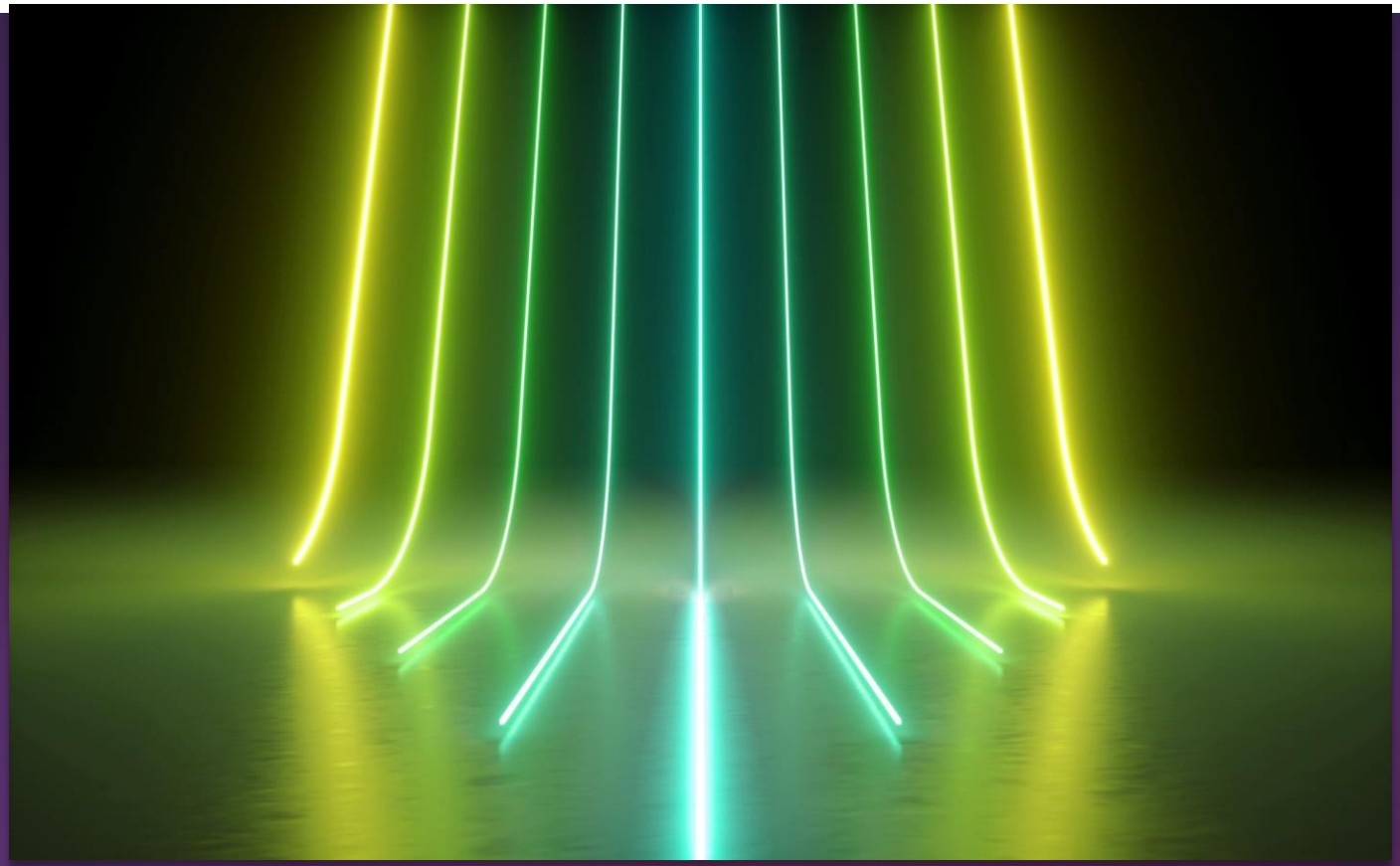


Drugs Used in the Management of Pain

DR T. N CHIDUMAYO

LEARNING OBJECTIVES

Describe the pain neural pathways

Describe the mechanisms of actions of drugs used in the management of pain

Definition

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.

(International association for the study of pain 1979)

Pain is a perception and not just a sensation, so may or may not correlate with a definable injury.

Introduction

- Drugs that have analgesic actions act by modulating the pain neural pathways in various ways that include:
  - Inhibition of activity at nociceptors
    - Inhibition of synthesis of mediators of nociception and pain transmission
  - Inhibition of transmission of pain signals
  - Potentiation of mediators that inhibit transmission of pain signals

Classification of Pain

Acute Pain: occurs over a brief period and usually associated with a temporary disorder

Chronic Pain: continuous and recurrent and sustained by different mechanisms.

Pain syndromes may also be classified into:

- **Nociceptive** pain: may be "referred" – e.g. injury to the hip referred to the knee
- **Neuropathic** pain
- **Psychogenic** pain
- **Idiopathic** pain

Methods of Management

Pharmacological

1. NSAIDs
2. Opioids
3. Adjunctive agents
4. Local anesthetics
5. General anesthetics

Non-pharmacological

1. Counseling
2. Acupuncture
3. TENS
4. Massage

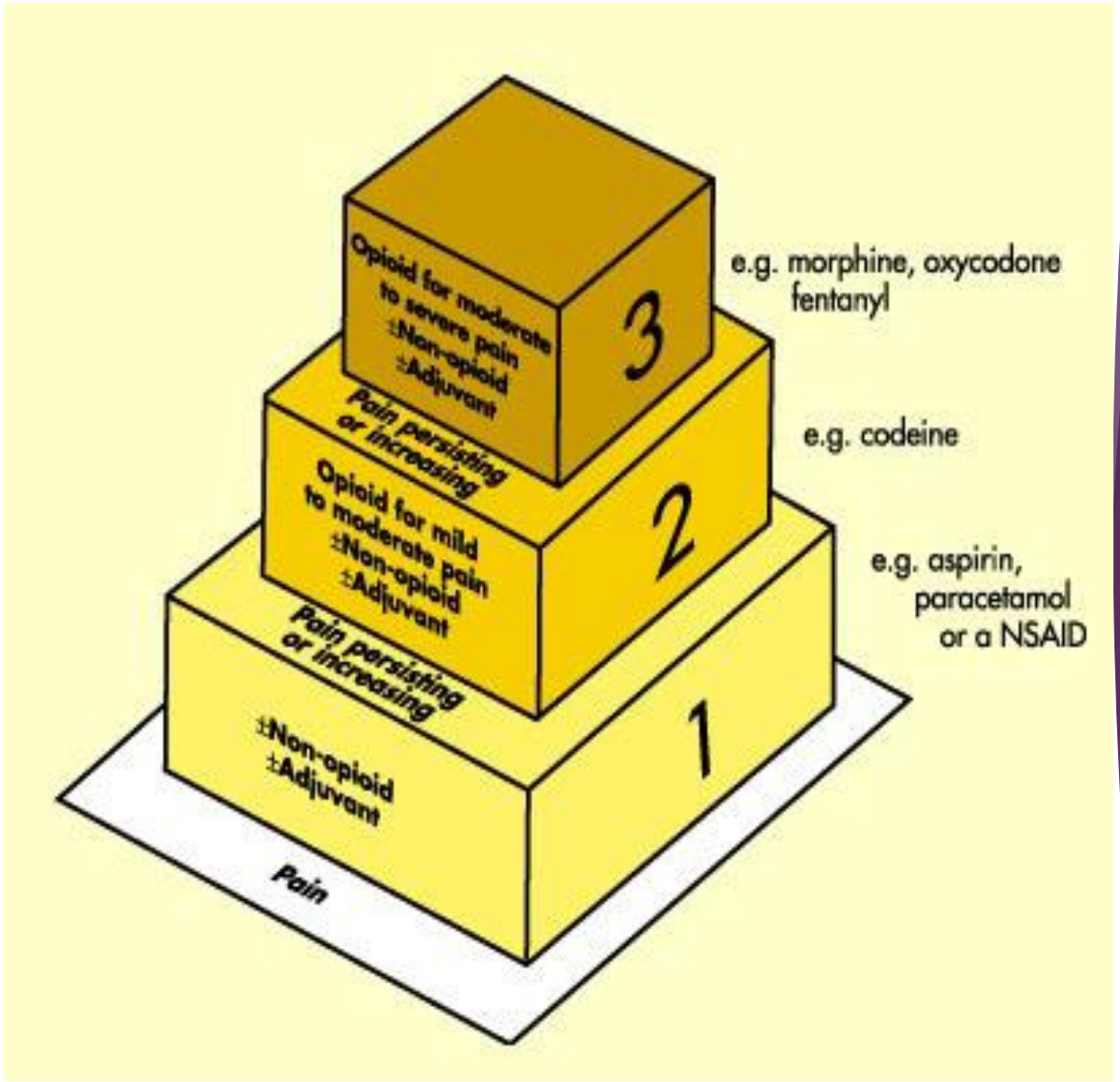
Analgesic Ladder

Stepwise management of pain

Step 1. Start with non-opioid (e.g. NSAID or paracetamol)

Step 2. Use an opioid for mild or moderate pain if pain persists e.g. codeine

Step 3. Use opioid for moderate to severe pain if pain persists e.g. morphine, fentanyl



WHO Analgesic Ladder

Pain stimulus is transmitted from pain receptors, through peripheral nerves to the spinal cord to the brain. Through two different types of nerves fibres:

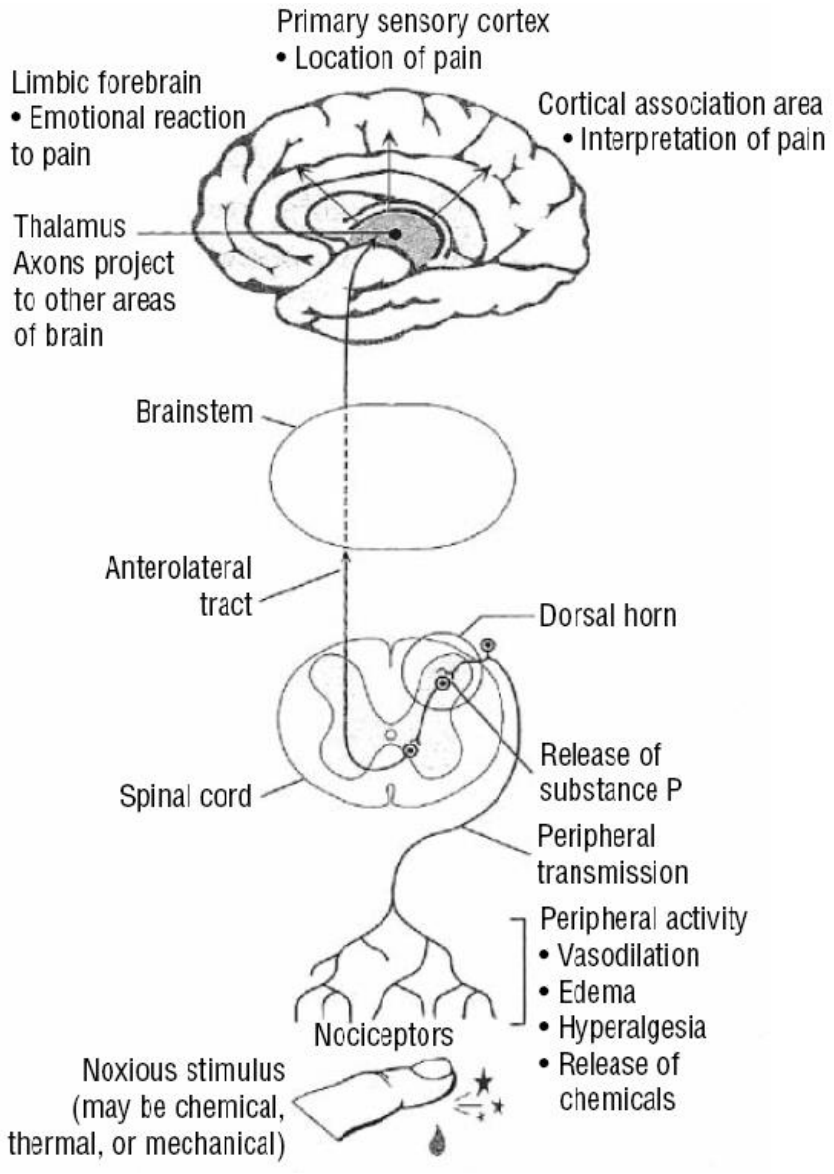
A-delta "fast pain" and

C-fibers "slow pain" nerve fibers.

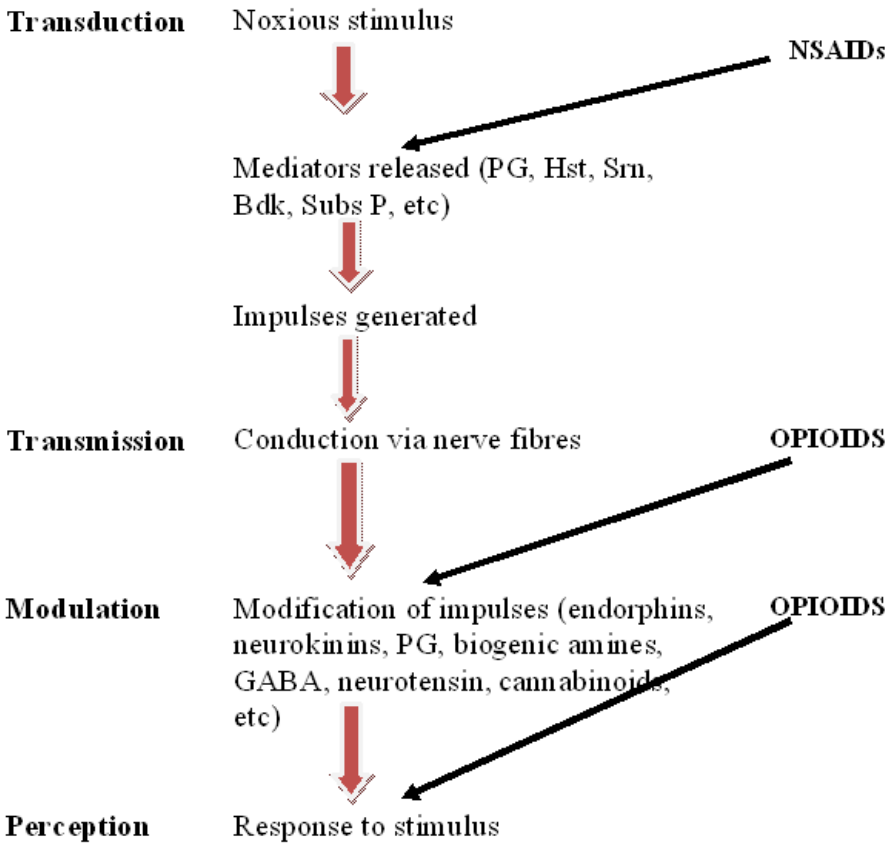
Physiological and psychological interactions suggests spinal gates in the dorsal horn at each segment of the spinal cord

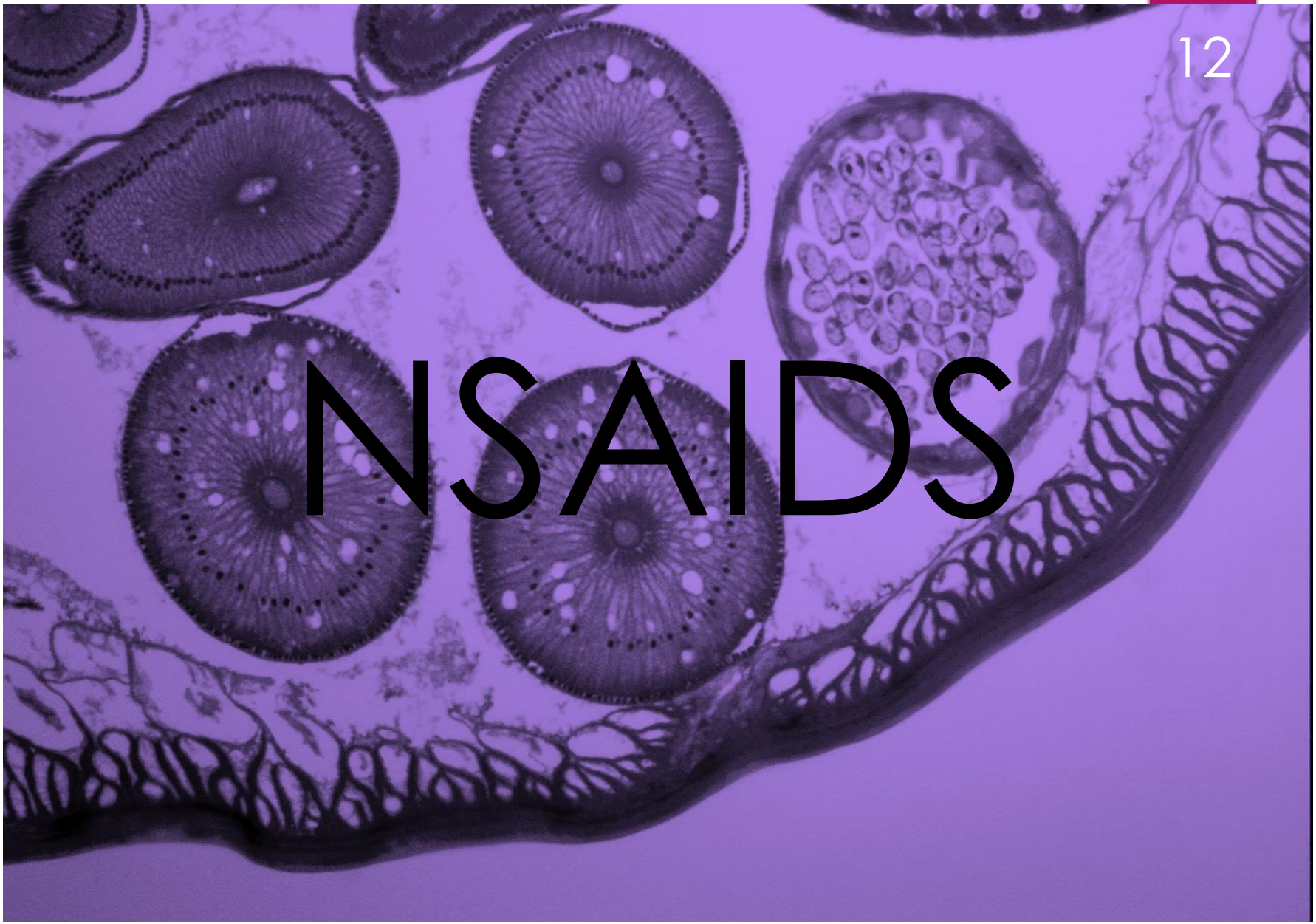
Competition at each gate for heat, touch or pain to be transmitted at each point

Gate Control Theory
Melzack and Wall 1965.

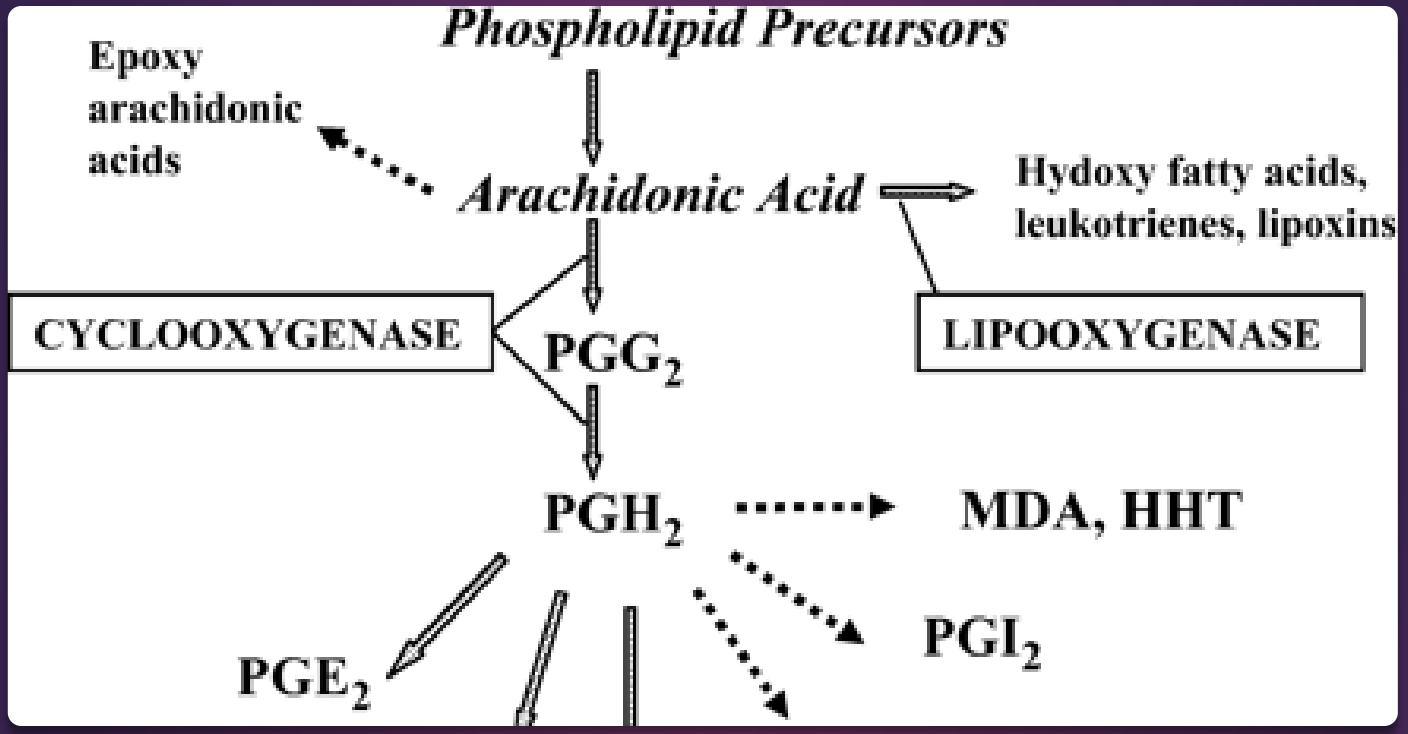

Primary sensory cortex
• Location of pain
Limbic forebrain
• Emotional reaction to pain
Cortical association area
• Interpretation of pain
Thalamus
Axons project to other areas of brain
Brainstem
Anterolateral tract
Dorsal horn
Release of substance P
Spinal cord
Peripheral transmission
Peripheral activity
• Vasodilation
• Edema
• Hyperalgesia
• Release of chemicals
Nociceptors
Noxious stimulus (may be chemical, thermal, or mechanical)

How does nociceptive pain occur?





NSAIDS



Biosynthesis of Eicosanoids

Classification of NSAIDs

Nonselective Cox Inhibitors:

- Aspirin
- Ibuprofen
- Piroxicam
- Meclofenamate
- Diclofenac
- Indomethacin

Selective Cox Inhibitors:

- Celecoxib
- Rofecoxib
- Meloxicam

Common Pharmacological Effects

- Analgesic (CNS and peripheral effect)
- Antipyretic (CNS effect)
- Anti-inflammatory (except acetaminophen)
- Some are Antiplatelete: inhibit activation, adhesion and aggregation of platelets & release of lysosomal enzymes
- Some are Uricosuric

OPIOIDS

Opioids: Nomenclature

- Opium: is the dried powdered mixture of alkaloids obtained from poppy
- Opiate: Any agent derived from opium
- Opioid: All substances (exogenous or endogenous) with morphine -like properties

Opioids: Classification

Alkaloid: derived from poppy plant

- Morphine
- Codeine

Semisynthetic: modification of morphine functional groups:

- Diacetylmorphine (heroin)
- Hydrocodone
- Hydromorphone
- Oxycodone
- Oxymorphone

Synthetic: *progressive reduction in the number of* fused rings in phenanthrene moiety:

- Meperidine
- Fentanyl
- Sufentanil
- Alfentanil

Receptor	Prototypic drug	Proposed actions
μ_1	Most endogenous , naturally-occurring or synthetic opioids	Supraspinal analgesia
μ_2	Morphine	Respiratory depression Cardiovascular effects
δ	Enkephalins	Spinal analgesia
κ	Ketocyclazocine and dynorphin	Spinal analgesia Sedation, miosis
σ	N - allylnormetazocine	Psycotomimetic effects

Opioid Receptor Classification

Opioid Intrinsic Activity

- Opioid drugs can be full agonists, partial agonists, mix agonist-antagonist, or antagonists.
  - Agonists produce a maximum biologic effect.
  - Antagonists have no intrinsic activity and prevent the access of agonists to the receptors .
  - Partial agonists have a submaximal response

Mixed Agonist-Antagonists

- Partial agonism: interaction at a single receptor type e.g. buprenorphine.

- Mixed Agonist-antagonists: have divergent activities at different receptors, acting simultaneously as an agonist at one receptor and an antagonist at another; e.g. pentazocine, butorphanol, nalbuphine.

Mixed Agonist-Antagonists

Opioid		Receptor Type			
		μ	κ	σ	δ
Buprenorphine		partial			
Butorphanol		antagonist	agonist	agonist	-
Nalbuphine		antagonist	partial	agonist	-
Pentazocine		antagonist	agonist	agonist	-

Mode of Analgesic Action of Opioid Agonists

Drugs that have agonist activity on opioid receptors produce analgesia

Opioid agonists analgesic effects:

- Activate the descending pathways from the midbrain and brain stem and exert a strong inhibitory effect on dorsal horn transmission
- Inhibit excitation of sensory nerve terminals in the periphery (increase pain threshold)

Primary Effect of Opioid Receptor Activation

- Release of pain-signaling neurotransmitters is regulated by endogenous opioid peptides or by exogenous opioid agonists.
  - Through **presynaptic inhibition of substance P release, thereby producing analgesia**
    - Involves changes in transmembrane ion conductance
      - Increase potassium conductance (hyperpolarization)
      - Inactivation of calcium channels

Pharmacological Effects

Sedation and anxiolysis

- Drowsiness and lethargy
- Apathy
- Cognitive impairment
- Sense of tranquility

Depression of respiration

- Main cause of death from opioid overdose.
- Combination of opioids and alcohol is especially dangerous.

Cough suppression

- Opioids suppress the "cough center" in the brain.

Pupillary constriction

- pupillary constriction in the presence of analgesics is characteristic of opioid use.

Pharmacological effects cont'd.

- **Nausea and vomiting**
  - Stimulation of receptors in an area of the medulla called the chemoreceptor trigger zone causes nausea and vomiting
  - Unpleasant side effect, but not life threatening
- **Gastrointestinal symptoms**
  - Opioids relieve diarrhea as a result of their direct actions on the intestines
  - Billiary tract spasm, especially of the sphincter of Oddi
    - Reversible by naloxone, nitroglycerin
- **Other effects**
  - Opioids can release histamines causing itching or more severe allergic reactions including bronchoconstriction
  - Opioids can affect white blood cell function and immune function

Morphine

Morphine: Prototype of the group

Routes: PO, IM, IV, SQ, nebulized & rectal

Morphine: conjugated in the liver

Has several active metabolites

Diamorphine (Heroin)

- Derived from morphine
- Higher potency than morphine
- More lipid soluble than morphine, so enters the CNS more readily
- Causes more euphoria than morphine and has higher abuse potential

Pethidine (meperidine)

Less potent than morphine

Less respiratory depression compared to morphine and has no effect on the cough reflex

Causes tremors, muscle twitches and rarely convulsions (due to a toxic metabolite – norpethidine)

Unlike other opioids, large doses cause pupil dilatation, tachycardia (has anti-muscarinic effects) and hyper-active reflexes (due to norpethidine)

Pethidine cont'd

Pethidine is preferred to morphine in the relief of labour pain because it has a shorter duration of action and causes less respiratory depression in the newborn (the newborn does not have glucuronidation enzyme for morphine and therefore cannot metabolise morphine)

Pethidine is also the preferred opioid analgesic in biliary and ureteric colic since it causes less smooth muscle spasm

Other Opioids

Methadone

- Equal analgesic potency with morphine
- Has a longer duration of action, is more orally active, induces less euphoria and has less sedative effects compared to morphine
- Used in the management of opioid dependence

Fentanyl, alfentanil and sufentanil

- More lipid soluble and more potent than morphine
- Used in general anaesthesia

Codeine

- Much less potent analgesic than morphine and produces less euphoria
- Good anti-tussive activity at doses that do not cause analgesia
- Has lower abuse potential than morphine
- Used for mild to moderate pain and for cough suppression

Other weak opioids

Propoxyphene and dextropropoxyphene

- Weaker analgesics than codeine
- Used in the treatment of mild to moderate pain
- Often used in combination with aspirin and paracetamol

Buprenorphine

- High efficacy opioid analgesic
- A partial agonist on mu receptors, and antagonist on delta and kappa receptors
- Can antagonize morphine

Pentazocine

- Is a mixed opioid receptor agonist-antagonist (agonist on kappa receptors and antagonist on mu receptors)
- Causes dysphoria rather than euphoria
- Promotes analgesia by activating opioid receptors in the spinal cord
- High doses increase blood pressure and can cause hallucinations, nightmares, tachycardia and dizziness

Tramadol

Moderate to moderately severe pain

- Binds to μ-opioid receptors.
- Inhibits reuptake of serotonin and norepinephrine in the CNS.

Crosses the placenta; enters breast milk.

Metabolised by CYP2D6 enzyme system which exhibits genetic polymorphism;

- ~7% of population may be poor metabolizers and small proportion are ultra–rapid metabolizers of CYP2D6 and have significantly ↑ concentrations of M1 metabolite. 30% eliminated unchanged in the urine.

Half-life: Tramadol– 6–8 hr, ER– 7.9 hr; active

metabolite– 7–9 hr;

- both are ↑ in renal or hepatic impairment.

Naltrexone

Antagonist

- Onset (oral tablet 15-30 min.)

Duration of action 24-72 hours

- Peak effect (6-12 hours)

EFFECTS

- Reverses the psychotomimetic effects of opiate agonists.
- Reverses hypotension and cardiovascular instability
  - potent vasodilators
- Inhibits Mu, Delta, and Kappa receptors.

Opioids: Clinical Uses

- Mild to moderate pain: codeine, dihydrocodeine, propoxyphene, dextropropoxyphene and buprenorphine
- Severe pain: morphine, diamorphine, pethidine and other high efficacy opioid analgesics
- Post-operative pain: morphine, pethidine
- General anaesthesia: fentanyl, alfentanil and sufentanil
- Acute myocardial infarction: morphine and diamorphine
- Pain of advanced malignant disease: fentanyl, morphine
- Treatment of opioid dependence: methadone

Combination Analgesics

- Hydrocodone with acetaminophen
- Vicoprofen (ibuprofen 200/7.5 mg hydrocodone)
- Note:

  " All opioids can be made equipotent or equianalgesic by adjusting for physicochemical and pharmacokinetic differences among individual opioids **by correcting for dose and route of administration.**"

Treatment of Breakthrough Pain

Intermittent flares of pain that can occur despite fixed schedule analgesic medication for pain control.

Ideal medication for this should

- Be easy to administer
- Have rapid onset of action
- Be eliminated within a short time
- **Oral transmucosal fentanyl citrate (ACTIQ) recommended by FDA**
- **Oxycodon and hydromorphone** may also be used

Opioid Withdrawal

- **Symptoms of opioid withdrawal:**
  - Diaphoresis (ex sweating)
  - Lacrimation
  - Coryza
  - Tachycardia
  - Hypertension
  - Abdominal cramps
  - Nausea
  - Vomiting


NEUROPATHIC
PAIN

NEUROPATHIC PAIN

Usually associated with damage to nerves centrally or peripherally

Several classes of pharmacological agents are available for its treatment

Many guidelines, but significant consistency

Consideration for Mx of Neuropathic Pain

- Comorbidities
- Medication efficacy
- Side effect profile of the drugs
- Drug interactions
- Abuse potential
- Economic burden

Tricyclic Antidepressants

E.g. nortriptyline, desipramine, amitriptyline, imipramine.

MOA: Blockade of 5HT, NA reuptake; block cholinergic, adrenergic, histaminergic transmissions; Block Na+ channels.

Useful for distal peripheral neuropathy, painful polyneuropathy, postherpetic neuralgia, postmastectomy pain.

Serotonin-norepinephrine Reuptake Inhibitors (SNRIS)

- E.g., Duloxetine, venlafaxine
- Useful for diabetic neuropathic pain
- Recommended 1st line treatment for neuropathic pain by the International Association for the Stu dy of Pain (I ASP)

GABA Analogs – gabapentin and pregabalin

Do not bind to GABA receptors; rather bind to a-2-delta subunit of voltage gated Ca2+ channels:

Reduced Ca2+ flux

Reduced release of glutamate, NA, and substance P

Useful for postherpetic neuralgia.