Opiates

- alkaloids found in the opium poppy (Papaver somniferum)
- [Gk. opion = “poppy juice”]

Opioids

- compounds with opiate-like actions, including, but not confined to opiates (e.g., synthetic, endogenous opioids)
1. Naturally-occurring
  ● opium
  ● sap from opium poppy

Two major active alkaloids
  ● morphine
  ● codeine

Types of opioids

Surgery, Obstetrics and General Practitioners

Paregoric

- Camphorated tincture of opium
- Tincture of paregoric
Morphine

- Morpheus (god of Dreams)
  - son of Hypnos
- ~10% of opium by weight

Codeine

- methylmorphine
- ~0.5% of opium
2. Semi-synthetics

Heroin
- diacetylmorphine
- addition of two acetyl groups to morphine
- ~ 10x more potent than morphine
- pharmacological effect usually thought to be identical to morphine
  - in brain: heroin > morphine
    (new data suggest morphine and heroin may have different actions; 1999)

Semi-synthetic analgesics
- Hydromorphone (Dilaudid®)
- Hydrocodone (Hycodan®, Vicodin®)
- Oxycodone (Percodan®, Oxycontin®)
### 3. Synthetics

<table>
<thead>
<tr>
<th>Phenylpiperidines</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Fentanyl “china white”</td>
<td></td>
</tr>
<tr>
<td>- Carfentanil (Wildnil®)</td>
<td></td>
</tr>
<tr>
<td>- Meperidine (Demerol®) (MPPP)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Methadone &amp; Congeners</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Methadone (Dolophon®)</td>
<td></td>
</tr>
<tr>
<td>- Propoxyphene (Darvon®)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Benzomorphans</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Pentazocine (Talwin®)</td>
<td></td>
</tr>
</tbody>
</table>
**Analgesic potency**

- **Mild to moderate pain**
  - codeine, propoxyphene (Darvon®)
- **Moderately severe pain**
  - meperidine (Demerol®)
- **Severe pain**
  - heroin, hydromorphone (Dilaudid®)

**4. Opioid antagonists**

- naloxone (Narcan®)
- naltrexone
- Suboxone® (buprenorphine + naloxone)
5. Endogenous opioids

- Enkephalins, endorphins and dynorphins
- Morphine & codeine?

History of use - opium

Since recorded history
Ingredient in all sorts of medicinal preparations

History of use - morphine

“Soldiers disease”
History of use

Ads for heroin

Major effects

Analgesia
  ● Relief of pain in absence of impairment in other sensory modalities

Euphoria - Pleasure
  ● Produce sense of well being, reduce anxiety, positive feelings

Other effects

● Nausea & vomiting
● Respiratory depression
● Miosis (opposite of mydriasis)
● Gastrointestinal effects
● Cough Suppression
● Motor effects
Effects of repeated administration

Tolerance, withdrawal & sensitization

Tolerance and withdrawal

Behavioral withdrawal score vs. Time (hr)

LC unit activity vs. Time (hr)

Sensitization

- Psychomotor stimulant effects
- Rewarding effects
  (conditioned place preference)
Mechanisms of action

- Primary action on opioid receptors located in CNS +/- periphery

Different effects due to action at
- Different receptor subtypes
- Receptors in different locations

Endogenous opioids

Translation

Post-translational processing

Opioid peptide gene families

Three different gene families
- Proopiomelanocortin (POMC)
- Proenkephalin
- Prodynorphin (‘proenkephalin B’)

Translation

Post-translational processing
**Precursor gene families**

Proopiomelanocortin (POMC)
- β-endorphin
- ACTH, melanocortin SH

Proenkephalin -> Enkephalins
- met-enkephalin & 2 extended met-enk
- leu-enkephalin

Prodynorphine - forms of leu-enkephalin
- Dynorphins, A and B
- Neoendorphins, μ and β

**Differential distribution**

Endorphins
- discrete
- hypothalamic - endocrine related

Enkephalins and Dynorphins
- wide distribution, local circuit and short axon projections

**Opioid receptors**
### Opioid receptors

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Preferred Ligand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mu (µ)</td>
<td>Morphine &amp; endorphins</td>
</tr>
<tr>
<td>Delta (δ)</td>
<td>Enkephalins</td>
</tr>
<tr>
<td>Kappa (κ)</td>
<td>Ketocyclazocine &amp; dynorphins</td>
</tr>
</tbody>
</table>

- Each subtype has subtypes

### Cellular actions

- G protein coupled receptors
- Inhibitory

*(-Diagram showing cellular actions with labels and illustrations*-)

Negatively-coupled

12.4
Role in drug action

Analgesia

Spinal actions
- Dorsal horn of spinal cord
- Primary pain afferents

Analgesia

Spinal actions
- Inhibit incoming pain signals

Opioid receptor

Spinal action
Supraspinal actions

- Stimulation > analgesia and inhibit cells in dorsal horn
- Lesion > block analgesia to systemic or local morphine

Dorsal horn 12.10
**Analgesia**

**Supraspinal actions**
- µ1 sites seem most important
- Specific blockade of µ1 shifts dose-response curve for morphine analgesia up to 12 fold to right

**Heroin vs. Morphine**
- difference pharmacokinetic?
- recent evidence for different receptors
  - MOR-1 knockouts

**Analgesia - MOR1 knockouts**


Morphine, but not heroin, analgesia abolished in Mor1 knockout mice

Heroin > 6-acetyl-morphine in vivo
Reinforcing effects

- All classical opioid drugs of abuse have a preference for $\mu$ sites (e.g., morphine, heroin, methadone, fentanyl etc.)
  - $\delta$ may contribute, but little known
- $\kappa$ compounds are not self-administered
  - psychomimetic and aversive in humans

Opioid/DA interaction

- Intra-VTA opioid support SA and CPP
- DA antagonist or 6-OHDA lesion impair SA
- DA antagonist into VTA or ACC impair SA
**Mechanism**

**μ compounds:**
- Increase DA cell firing
- Increase DA release in ACC
- Accompanied by locomotor activation

**Model for reinforcing effects**

**Site of action**
- VTA – accumbens DA system

“Disinhibition”

**κ compounds**
- Decrease DA cell firing
- Decrease DA release
- Decrease locomotion
Respiratory depression

µ2 sites?
- Specific µ1 antagonist (naloxonazine) shifts analgesia dose - response curve for morphine to right
- Not shift dose-response curve for:
  - elevation of pCO2
  - depression of pO2
- Respiratory neurons in medulla in region of n. solitary tract

Gastrointestinal effects

µ and κ sites
- In stomach, small and large intestine
- Decreased motility
- Common bioassay > ability to inhibit intestinal contractions

MOR Knockouts

- Morphine has affinity for all opioid receptor subtypes (much stronger for mu)
- Evidence for site of action from pharmacological experiments with drugs that may act at multiple sites
- Which effects due to action at which receptor subtypes?
### MOR Knockouts (MOR-/-)

<table>
<thead>
<tr>
<th>Effect</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine effect</td>
<td>Abolished</td>
</tr>
<tr>
<td>Spinal analgesia</td>
<td>Abolished</td>
</tr>
<tr>
<td>Supraspinal analgesia</td>
<td>Abolished</td>
</tr>
<tr>
<td>Reward</td>
<td>Abolished</td>
</tr>
<tr>
<td>Withdrawal</td>
<td>Abolished</td>
</tr>
<tr>
<td>Respiratory depression</td>
<td>Abolished</td>
</tr>
<tr>
<td>Inhibition GI motility</td>
<td>Abolished</td>
</tr>
<tr>
<td>Psychoactivating effect</td>
<td>Abolished</td>
</tr>
</tbody>
</table>

(All effects maintained in DOR-/- and KOR-/-)


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### The Politics of Pain and Pain Management

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### Introduction

- **Prevalence**
  - Pain accounts for 80% of all medical complaints (30% debilitated at some time)
  - Pain is patient’s #1 reason why they fear disease
  - Pain affects 90% of patients with terminal disease (50% of ambulatory patients)

- **Obstacles for treatment**
  - Fear—patient, prescriber
  - Social and Legal obstacles
  - Lack of education
Political and Social Obstacles

- Overstated abuse potential of opiate drugs has been a serious obstacle to pain treatment
- Pain patients have been a casualty of the war on drugs
- No field to study pain until the 1970s (opiate receptor cloned)
- Very little formal training on pain management as part of medical school curriculum (often 1 hour)

Politics of pain

- Most doctors misinformed about the addictiveness of therapeutic opiates (e.g., vicodin v heroin or significance of routes of administration in addiction)
- Even when habit-forming this addiction outweighed thinking about patient's quality of life.
- Fear of reprisals on license by DEA a major issue
- Drug companies avoided new opiates

Politics of pain

- Pain patients looked down upon for complaining about pain (especially chronic pain)
- Pain treated as a valuable diagnostic indicator by doctors "don't want to cover up the pain" (even chronic neuropathic pain)
Politics of pain

Revolution in pain management had multifaceted roots- began in 1970s
  - conference on Pain formed unified field to study Pain, 1977 - American Pain Society (www.ampainsoc.org) 28-3600
  - discovery of endogenous opioids
  - activism by Bonica, Liebeskind, etc.
  - revolt by San Francisco cancer doctors
  - Centers for Pain Management Policy (e.g., Wisconsin)

Politics of pain

- Several states enacted legislation to protect doctors and patients (e.g., California's "pain patients bill of rights")
- Softening of war on drugs by Clinton administration
- Doctor's take back their rights (Doctor's make medical decisions)
- Medical marijuana acts

Politics of pain

- In cancer was clear need to treat pain outweighed any addiction
- It became clear most pain patients either didn't become addicted at all or developed mild dependence
- Pain management clinics have appeared all over the place (including Emory)
- Still many obstacles to adequate pain management, e.g., patient access is still very low and too many drug side-effects
Many obstacles remain

- Still difficult for patients to get treatment
- Triplicate prescriptions
- Cannot be called in
- Cannot be refilled
- Policing by DEA
- Few experts in pain
- Strong slow-release drugs are expensive
- Pain patients often poor, uninsured, and cannot travel or work

What is Pain?

• Medical 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*

• Operative Definition
  “Pain is whatever the experiencing person says it is, existing whenever he/she says it does.”
- Patient’s appearance can be very deceptive

What is Pain?

Current definitions of pain don’t work well for:
- Children who can’t speak or even older ones who can’t express themselves well
- Those who are mute or mentally ill
- Animals
- Those who hide their pain
- Emphasis on pain behaviors emerging
Reflection tells me that I am so far from being able to define pain, of which I here write, that the attempt could serve no useful purpose. Pain, like similar subjective things, is known to us by experience and described by illustration.


---

**Definitions**

**Nociception:** Potentially tissue damaging thermal, mechanical or chemical energy impinging upon specialized nerve endings of A-δ and C fibers.

**Pain:** Perceived nociceptive input to the nervous system.

**Pain can occur without nociception!**
### Pain syndromes without nociception

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalamic syndrome</td>
<td>Phantom limb pain</td>
</tr>
<tr>
<td>Tic douloureux</td>
<td>Arachnoiditis</td>
</tr>
<tr>
<td>Postherpetic neuralgia</td>
<td>Atypical facial pain</td>
</tr>
<tr>
<td>Postparaplegia pain</td>
<td>Nerve root avulsion pain</td>
</tr>
<tr>
<td>Postthoracotomy pain</td>
<td>Neuropathic pain</td>
</tr>
</tbody>
</table>

### Pain is a major cause of suffering!

**Suffering:** Negative affective response generated in higher nervous system regions in response to pain and other situations including fear, anxiety, isolation, depression, etc.

### Pain behavior

All forms of behavior generated by the individual that are commonly understood to reflect the presence of nociception; for example, grimacing, saying ouch, limping, lying down, taking medicines, seeking health care, refusal to work.
Types of Pain

- Nociceptive Pain
  - Stimulation of somatic and visceral peripheral nociceptors by stimuli that damage tissue
- Neuropathic Pain
  - Pain resulting from non-inflammatory dysfunction of the peripheral/central nervous system in the absence of stimuli

Neuropathic Pain

- Prevalence
  - General population 0.6-1%
- Causes
  - Compression/infiltration of nerves by:
    - Tumors
    - Nerve Trauma secondary to procedures
    - Nervous System Injury
    - E.g., phantom-limb pain, neuralgia
      back injury, post-surgical pain

Types of Pain

- Transient Pain
  - Studied extensively in man and animals
  - Does not involve tissue damage
  - Activation of nociceptors in resting state
  - Not clinically relevant, save for procedural pain such as venipuncture, LP
Types of Pain

Acute Pain
- Activation of nociceptors in region of tissue damage
- Nociceptor function is altered by tissue changes
- Healing processes can eliminate tissue damage; nociceptor function returns to baseline

Chronic Pain
- Activation of nociceptors in region of tissue damage
- Nociceptor function is altered by tissue damage; CNS adapts permanently
- Body cannot heal injury, or damage to nervous system
- Organic cause unknown and untreatable (often iatrogenic)

Chronic pain is a special problem

Chronic Pain
- Associated with a social stigma
  - people expect you to get over illness
  - "get back to work"
  - associated with a lot of hiding of pain
- Debilitating and depressing producing lots of psychological problems
  - Especially poorly treated
  - lack of expertise and desire to treat by docs
  - lack of effective treatment
**Afferent pain transmission**

- Afferent fibers go to the CNS transmitting nociceptive message from trauma to dorsal horn of spinal cord
- A alpha, A beta, A gamma, A delta, B, or C
- Nociceptive transmission takes place in the A delta fibers (well-localized pain); C fibers (persistent pain)

**Transduction of nociception**

- Conversion of stimuli into electrical action potential
- What types of stimuli?
  - Heat or cold (e.g. radiation damage)
  - Pressure (e.g. tumor infiltration into bone)
  - Chemical (e.g. chemotherapy)

**Peripheral Nociceptors**

- What is a nociceptor?
  - Not spontaneously active
  - Level of stimulation must exceed threshold
  - Sensitization produces hyperalgesia
  - Tissue damage changes the sensitivity
- Sensitization is manifested as:
  - Decreased threshold
  - Increased intensity-prolonged firing
  - Spontaneous activity
Pain Theories and Pathways

- Spinal cord transmission—spinothalamic tract carries pain impulses; the lateral pathway (sharp, localized pain), the ventral pathway (dull, nonlocalized pain)
- Pathways merge in thalamus and connect in cortex
- Anterior Cingulate cortex—pain perception area

Types of Peripheral Nerve Fibers

- A Fibers (Fast Transmission)
  - Alpha - Proprioception (Muscles & Joints)
  - Beta - Mechanoreception (Cutaneous Tissue)
  - Delta - Primary nociceptive neurons

- C Fibers (Slow Transmission)
  - Primary nociceptive neurons

Neuronal Activities in Normal States

<table>
<thead>
<tr>
<th>Stimulus</th>
<th>Primary Afferent</th>
<th>Sensation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Intensity</td>
<td>A-Beta</td>
<td>Innocuous</td>
</tr>
<tr>
<td>High Intensity</td>
<td>A-Delta/C</td>
<td>Pain (nociception)</td>
</tr>
</tbody>
</table>
Neuronal Activities in Pain States

<table>
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<th>Stimulus</th>
<th>Pri Afferent</th>
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<tbody>
<tr>
<td>Low Intensity</td>
<td>A-Beta</td>
<td>Pain (alldynia)</td>
</tr>
<tr>
<td>High Intensity</td>
<td>A-Delta/C</td>
<td>Hyperalgesia</td>
</tr>
</tbody>
</table>

Pain Theories and Pathways

- Clusters of opiate receptors throughout ascending and descending pain pathways
- Endogenous opioids also in brain
- Opiate receptors—µ (µ1 and µ2), δ (delta), κ (kappa), σ (sigma) and ε (epsilon)
  - µ1 are primarily responsible for analgesic effects (but maybe also δ, κ, ε)

Opioid (Narcotic) analgesics

- Morphine
- Meperidine (Demerol)
- Codeine (Tylenol-3)
- Hydromorphone (Dilaudid)
- Hydrocodone and acetaminophen (Vicodin)
- Methadone (Dolophine)
- Fentanyl, alfentanil, sufentanil, remifentanil (e.g., sublimaze & duragesic)
- Oxycodone (Percodan)
- Oxycodone and acetaminophen (Percocet)
- Propoxyphene (Darvon)
Opioids

- Inhibit the transmission of pain impulses in sensory pathways in the spinal cord
- Reduce cortical responses all over the brain
- Alter behavioral responses to pain
- Tolerance & dependence may develop, not necessary a sign of abuse or addiction

Opioids

- Despite reports of abuse vast majority of pain patients use chronically without addiction or dependence
- Long-acting much better than short-acting (prevents on-off and sensitization)
- ATC (around-the-clock) preferable to PRN

Non-narcotic analgesics

- Salicylates (aspirin–historically there were several derivatives)
- Aniline derivatives (Tylenol-acetaminophen)
- Non-steroidal anti-inflammatory agents (NSAIDS)
**NSAIDs**

**COX 1 & COX 2 inhibitors**
- ibuprofen (Motrin, Advil)
- naproxen (Aleve)
- diclofenac (Voltaren)
- indomethacin (Indocin)
- ketorolac (Toradol)
- sulindac (Clinoril)
- mefanamic (Ponstel)
- piroxicam (Feldene)
- flurbiprofen (Ansaid)
- ketoprofen (Orudis)

**Selective COX 2 inhibitors**
- celecoxib (Celebrex)
- rofecoxib (Vioxx)
- valdecoxib (Bextra)

**Celebrex & Vioxx**

- Aspirin and most commonly used NSAIDs nonselectively inhibit COX 1 and COX 2
- COX 2 agents have a lower incidence of the ulcerogenic side effects (they increase the risk of heart attack, stroke, and clotting disorders, however)
- Identified by genetic screen of aspirin
- Side effects include headache

**Therapeutic effects of NSAIDs**

- Antipyretic
- Analgesic—low to moderate pain intensity; lack unwanted CNS effects of opioids
- Antiinflammatory
- Side effects still include ulcers, blood-thinning, and sensitivity
- Only aspirin proven to show anti-MI effects and still in its own category
Aniline derivatives–Acetaminophen (Tylenol)

- Centrally mediated hypothalamic stimulation to alter pain perception
- Clinical use–analgesic, weak antipyretic
- No action as anti-inflammatory
- Overdosage is associated with hepatic necrosis/must be treated within 10 hours - SERIOUS PROBLEM

Pain adjuvants

- Tricyclic antidepressants and SSRIs
- Anticonvulsants
- Corticosteroids
- Muscle relaxants
- Capsaicin
- Local anesthetics (lidocaine, benzocaine)
- Non-pharmacologic therapies
- NMDA receptor antagonists (ketamine, DXM, CPP)
- Patient-controlled analgesia/epidural analgesia

Clinical applications

- Review history (drug abuse, allergy)
- Assess level of function and pain level
- Monitor patient pain relief, tolerance
- Level of function after treatment
- Surgical treatment of chronic pain is a last resort (exception = pumps, stimulators, rhizotomy), usually makes things worse