PAIN PHYSIOLOGY AND PHARMACOLOGY

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ESA On-Line Assessment (OLA) Subcommittee Chairperson
LECTURE OUTLINE

Pain

• Definition
• Theories
• Anatomy and Physiology
• Classification
• Assessment
• Pharmacologic Treatment
SOURCES OF INFORMATION
General textbooks on pain

Excellent textbooks, however, for preparation of EDAIC examinations read such textbooks only if you have plenty of time to prepare.

etc.
• Fundamental Textbooks of Anaesthesiology
• Textbooks of Physiology and Pharmacology for Anaesthetists
What is pain?

Definitions

An unpleasant sensory and emotional experience associated with actual or potential tissue damage.
What is pain?

Definitions

Pain is the psychical adjunct to an imperative protective reflex.


- Sherrington CS The Integrative Action of the Nervous System. New Haven, Yale University Press, 1906

Sir Charles Scott Sherrington
1857-1952
Why pain is necessary?

Protective function

• Alerts about a problem in the body
• Protects the body from further injury
  • Activation of flexor motor neurons generates the withdrawal reflex to protect the body
• Aids healing
  • Forces the body to stay in rest
Congenital insensitivity to pain

• Some people are born without a sense of pain.

• Some people may feel pain but lack the affective response accompanying pain.

• This may lead to multiple traumas and injuries and even to early death.
Kneeling figure of Descartes (1664 from Traite de l’homme).
© Corbis/Bettmann. A nerve filament in the foot is irritated by the fire and the burning sensation ascends to the brain via that nerve filament.
PAIN THEORIES

- Direct ascent to the brain (Descartes, 17th century)
- Neural specificity theory (Von Frey, 1894)
- Pattern theory (Goldschneider, 1896)
- Gate control theory (R. Melzak, P. Wall, 1965)
- Neuromatrix theory (R. Melzak, 1991)
Knowledge of anatomical pathways and physiological and biochemical mechanisms of pain remains incomplete and will continue to expand over many years.
PAIN ANATOMY AND PATHOPHYSIOLOGY
# Classification of Nerve Fibres

## Motor nerve fibres

<table>
<thead>
<tr>
<th>Type</th>
<th>Erlanger-Gasser Classification</th>
<th>Diameter</th>
<th>Myelin</th>
<th>Conduction velocity</th>
<th>Associated muscle fibers</th>
</tr>
</thead>
<tbody>
<tr>
<td>α</td>
<td>Aα</td>
<td>13-20 μm</td>
<td>Yes</td>
<td>80–120 m/s</td>
<td>Extrafusal muscle fibers</td>
</tr>
<tr>
<td>γ</td>
<td>Aγ</td>
<td>5-8 μm</td>
<td>Yes</td>
<td>4–24 m/s [2][3]</td>
<td>Intrafusal muscle fibers</td>
</tr>
</tbody>
</table>

## Sensor nerve fibres

<table>
<thead>
<tr>
<th>Type</th>
<th>Erlanger-Gasser Classification</th>
<th>Diameter</th>
<th>Myelin</th>
<th>Conduction velocity</th>
<th>Associated sensory receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>Aα</td>
<td>13–20 μm</td>
<td>Yes</td>
<td>80–120 m/s[4]</td>
<td>Responsible for proprioception</td>
</tr>
<tr>
<td>Ib</td>
<td>Aα</td>
<td>13–20 μm</td>
<td>Yes</td>
<td>80–120 m/s</td>
<td>Golgi tendon organ</td>
</tr>
<tr>
<td>II</td>
<td>Aβ</td>
<td>6–12 μm</td>
<td>Yes</td>
<td>33–75 m/s</td>
<td>Secondary receptors of muscle spindle All cutaneous mechanoreceptors</td>
</tr>
<tr>
<td>III</td>
<td>Aδ</td>
<td>1–5 μm</td>
<td>Thin</td>
<td>3–30 m/s</td>
<td>Free nerve endings of touch and pressure Nociceptors of neospinothalamic tract Cold thermoreceptors</td>
</tr>
<tr>
<td>IV</td>
<td>C</td>
<td>0.2–1.5 μm</td>
<td>No</td>
<td>0.5–2.0 m/s</td>
<td>Nociceptors of paleospinothalamic tract Warmth receptors</td>
</tr>
</tbody>
</table>

## Preganglionic and postganglionic fibers

<table>
<thead>
<tr>
<th>Type</th>
<th>Erlanger-Gasser Classification</th>
<th>Diameter</th>
<th>Myelin</th>
<th>Conduction velocity</th>
</tr>
</thead>
<tbody>
<tr>
<td>preganglionic fibers</td>
<td>B</td>
<td>1–5 μm</td>
<td>Yes</td>
<td>3–15 m/s</td>
</tr>
<tr>
<td>postganglionic fibers</td>
<td>C</td>
<td>0.2–1.5 μm</td>
<td>No</td>
<td>0.5–2.0 m/s</td>
</tr>
</tbody>
</table>
Nociceptors

- peripheral receptors sensitive to painful mechanical and chemical stimuli, extreme heat or cold
- free nerve endings with small receptive fields
- specific for pain
- do not adapt to repeated stimulation as do low-threshold mechano/thermoreceptors
- are capable of differentiating between innocuous and noxious stimuli
- can be sensitized by tissue injury
Nociceptors
NOCICEPTION

• activation of nociceptors by noxious stimuli
• perception of a potentially tissue-damaging stimulus by the receptors attached to the Aδ and C fibres
• subsequent transmission of encoded information to brain
Types of nociception

First or Epicritic Pain

• perception of a sharp, pricking pain at the moment of injury
• localized to a well-defined part of body surface
• high threshold mechano-heat receptors respond to thermal and noxious mechanical stimuli
• thinly myelinated primary afferent Aδ axons.

Second or Prothopathic Pain

• a dull aching pain lasts long after the termination of the stimulus
• often not clearly localized
• polymodal nociceptors respond to 3 major modalities of tissue damaging stimuli (chemical, thermal and mechanical)
• receptors of the unmyelinated primary afferent axons (C fibres)
Tissue injury

stimulates the release of inflammatory mediators from

• tissues
• immune cells
• sympathetic and sensory afferent nerve fibres
• blood vessels
## Algogenic substances

<table>
<thead>
<tr>
<th>Substance</th>
<th>Main effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Kinins:</strong></td>
<td></td>
</tr>
<tr>
<td>• bradykinin (in blood)</td>
<td>nociceptor activation</td>
</tr>
<tr>
<td>• kallidin (in tissues)</td>
<td></td>
</tr>
<tr>
<td>Serotonin</td>
<td></td>
</tr>
<tr>
<td>Histamine</td>
<td>vasodilation, oedema, itching, nociceptor sensitization</td>
</tr>
<tr>
<td>Prostaglandins</td>
<td>nociceptor sensitization</td>
</tr>
<tr>
<td>Leukotrienes</td>
<td></td>
</tr>
<tr>
<td>$H^+$</td>
<td>hyperalgesia</td>
</tr>
<tr>
<td>Cytokines</td>
<td>nociceptor sensitization and stimulations</td>
</tr>
<tr>
<td>Adenosine</td>
<td>hyperalgesia</td>
</tr>
</tbody>
</table>
Algogenic substances
Neurotransmitters of Nociception

- Neuropeptides
- Tachykinins
- Substance P
- Calcitonin gene-related peptide
- Aspartate
- Glutamate
- Somatostatin
- Neurotrophins
  - Nerve growth factor (NGF)
  - Brain-derived neurotrophic factor (BDNF)
  - Neurotrophin-3
  - Neurotrophin-4
  - Neurotrophin-5
Receptors

- Neurotrophin receptors
  - tyrosine kinase (trKA) receptor
  - transient receptor potential (vanilloid) receptors
    - TRPV I receptors
    - TRPV3 receptors
- Tachykinin receptors
- Purinergic receptors
- Adenosine triphosphate receptors
- Opioid receptors
- Cannabinoid receptors
PAIN PATHWAYS

1. first order neurone (cell body in the dorsal root ganglion) transmits pain from a peripheral receptor to

2. second order neurone in the dorsal horn of the spinal cord. This axon crosses the midline to ascend in the spinothalamic tract to the thalamus where

3. third order neurone projects to the postcentral gyrus (via the internal capsule)
PAIN PROCESSING

- Transduction
- Transmission
- Modulation
- Perception

Neuroplastic changes

Sensitisation
PAIN PROCESSING

**Perception**
- Parenteral opioids
- $\alpha_2$ agonists
- General anesthetics

**Transmission**
- Local anesthetics—peripheral nerve, plexus, epidural block

**Modulation**
- Spinal opioids
- $\alpha_2$ agonists
- NMDA receptor antagonists
- Anticholinesterases, NSAIDs, CCK antagonists, no inhibitors, potassium channel openers

**Transduction**
- NSAIDs
- Antihistamines
- Membrane stabilizing agents
- Local anesthetic cream
- Opioids
- Bradykinin and serotonin antagonists

**Descending inhibitory fibers**

**Dorsal horn**

**Spinothalamic tract**
ANTI-NOCICEPTIVE SYSTEM

• GABA
• glycine
• endorphins
• encephalins
• dynorphins

• Opioid system
  • The highest concentration of opioid receptors in the spinal cord is around the C-fibre terminal zones in laminae I and II:
    • 70 % μ receptors
    • 24 % δ receptors
    • 6 % κ receptors
Descending control

Serotonergic pathway

Periaqueductal grey matter

Rostroventral medulla

Dorsolateral funiculus

Dorsal horn (same side)

Noradrenergic pathway

Periaqueductal grey matter

Locus coeruleus (pons)

Dorsal horn
PAIN CLASSIFICATION

There is no single system for classifying pain patients that is universally accepted by clinicians or researchers.
PAIN CLASSIFICATION

according to

• etiology
• mechanism
• duration
• location
• character
• intensity
PAIN CLASSIFICATION

- Acute
  - Nociceptive
    - Somatic
  - Neuropathic
  - Visceral
- Chronic
  - Psychogenic
  - Idiopathic
PAIN CLASSIFICATION

Acute vs chronic

Acute pain
• Pain of recent onset and probable limited duration.
• It usually has an identifiable temporal and causal relationship to injury or disease.

Chronic pain
• Pain lasting for long periods of time and persisting beyond the time of healing of an injury
• Often there is no clearly identifiable cause.
PAIN CLASSIFICATION

Acute vs chronic
PAIN CLASSIFICATION

Nociceptive vs neuropathic

Nociceptive pain

• pain signaling pathways are intact and its biological value is clear
• when acute
  • physiologic pain
  • serves a protective function
• when chronic
  • pathologic

Neuropathic pain

• disease of the pain signaling system
• There is a central or peripheral malfunction in the pain signaling pathway
• perception of pain in the absence of tissue damage
• serves no useful biological purpose
Neuropathic pain

Hyperalgesia and allodynia

the hallmarks of neuropathic pain

• Hyperalgesia - an increased response to a normally painful stimulus

• Allodynia - a painful response to a normally non-painful stimulus
Neuropathic pain

Hyperalgesia and allodynia

Pain sensitization

Stimulus intensity

Stimulus intensity

Hyperalgesia

Allodynia

Injury

Normal pain response

Pain intensity
VISCERAL PAIN

• much less is known about the mechanism of visceral pain
• differences in the innervation of viscera and skin
• biological role of visceral innervation is to warn of internal threat of disease
• density of visceral nociceptors is less than 1 % vs somatic afferents
• cortical mapping is much less detailed
CHARACTERISTICS OF VISCERAL PAIN

- Not evoked from all viscera – liver, kidney and lung parenchyma are not sensitive to pain even after major destruction
- Not always linked to visceral injury, e.g. stretching of the urinary, gastrointestinal tracts, gall bladder produces pain
- Diffuse and poorly localized. Usually perceived as arising from the midline, either anterior or posterior
- Referred to other locations. Area is usually segmental and superficial, i.e. to muscle, skin or both and innervated by the same spinal nerves as the viscus. The site of referral may also show hyperalgesia
- Accompanied by autonomic reflexes, e.g. nausea, vomiting, lower back muscle tension which may be prolonged
PAIN CLASSIFICATION

Idiopathic pain

• no underlying lesion found despite investigation

• pain disproportionate to the degree of clinically discernible tissue injury
PAIN CLASSIFICATION

Psychogenic pain

- attributable primarily to psychological factors in the absence of any objective physical pathology that could account for pain
- is not an official diagnostic term
- the term is commonly used in a pejorative sense
- usually not a helpful method of describing a patient
- diagnosis: only when all other causes are ruled out
PAIN ASSESSMENT
PAIN ASSESSMENT

Pain assessment ≠ Pain measurement

Pain assessment ≥ Pain measurement
PAIN ASSESSMENT

Pain History

- O – Onset
- P – Provoking / Palliating factors
- Q – Quality / Quantity
- R – Radiation
- S – Severity
- T – Timing
PAIN MEASUREMENT
Pain threshold

• the minimal stimulus required to produce a sensation of pain on 50% of occasions
• mediated by A\(\delta\) fibres
• relatively constant across subjects
• reproducible
• a useful scientific tool
• temperature (44°C) is often the stimulus used to measure it
Pain tolerance

• the greatest level of pain that a subject may tolerate
• mediated by C fibres
• highly variable among subjects and is less reproducible than the pain threshold
• can be measured by the submaximal effort tourniquet test, McGill pain questionnaire or VAS
• clinically more important than the pain threshold
McGill pain questionnaire (MPQ)
Ronald Melzak 1975
Short form of the same questionnaire (SF-MPQ)  
Ronald Melzak 1984, 1987

### Short-Form McGill Pain Questionnaire (SF-MPQ)

**A. PLEASE DESCRIBE YOUR PAIN DURING THE LAST WEEK. (Check off one box per line.)**

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Throbbing</td>
<td>0 □</td>
<td>1 □</td>
<td>2 □</td>
<td>3 □</td>
</tr>
<tr>
<td>2. Shooting</td>
<td>0 □</td>
<td>1 □</td>
<td>2 □</td>
<td>3 □</td>
</tr>
<tr>
<td>3. Stabbing</td>
<td>0 □</td>
<td>1 □</td>
<td>2 □</td>
<td>3 □</td>
</tr>
<tr>
<td>4. Sharp</td>
<td>0 □</td>
<td>1 □</td>
<td>2 □</td>
<td>3 □</td>
</tr>
<tr>
<td>5. Cramping</td>
<td>0 □</td>
<td>1 □</td>
<td>2 □</td>
<td>3 □</td>
</tr>
<tr>
<td>6. Gnawing</td>
<td>0 □</td>
<td>1 □</td>
<td>2 □</td>
<td>3 □</td>
</tr>
<tr>
<td>7. Hot-burning</td>
<td>0 □</td>
<td>1 □</td>
<td>2 □</td>
<td>3 □</td>
</tr>
<tr>
<td>8. Aching</td>
<td>0 □</td>
<td>1 □</td>
<td>2 □</td>
<td>3 □</td>
</tr>
<tr>
<td>9. Heavy (like a weight)</td>
<td>0 □</td>
<td>1 □</td>
<td>2 □</td>
<td>3 □</td>
</tr>
<tr>
<td>10. Tender</td>
<td>0 □</td>
<td>1 □</td>
<td>2 □</td>
<td>3 □</td>
</tr>
<tr>
<td>11. Splitting</td>
<td>0 □</td>
<td>1 □</td>
<td>2 □</td>
<td>3 □</td>
</tr>
<tr>
<td>12. Tiring-Exhausting</td>
<td>0 □</td>
<td>1 □</td>
<td>2 □</td>
<td>3 □</td>
</tr>
<tr>
<td>13. Sickening</td>
<td>0 □</td>
<td>1 □</td>
<td>2 □</td>
<td>3 □</td>
</tr>
<tr>
<td>14. Fear-causing</td>
<td>0 □</td>
<td>1 □</td>
<td>2 □</td>
<td>3 □</td>
</tr>
<tr>
<td>15. Punishing-Cruel</td>
<td>0 □</td>
<td>1 □</td>
<td>2 □</td>
<td>3 □</td>
</tr>
</tbody>
</table>

**B. PLEASE RATE YOUR PAIN DURING THE LAST WEEK.**  
The following line represents pain of increasing intensity from "no pain" to "worst possible pain". Place a vertical mark (|) across the line in the position that best describes your pain during the last week.

![Vertical mark placement](image)

<table>
<thead>
<tr>
<th>No Pain</th>
<th>Worst Possible Pain</th>
<th>Score in mm (Investigator's use only)</th>
</tr>
</thead>
</table>

**C. CURRENT PAIN INTENSITY**

- □ No pain
- □ Mild
- □ Discomforting
- □ Distressing
- □ Horrible
- □ Excruciating

Questionnaire Developed by Ronald Melzack  
Copyright R. Melzack, 1984, 1987
Visual Analogue Scale

No pain  |  Pain as bad as it could be

Numerical Rating Scale

0  1  2  3  4  5  6  7  8  9  10
No pain  |  Pain as bad as it could be

Verbal (Categorical) Rating Scale

( ) No pain
( ) Mild pain
( ) Moderate pain
( ) Severe pain
Wong-Baker FACES® pain rating scale

Donna Lee Wong
1948–2008

Connie Baker
Welcome to the Wong-Baker FACES Foundation

The official home of the

Wong-Baker FACES® Pain Rating Scale

0  2  4  6  8  10
No Hurt  Hurts Little Bit  Hurts Little More  Hurts Even More  Hurts Whole Lot  Hurts Worst

This tool was originally created with children for children to help them communicate about their pain. Now the scale is used around the world with people ages 3 and older, facilitating communication and improving assessment so pain management can be addressed.
A visual-analogue scale
PAIN TREATMENT
Why to treat pain?

Pain is part of life, but it doesn't have to rule the life

• ↓ the negative impact on the body
• ↓ complications  → next slide
• ↓ likelihood of chronic pain development
• improve the outcome
  • ↑ speed of recovery → ↓ length of stay → ↓ cost
• ↑ patient satisfaction
• make the period of disease accompanied by pain less unpleasant
• ↑ productivity and the quality of life
# Consequences of poorly managed acute pain

<table>
<thead>
<tr>
<th>System</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>tachycardia, hypertension, increase in cardiac workload</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>respiratory muscle spasm, decrease in VC, atelectasis, hypoxia, increased risk of pulmonary infection</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>postoperative ileus</td>
</tr>
<tr>
<td>Renal</td>
<td>increased risk of oliguria and urinary retention</td>
</tr>
<tr>
<td>Coagulation</td>
<td>increased risk of thromboembolism</td>
</tr>
<tr>
<td>Immunologic</td>
<td>impaired immune function</td>
</tr>
<tr>
<td>Muscular</td>
<td>muscle weakness and fatigue, limited mobility can increase the risk of thromboembolism</td>
</tr>
<tr>
<td>Psychological</td>
<td>anxiety, fear, frustration, poor patient satisfaction</td>
</tr>
</tbody>
</table>
Main groups of pain treatment methods

- Psychological
- Physical
- Interventional
- Surgical
  - Peripheral
  - Central (gyrotomy, leucotomy, cingulotomy, lobotomy etc.)
- Implanted neurostimulators
- Pharmacologic
Pharmacologic treatment of pain
Main groups of analgesics

- paracetamol
- NSAIDs
- opioids
Paracetamol

Acetaminophen
Paracetamol

The mode of action of paracetamol is not completely understood

• acts mainly in the brain
• only weak action in the peripheral anti-inflammatory systems

Current theories of action

• weak effects on the COX-1 and COX-2 enzymes
• CNS prostaglandin inhibition
• serotonergic pathway activation or inhibition of injury induced hyperalgesia
• mechanisms involving substance P or nitric oxide
• NMDA antagonism
• COX-3 mechanism
Paracetamol

metabolized by the liver where it is conjugated to:

• 60–80 % glucuronide
• 20–30 % sulphate
• 3–10 % is metabolized by cytochrome P-450 into $N$-acetyl-p-amino-benzoquinone imine (NAPQI)
  • under normal conditions rapidly detoxified by reduced glutathione and eliminated in the urine after conjugation with cysteine and mercapturic acid
  • potentially hepatotoxic, increases significantly with overdose
Non-steroidal anti-inflammatory drugs

Mechanism of action

[Diagram showing the mechanism of action of COX-1 and COX-2 enzymes in relation to Prostaglandins and Thromboxane, highlighting their roles in GI mucosal protection, platelet function, and the mediation of pain, inflammation, and fever.]
Non-steroidal anti-inflammatory drugs

Metabolism

NSAIDs share common metabolic pathways

• hepatic biotransformation by CYP 450 mediated oxidation or glucuronidation
• renal excretion of unmetabolized drug is much less important < 10%
• biliary excretion has been described for certain NSAIDs, clinically insignificant
Non-steroidal anti-inflammatory drugs

In Vitro Selectivity: COX-2/COX-1 Ratio

- Lumiracoxib
- Etoricoxib
- Rofecoxib
- Valdecoxib
- Etodolac
- Nimesulide
- Diclofenac
- Celecoxib
- Meloxicam

> 50-fold COX-2 selective
5-50-fold COX-2 selective
< 5-fold COX-2 selective

Range of COX Selectivity for COX-1 and COX-2
(log$_{10}$ IC$_{50}$ COX-2/COX-1)

Non-steroidal anti-inflammatory drugs

COX-2 selectivity of NSAIDs

Percent inhibition of COX-1 when COX-2 is inhibited by 80%

Warner et al, PNAS 1999
OPIOIDS
OPIOIDS

Some terminology

• “narcotic” – obsolete term used to refer to what is now called opioid.
  • current usage is primarily in a legal context to refer to a wide variety of substances of potential abuse

• “opiate” – refers to all naturally occurring substances with morphine-like properties

• “opioid” is a more general term that includes synthetic substances that have an affinity for opioid receptors
# OPIOID RECEPTORS

## Major subtypes

<table>
<thead>
<tr>
<th>Classical names</th>
<th>Other names</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>μ</strong>-Receptor</td>
<td>OP₃</td>
</tr>
<tr>
<td><strong>κ</strong>-Receptor</td>
<td>OP₂</td>
</tr>
<tr>
<td><strong>δ</strong>-Receptor</td>
<td>OP₁</td>
</tr>
<tr>
<td>N/OFQ receptor</td>
<td>ORL₁</td>
</tr>
</tbody>
</table>
# OPIOID RECEPTORS

## Major subtypes

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Subtypes</th>
<th>Location</th>
<th>Function</th>
</tr>
</thead>
</table>
| mu (µ)  | µ₁, µ₂, µ₃ | • brain  
  • cortex (laminae III and IV)  
  • thalamus  
  • striosomes  
  • periaqueductal gray  
  • rostral ventromedial medulla  
  • spinal cord  
  • substantia gelatinosa  
  • peripheral sensory neurons  
  • intestinal tract | µ₁  
  • analgesia  
  • physical dependence | µ₂  
  • respiratory depression  
  • meiosis  
  • euphoria  
  • reduced GI motility  
  • physical dependence | µ₃  
  • possible vasodilation |
# OPIOID RECEPTORS

## Major subtypes

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Subtypes</th>
<th>Location</th>
<th>Function</th>
</tr>
</thead>
</table>
| delta (δ) | δ₁, δ₂ | • brain  
• pontine nuclei  
• amygdala  
• olfactory bulbs  
• deep cortex  
• peripheral sensory neurons | • analgesia  
• antidepressant effects  
• convulsant effects  
• physical dependence  
• may modulate μ-receptor-mediated respiratory depression |
# OPIOID RECEPTORS

## Major subtypes

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Subtypes</th>
<th>Location</th>
<th>Function</th>
</tr>
</thead>
</table>
| kappa (κ) KOR KOP OP₂ | $K_1, K_2, K_3$ | • brain  
  • hypothalamus  
  • periaqueductal gray  
  • claustrum  
  • spinal cord  
  • substantia gelatinosa  
  • peripheral sensory neurons | • analgesia  
  • anticonvulsant effects  
  • depression  
  • hallucinogenic effects  
  • diuresis  
  • dysphoria  
  • meiosis  
  • neuroprotection  
  • sedation  
  • stress |
## OPIOID RECEPTORS
### Major subtypes

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Subtypes</th>
<th>Location</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nociceptin receptor</td>
<td>ORL₁</td>
<td>• brain</td>
<td>• anxiety</td>
</tr>
<tr>
<td>N/OFQ NOR NOP OP₄</td>
<td></td>
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The mechanism of action of opioids
Types of opioid analgesics

• Pure agonists
  • act predominantly at μ-receptors
  • may also produce lesser effects on δ- and κ-receptors

• Agonist–antagonists
  • have agonist or partial agonist effects on some opioid receptors, but antagonist effects on others
Problems With Current Treatment Options

Opioids are still the drug of choice, but use is limited by adverse events

- Nausea/vomiting
- Rash/hives or itching

Many patients refuse opioids because of nausea
Opioids have their place but anything that is opioid dose-sparing may be beneficial
Other Treatment Options

- **Anticonvulsants**
  - Gabapentin
    - Produces significant opioid-sparing effects
    - May improve postoperative pain score, compared to controls
  - Pregabalin
    - Similar mechanism of action to gabapentin
    - Better pharmacokinetic profile
    - Mixed results in studies for postoperative pain; research ongoing

- **Ketamine (subanesthetic doses)**

- **Others**
  - NSAIDs
  - COX-2 inhibitors
  - TCAs

Multimodal Therapy

Synchronous administration of ≥ 2 pharmacological agents or approaches, each with a distinct mechanism of action


Adjuvant medications

• Antidepressants
• Anticonvulsants
• Neuroleptic agents
• Antiarrhythmic drugs
• Corticosteroids
• Osteoclast inhibiting medications
• Spasmolytics
• Alpha blockers
• Alpha 2 agonists
Adjuvant medications

Adjuvant analgesics differ from opioid analgesics in important conceptual ways

- Adjuvants may or may not elicit pain relief.
- The nature of the dose/response relationship is not predictable.
- They are mainly useful in neuropathic pain.
THANKS FOR ATTENTION

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