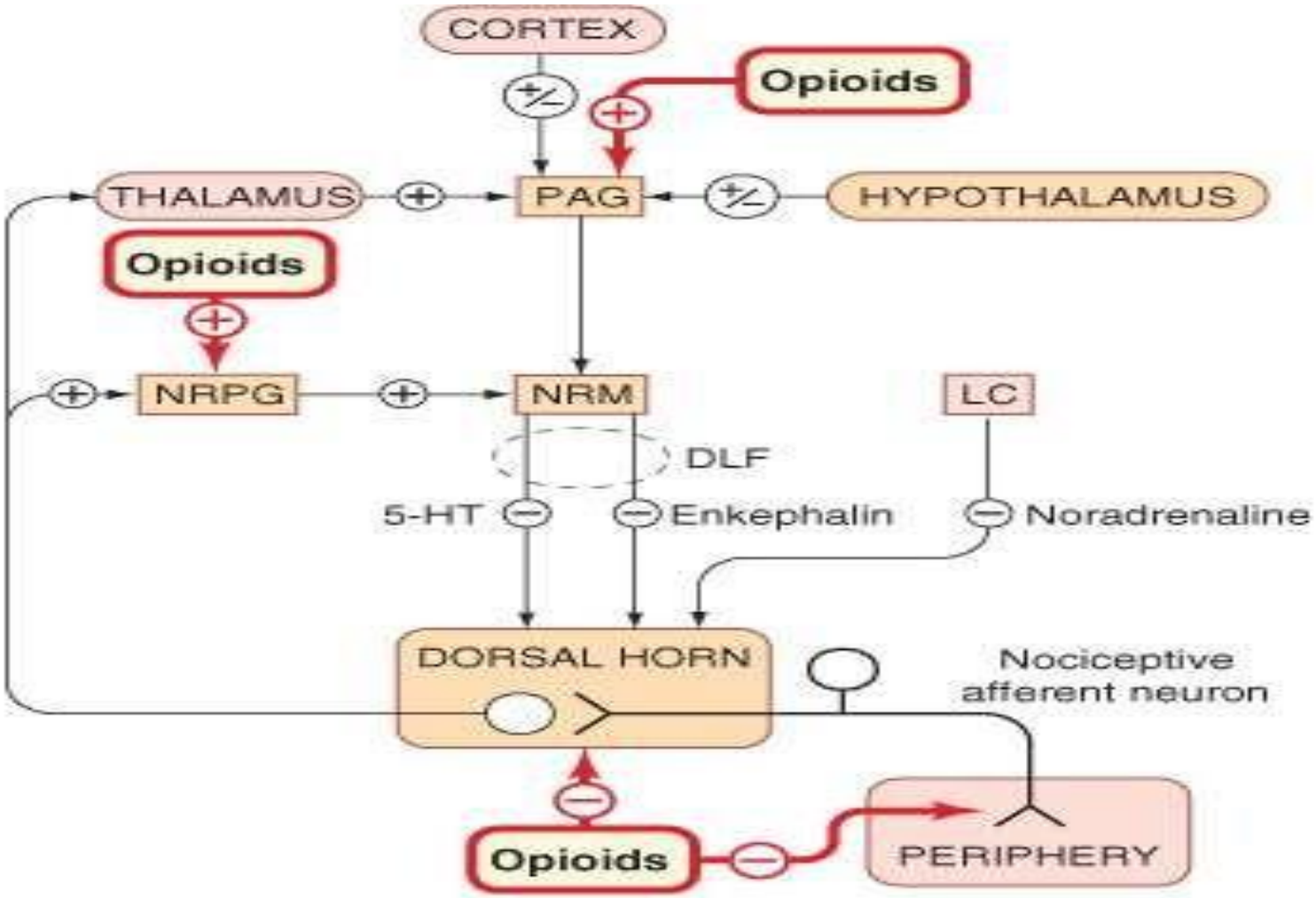
Spinal sites of opioid action.

hyperpolarize
second-order pain transmission neurons by increasing K+ conductance, evoking an inhibitory postsynaptic potential



reduce transmitter release
from presynaptic terminals of nociceptive primary afferents

The descending control system, showing the main sites of action of opioids on pain transmission



Analgesic features of Morphine

Efficacy

- Morphine is a strong analgesic.
- Higher doses can mitigate even severe pain
- Degree of analgesia increasing with dose.
- Simultaneous action at spinal and supraspinal sites greatly amplifies the analgesic action.

Selectivity

- Suppression of pain perception is selective
- No affect on other sensations
- proportionate generalized CNS depression (contrast general anaesthetics).

Type of pain

- Dull, poorly localized visceral pain is relieved better than sharply defined somatic pain
- Nociceptive pain arising from stimulation of peripheral pain receptors is relieved better than neuritic pain due to inflammation or damage of neural structures

Mood and subjective effects

- Morphine has a calming effect.
- The associated reactions to intense pain
  - apprehension,
  - fear,
  - autonomic effects are also depressed.
- Perception of pain and reaction to it are both altered so that pain is no longer as unpleasant or distressing, i.e. patient tolerates pain better.

Mood and subjective effects

- Other effects include
  - feeling of detachment,
  - Lack of initiative,
  - limbs feel heavy and body warm,
  - mental clouding and inability to concentrate.
- In normal people, in the absence of pain or apprehension, these are generally appreciated as unpleasant

Mood and subjective effects

- Patients in pain or anxiety and addicts
  - specially perceive it as pleasurable
  - Refer it as 'high'.
- Rapid IV injection by addicts - gives them a 'kick' or 'rush' which is intense, pleasurable—akin to orgasm.
- Thus one has to learn to perceive the euphoric effect of morphine.

Mood and subjective effects

In patients - Pain relief
No addiction

In normal persons
Dependence and
Addiction

Other pharmacological actions

Gastrointestinal system :

- Increase in tone ,
- reduced motility ,
- contraction of sphincters ,
- decrease of G.I. secretions
- leading to constipation .(μ , k , δ receptors).

Other effects

Respiratory centre

- Morphine depresses respiratory centre in a dose dependent manner
- Rate and tidal volume are both decreased
- Death in poisoning is due to respiratory failure
- Neurogenic, hypercapnoeic and later hypoxic drives are suppressed in succession

Other effects

- C.V.S. :
  - Vasodilatation due to direct decrease of tone of blood vessels
  - Shift of blood from pulmonary to systemic circuit
  - histamine release and
  - depression of vasomotor centre
- Urinary bladder
  - Detrusor contraction leading to urgency .
  - Sphincter contraction leading to retention of urine

Other effects

- Bronchoconstriction
  - due to histamine release by morphine .
- Uterus may be relaxed .
- Mild hyperglycemia due to central sympathetic stimulation .
- It has weak anticholinesterase action .

Pharmacokinetic features

- Oral absorption is unreliable
- Metabolized by glucuronide conjugation.
- Morphine-6-glucuronide is an active metabolite (more potent than morphine)
- freely crosses placenta
- $t_{1/2}$of morphine averages 2-3 hours
- Effect of a parenteral dose lasts *4-6* hours

ADVERSE EFFECTS

- The toxic effects of morphine are an extension of their pharmacological effects
- Idiosyncrasy and allergy
  - Urticaria, itch,swelling of lips.
  - A local reaction at injection site may occur due to histamine release.
- Allergy is uncommon and anaphylactoid reaction is rare.

ADVERSE EFFECTS

- Apnoea This may occur in new born when morphine is given to mother during labour.
- The BBB of foetus is undeveloped, morphine attains higher concentration in foetal brain
- Naloxone 10 µg/kg injected in chord is the treatment of choice.

Tolerance

Onset

- Tolerance to morphine develops rapidly and can be detected within 12 – 14 hours of morphine administration
- within 3 days the equianalgesic dose is increased 5 fold .

Tolerance - effects

- Tolerance extends to most actions of morphine
  - analgesia ,
  - euphoria ,
  - respiratory depression
- not to the constipation miosis and convulsions
- Cross tolerance occurs between drugs acting at the same receptor , but not drugs acting on different receptor

Tolerance - Mechanism

- The tolerance is not pharmacokinetic but due to the true cellular adaptive response
- Two proposed mechanisms
  - upregulation of cAMP system
  - Downregulation of μ receptors
- Recent research suggests tolerance results due to uncoupling between μ receptor and G proteins
- Leading to reversal of second messenger (cAMP) and ion channel system

Tolerance - Mechanism

- Recently the NMDA antagonists and nitric oxide synthase inhibitors have been found to block morphine tolerance and dependence in animals.
- Thus, analgesic action of morphine can be dissociated from tolerance and dependence which contribute to its abuse by
  - NMDA receptor antagonists
  - Agents that recouple μ receptor and G proteins

Dependence

Dependence comprises two components

- Physical dependence - associated with the withdrawal syndrome, lasting for a few days
- Psychological dependence - associated with craving, lasting for months or years.

Withdrawal symptoms

- Withdrawal of the drug causes significant distress to cause a drug seeking behavior manifested by
  - sweating ,lacrimation, dehydration,fear
  - anxiety , restlessness , mydriasis , tremor , colic
  - hypertension , tachycardia and weight loss .
- Weak long acting receptor agonist methadone used to relieve withdrawal syndrome.

Psychological dependence

- Opioids facilitate DA transmission in mesolimbic /mesocortical pathways and activate endogenous reward pathways in brain.
- Important in intiating and mantaining drug seeking behaviour
- Psychological dependence rarely occurs in patients being given opioids as analgesics

Acute morphine poisoning

- 50 mg morphine i.m. produces serious toxicity.
- lethal dose : 250 mg.
- Manifestations are extension of pharm. action.
- Stupor, flaccidity, shallow breathing, cyanosis, miosis, ↓BP & shock. Convulsions, pulmonary edema,coma occur at terminal stages
- Death is due to respiratory failure.

Treatment

- Respiratory support
- Maintenance of BP
- Gastric lavage with pot. Permanganate
- Naloxone 0.4-0.8 mg i.v. repeated every 2-3 min till respiration picks up. Repeat every 1- 4 hrs later on, according to response.
- preferred specific antagonist : does not have any agonistic action and resp. depression

Precautions and C/I

- Infants and the elderly
- Patients with respiratory insufficiency
- Bronchial asthma
- Head injury
- Hypotensive states and hypovolemia
- Undiagnosed acute abdominal pain
- Elderly male
- Hypothyroidism, liver and kidney disease
- Unstable personalities

Drug interactions

- Drugs which poteniate morphine
  - Phenothiazines, TCA, MAO inhibitors,
  - Amphetamine and Neostigmine
- Morphine retards absorption of many orally administered drugs by delaying gastric emptying..

Therapeutic uses

- Morphine / parenteral congeners indicated as analgesic in
  - traumatic, visceral, ischaemic (myocardial infarction),
  - postoperative, burns, cancer pain.
- Relieves anxiety and apprehension in serious and frightening disease accompanied by pain: myocardial infarction,

Therapeutic uses

Acute left ventricular failure (cardiac asthma)

- Morphine rapid i.v. affords dramatic relief by
  - ↓ preload and peripheral pooling of blood.
  - shift blood from pulmonary to systemic circuit
  - relieves pulmonary congestion and edema.
  - Allays air hunger by depressing respiratory centre.
  - Cuts down sympathetic stimulation by calming the patient, reduces cardiac work.

Epidural and intrathecal injection of Morphine

- It is being used for
  - analgesia in abdominal, lower limb and pelvic surgeries
  - labour, postoperative, cancer and other intractable pain.
  - Preanaesthetic medication
- produces segmental analgesia for 12 hour without affecting sensory, motor or autonomic modalities.
- Resp. depression occurs after delay due to ascent through subarachnoid space to the resp. centre.

Codiene (Methyl Morphine)

- low-efficacy opioid a prodrug (t1/2 3 h).
- lacks efficacy for severe pain
- most of its actions 1/10th those of morphine.
- Large doses cause excitement.
- Dependence much less than with morphine.
- principal use: mild to moderate pain & cough
- 60 mg coeine = 600 mg aspirin

Pethidine

- Pethidine differs from morphine in that it:
- does not usefully suppress cough
- less likely to constipate
- less likely to cause urinary retention & prolong childbirth
- little hypnotic effect
- shorter duration of analgesia (2-3 h).
- Dose: 50-100mg SC or IM

Methadone

- principal feature of methadone is long duration, analgesia may last for 24 h.
- If used for chronic pain in palliative care (12-hourly) an opioid of short t ½ *should be provided for* breakthrough pain rather than an extra dose of methadone.
- Also used in opioid withdrawal
- Dose: 2.5 mg to 10 mg oral or IM

Patient controlled analgesia (PCA)

- An attractive technique of postoperative pain control
- patient himself regulates the rate of i.v. fentanyl infusion according to intensity of pain felt.
- Transdermal fentanyl is a suitable option for chronic cancer and other terminal illness pain

Dextropropoxyphene

- Less analgesic, antitussive, and less dependence
- Its analgesic usefulness equal to codeine.
- Commonly combined with paracetamol
- Dextropropoxyphene interacts with warfarin, enhancing its anticoagulant effect.
- Dose= 60-120 mg

Tramadol

- Relieves pain by opioid as well as other mechanisms
- 100 mg IV Tramadol = 100 mg IM morphine
- Dose: 50-100 mg TDS
- Less respiratory depression, sedation, constipation, urinary retention, ↑intrabiliary pressure & dependence than morphine
- As effective as pethidine for postoperative pain and as morphine for moderate chronic pain.

Pentazocine

- Weak μ antagonist action and marked κ agonist action
- Analgesia is primarily spinal (K1)
- can cause a withdrawal syndrome in addicts
- Dose= 30-60 mg IM OR 50 -100 mg oral
- shorter duration of pain relief 4-6 hrs,
- less dependence, sedation & resp. depression
- Use: post operative, moderately severe burns

Butorphanol

- K analgesic like pentazocine but more potent
- Psychomimetic effects less marked
- Neither substitute nor antagonize morphine
- Dose: 1-4 mg IM / IV
- Use:
  - Post operative
  - Short lasting painful conditions (renal colic)

A- *Nonselective COX inhibitors (conventional NSAIDs)*

- ***Salicylates:*** Aspirin, Diflunisal.
- *Pyrazolone derivatives:* Phenylbutazone, Oxyphenbutazone.
- ***Indole*** *derivatives:* Indomethacin, Sulindac.
- *Propionic acid derivatives:* Ibuprofen, Naproxen, ketoprofen, Flurbiprofen.
- *Anthranilic acid derivative:* Mephenamic acid.
- *Aryl-acetic acid derivatives:* Diclofenac.
- *Oxicam derivatives:* Piroxicarn, Tenoxicam.
- ***Pyrrole-pyrrole*** *derivative:* Ketorolac.

B- *Preferential COX-2 inhibitors*

Nimesulide, Meloxicam, Nabumetone

C- *Selective COX-2 inhibitors*

Celecoxib, Rofecoxib, Valdecoxib

D- *Analgesic- antipyretics with poor antiinflammatory action*

Paraaminophenol derivative: **Paracetamol** (Acetaminophen).

Pyrazolone derivatives: Metamizol (Dipyrone), Propiphenazone.

Benzoxazocine derivative: Nefopam.

Benefits due to PG Synthesis inhibition

- Analgesia: prevention of pain nerve ending sensitization
- Antipyretic
- Anti-inflammatory
- Antithrombotic
- Closure of ductus arteriosus

Toxicities due to PG synthesis inhibition

- Gastric mucosal damage
- Bleeding: inhibition of platelet function
- Limitation of renal blood flow : Na and water retention
- Delay/prolongation of labour
- Asthma and anaphylactoid reactions in susceptible individuals

Adverse effects of NSAIDs

Gastrointestinal-

•Gastric irritation, erosions, peptic ulceration, gastric bleeding/perforation, esophagttis

Renal

- Na and water retention, chronic renal failure, interstitial nephritis, papillary necrosis (rare)

Hepatic

- Raised transaminases, hepatic failure (rare)

CNS

- Head ache, mental confusion. Behavioural disturbances, Seizure precipitation.

Haematological

- Bleeding, thrombocytopenia, haemolytic anaemia, agranulocytosis

Others

- Asthma exacerbation, nasal polyposis skin rashes, pruritis, angioedema.

USES

- Analgesic- headache, backache, myalgia, joint pain, dysmenorrhoea;
- *Antipyretic*-fever of any origin; paracetamol being safer.
- *Acute rheumatic fever-* the first drug to be used

- *Rheumatoid arthritis -* Aspirin in a dose of 3-5 g/day is effective in most cases; produces relief of pain, swelling and morning stiffness.

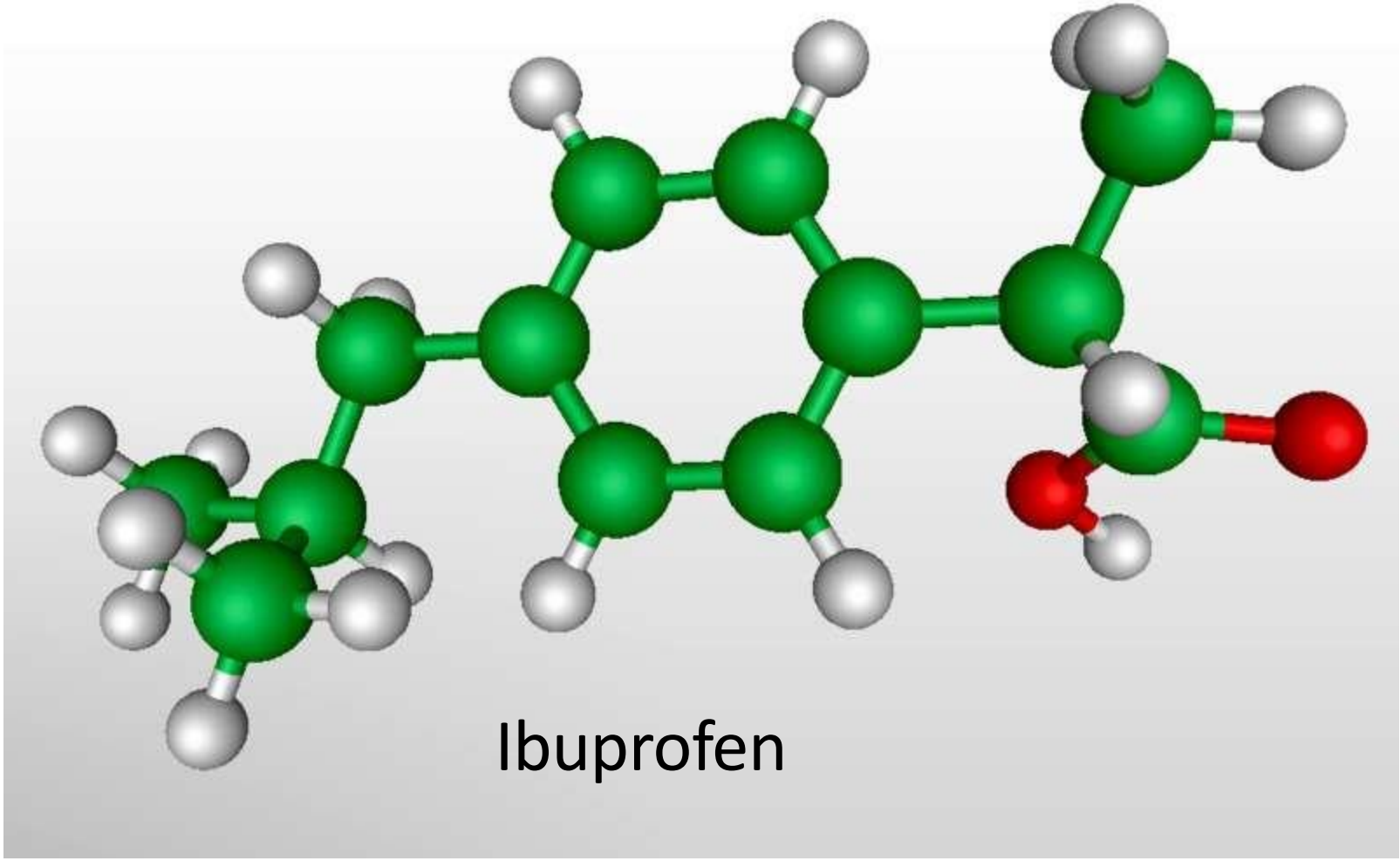
- *Osteoarthritis* - It affords symptomatic relief only; paracetamol is the first choice analgesic

- *Post myocardial infarction and post stroke patients* By inhibiting platelet aggregation it lowers the incidence of reinfarction.

Other uses are:

- Pregnancy induced hypertension and pre eclampsia.
- To delay labour
- Patent ductus arteriosus

PROPIONIC ACID DERIVATIVES



Ibuprofen

- Better tolerated than aspirin.
- The analgesic, antipyretic and antiinflammatory efficacy is lower than high dose of aspirin.
- All inhibit PG synthesis- naproxen being most potent;
- They inhibit platelet aggregation and prolong bleeding time.

Indomethacin

Potent antiinflammatory drug comparable to phenylbutazone.

Potent and promptly acting anti•pyretic.

Analgesic action is better than phenylbutazone, but it relieves only inflammatory or tissue injury related pain.

highly potent inhibitor of PG synthesis and suppresses neutrophil motility.

Uses

- Rheumatoid arthritis not controlled by aspirin;
- Ankylosing spondylitis, acute exacerbations of destructive arthropathies and psoriatic arthritis.
- It acts rapidly in acute gout.
- Malignancy associated fever refractory to other antipyretics.
- Medical closure of patent ductus arteriosus

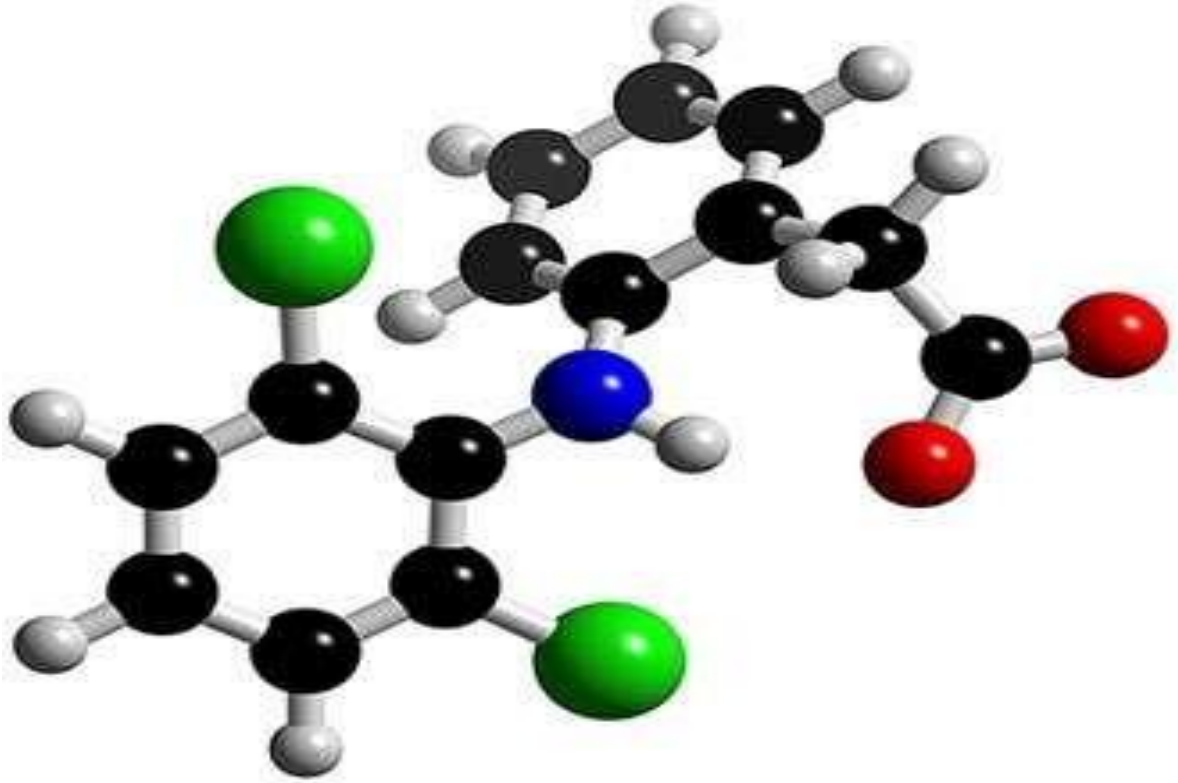
MEPHENAMIC ACID

- Analgesic, Antipyretic and Anti-inflammatory drug which inhibits COX & antagonizes actions of PGs.
- Exerts peripheral & central analgesic action.

Uses

- analgesic in muscle, joint and soft tissue pain - strong anti-inflammatory action is not needed.
- It is quite effective in dysmcnorrhoea.
- useful in some cases of rheumatoid and osteoarthritis

ARYL-ACETIC ACID DERIVATIVE



DICLOFENAC SODIUM

DICLOFENAC SODIUM

- **An analgesic-antipyretic-**antiinflammatory drug similar in efficacy to naproxen.
- short lasting antiplatelet action.
- Neutrophil chemotaxis and superoxide production at the inflammatory site are reduced.

USE

- most extensively used in rheumatoid and osteoarthritis, bursitis, ankylosing spondylitis, dysmenorrhoea, post-traumatic and postoperative inflammatory conditions—affords quick relief of pain and wound edema.