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Opioid Analgesic Drugs

1. **Classification of Analgesic Drugs**
   - A. Opioid analgesics (Narcotic analgesics)
     Opiates- Morphine derivatives
     Examples: morphine, codeine, heroin, fentanyl
     Uses: moderate to severe pain
   - B. Non-opioid Analgesic
     Weak analgesics (Non-narcotic analgesics or Non-steroidal anti-inflammatory drugs)
     Examples: aspirin, acetaminophen (Tylenol), ibuprofen (Advil, Motrin)
     Uses: mild pain, anti-inflammatory
2. **Putative sites of action of opioid analgesics**
   Sites are labeled A – E (see Figure below)
   A: nociceptive nerve endings
   B: spinal cord
   C: thalamus
   D: mid brain
   E: medulla
   Sites A – C are in the ascending pain sensory pathway
   Sites D and E are in the descending pain modulation pathway

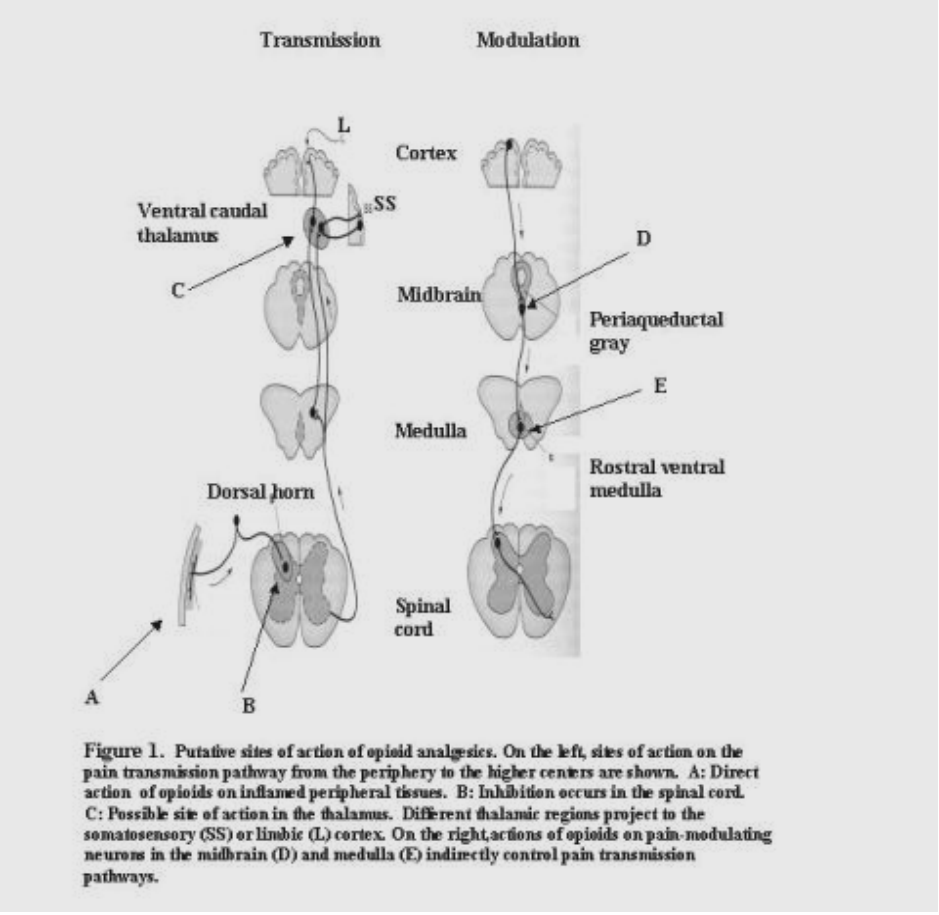


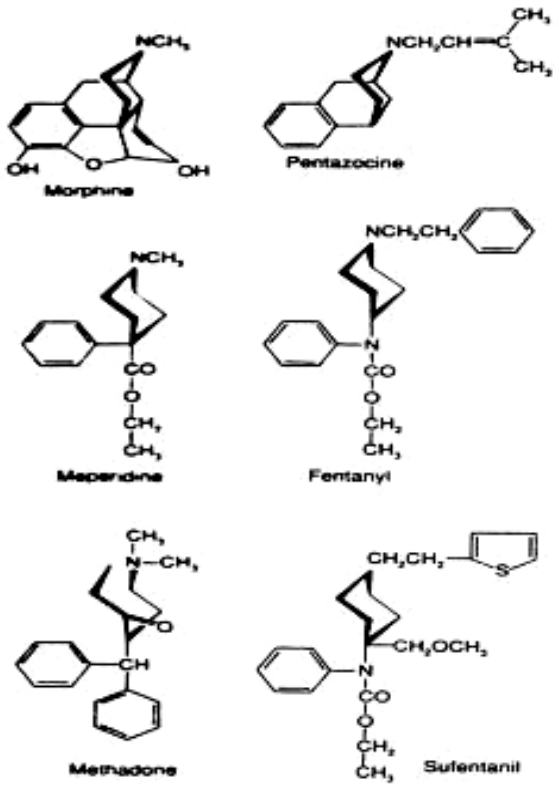
Figure 1. Putative sites of action of opioid analgesics. On the left, sites of action on the pain transmission pathway from the periphery to the higher centers are shown. A: Direct action of opioids on inflamed peripheral tissues. B: Inhibition occurs in the spinal cord. C: Possible site of action in the thalamus. Different thalamic regions project to the somatosensory (SS) or limbic (L) cortex. On the right, actions of opioids on pain-modulating neurons in the midbrain (D) and medulla (E) indirectly control pain transmission pathways.

3. Opioid Analgesic Drugs

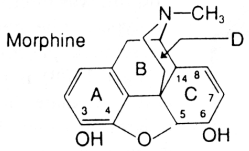
The drugs used to alleviate moderate to severe pain are either opiates (derived from the opium poppy) or opiate-like (synthetic drugs). These drugs are together as **OPIOIDS.**

Examples: Opiates: morphine, codeine
Opiate-Like: fentanyl, meperidine, methadone

See below the structures of some opioid analgesic drugs and derivatives

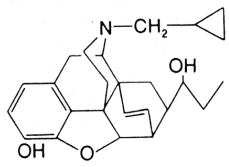


Morphine analogues



Drug	Substituents 3	6	N	14
Morphine	—OH	—OH	—CH_3	—H
Heroin	—OCO · CH_3	—OCO · CH_3	—CH_3	—H
Codeine	—OCH_3	—OH	—CH_3	—H
Levorphanol	—OH	—H	—CH_3	—H (lacks —O— at C_4–C_5)
Dihydrocodeine	—OCH_3	—OH	—CH_3	—H (lacks double bond C_7–C_8)
Nalorphine	—OH	—OH	—$CH_2CH{=}CH_2$	—H
Nalbuphine	—OH	—OH	—CH_2—cyclobutyl	—OH (lacks double bond C_7–C_8)
Butorphanol	—OH	—H	—CH_2—cyclobutyl	—H (lacks —O— at C_4–C_5 & double bond C_7–C_8)
Naloxone	—OH	=O	—$CH_2CH{=}CH_2$	—HO (lacks double bond C_7–C_8)

Buprenorphine



4. Endogenous Opioids:

Enkepalins , Endorphins, Dynorphins, Endomorphins

Enkepalins:

Met-Enkepalin	Tyr-Gly-Gly-Phe-**Met**
Leu- Enkepalin	Tyr-Gly-Gly-Phe-**Leu**

Endorphins:

α-neoendorphin	**Tyr-Gly-Gly-Phe-Leu-Arg-Lys-Tyr-Pro**-Lys
β-neoendorphin	**Tyr-Gly-Gly-Phe-Leu-Arg-Lys-Tyr-Pro**

βh-endorphin **Tyr-Gly-Gly-Phe-**Met-Thr-Ser-Glu-Lys-Ser-Gln-Thr-Pro-Leu-Val-Thr-leu-Phe-Lys-Asn-Ala-Ile-Ile-Lys-Asn-Ala-Tyr-Lys-Lys-Gly-Glu (31-Residues)

Dynorphins:

Dynorphin A **Tyr-Gly-Gly-Phe-Leu-**Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys-Trp-Asp-Asn-Gln

Dynorphin B **Tyr-Gly-Gly-Phe-Leu-**Arg-Arg-Gln-Phe-Lys-Val-Val-Thr

Endomorphins:

Endomorphin 1	Tyr-Pro-Trp-Phe-NH_2
Endomorphin 2	Tyr-Pro-Phe- Phe-NH_2

Endogenous Opioid peptides are derived from precursor peptides (proopiomelanocortin [POMC]) by protelytic clevage of POMC. POMC present in high level in the CNS (arcuate nuecleus, limbic, brain stem, spinal cord). Enkephalins activate mu (μ) and delta (δ) opioid receptors. Enkephalins have slightly higher affinity for the δ than for the μ opioid receptor. Endomorphins have very high affinity for the μ opioid receptor.

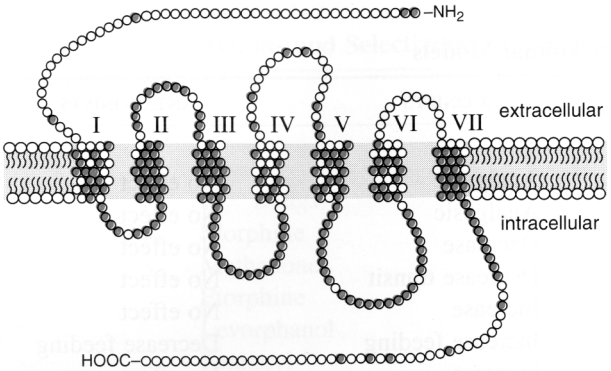
5. Selected Synthethetic Opioid Peptides:

DAMGO	**[D-Ala^2, MePhe^4, Gly(ol)^5] enkephalin**
DPDPE	**[D-Pen^2, D-Pen^5] enkephalin**
DSLET	**[D-Ser^2, Leu^5] enkephalin-Thr^6**
DADL	**[D-Ala^2, D-leu^5] enkephalin**
CTOP	**D-Phe-Cys-Tyr-D-Trp-Orn-Pen-Thr-NH_2**
FK-33824	**[D-Ala^2 , N-MePhe^4, Met(O)^5 –ol] enkephalin**
[D-Ala^2] Deltorphin I	**Tyr-D-Ala-Phe-Asp-Val-Val-Gly-NH_2**
[D-Ala^2, Glu^4] Deltorphin II	**Tyr-D-Ala-Phe-Glu-Val-Val-Gly-NH_2**
Morphiceptin	**Tyr-Pro-Phe-Pro-NH_2**
PL-017	**Tyr-Pro-MePhe-D-Pro-NH_2**
DALCE	**[D-Ala^2, Leu^5, Cys^6] enkephalin**

6. OPIOID RECEPTORS

Opioids bind to specific receptor molecule that mediates its effects. Several opioid specific receptors have been cloned: Mu (μ), Kappa (κ), and Delta (δ) receptors. These receptors belong to G protein-coupled seven transmembrane receptor family. The amino acid sequences are approximately 65% identical among these receptors, but they have little homology with other G protein-coupled receptors (see below the Figure).

A. Mechanism of Opioid Receptor Function:



μ, δ, and κ are functionally coupled to pertussis toxin sensitive heterotrimeric G proteins (G_i) to inhibit adenylyl cyclase activity.

1. Activates receptor-activated K^+ currents which increase K^+ efflux (hyperpolarization)
2. Reduces voltage-gated Ca^{2+} entry.

Hyperploarization of membrane potential by K^+ currents and inhibition of the Ca^{2+} influx prevents neurotransmitter release and pain transmission in varying neuronal pathways.

B. OPIOID RECEPTOR EXPRESSION

μ receptor	periaqueductal gray, spinal trigeminal nucleus, cuneate and gracile nuclei, thalamus regions	Pain perception (morphine analgesia)
	nucleus of solitract, nucleus ambiguus	Morphine-control respiration
	parabrachial nucleus	Morphine- depress respiration
	neurons of the postrema	Nauesea and vomiting
κ receptor	hyphothalamic region	Neuroendocrine effects
δ receptor	dorsal horn of the spinal cord	

7. CLASSIFICATION OF OPIOID ANALGESIC DRUGS

Strong Agonists:

Morphine- 4 hr
Meperidine- 2 hr
Methadone- long acting (half life 24 hrs)
Heroin- 2 hr; 3-fold increase in potency, no acceptable medical value in US
Fentanyl- 5 to 45 min, anesthetic

Moderate Agonists:

Propoxyphene
Codeine

Mixed Agonist-Antagonists:

Pentazocine- agonist on κ receptor and weak antagonist at μ and δ receptor
Nalbuphine- similar to Pentazocine but potent anatagonist at μ receptor
Buprenorphine- lipophilic, about 0.4 mg equivalent to 10 mg morphine, partial μ agonist receptor, anatagonist at κ receptor

Antagonists:

Naloxone- it rapidly displaces bound opioids from receptor within 30 sec of IV injection, reverses the respiratory depression and coma due to heroin overdose, competitive antagonist for μ, κ, and δ receptors with a 10-fold higher affinity for μ receptor than for κ.
Naltrexone- longer duration of action than naloxone, a single oral dose blocks the effects of injected heroin (48 hrs)

8. SELECTIVITY OF OPIOID DRUGS AND PEPTIDES FOR DIFFERENT RECEPTORS

Compund	μ	δ	κ
Agonists			
Morphine	+++		+
Methadone	+++		+
Meperidine	++	+	+
Codeine	+	+	+
Etorphine	+++	+++	+++
Fentanyl	+++		
Sufentanil	+++	+	+
Endogenous Peptides			
Met-enkephalin	++	+++	
Leu-enkephalin	++	+++	
β-Endorphin	+++	+++	
α-Neoendorphin	+	+	+++
Dynorphin A	++		+++
Antagonists			
Naloxone	- - -	-	- -
Naltrexone	- - -	-	- -
Mixed aganists/antagonists			
Pentazocine	-		+
Nalbuphine	- -		++
Buprenorphine	++		- -
Synthetic opioid peptides			
DAMGO	+++		+
CTOP	- - -		-

(+) agonist; (-) antagonist

9. PHARMACOLOGIC ACTIONS

Morphine and related opioids produce their major effects on the central nervous system and gastrointestinal tract

A. Central Nervous System

1. Analgesia

i. produces selective attenuation of pain perception; effect is dose-dependent

ii. therapeutic dose (10 mg; parentral)
pain less intense (pain threshold not elevated)
less discomfort (more effective for dull pain)
euphoria
drowsiness

iii. higher doses (15 – 20 mg; parentral)
pain threshold elevated
respiratory depression may be significant
sharp intermittent pain relieved

these doses DO NOT produce slurred speech, motor ataxia or protection from seizures

iv. sites of action
Periaqueductal Grey (PAG)
Caudal brain stem (nucleus raphe magus, magnocellular reticular formation)
Spinal cord
Limbic system

v. mechanism of action

opioids generally produce inhibition of neuronal activity
opioids inhibit the release of neurotransmitters
opioids activate descending inhibitory systems

2. SEDATION

In humans, opioids usually produce sedation
However, in extremely high doses opioids produce convulsions (e.g., meperidine)

3. EUPHORIA

Euphoria is often produced by opioids
Euphoria is more prominent in those previously addicted to opioids

4. MENTAL CLOUDING

The environment is perceived as indistinct and unreal

5. RESPIRATORY DEPRESSION

Produced even in small doses

Large doses may induce respiratory failure
Death from morphine overdose is usually due to respiratory failure
Pain can stimulate respiration
Opioids decrease sensitivity of brain stem centers to CO_2 (i.e., depress CO_2 sensing capacity)
Pure oxygen can induce apnea during severe respiratory depression

6. NAUSEA AND VOMITING

Opioids can stimulate the chemoreceptor trigger zone (CTZ)
Located in the area postrema in the medulla oblongata
Depression of the vomiting center is also produced
Symptoms can be controlled by Phenothiazines (agonist on κ receptor weak antagonist on μ receptor

7. COUGH REFLEX (antitussive effect)

Opioids suppress the cough reflex
Produced by depression of neurons in medulla which control the cough reflex
Codeine is a potent inhibitor of the cough reflex
Meperidine has a weak effect
Dextromethorphan has no GI effects, no respiration depression, no analgesia

8. PUPILLARY DIAMETER

Opioids cause miosis (pupillary constriction). Opioids act on μ and κ receptors to stimulate oculomotor nucleus to constrict pupil. Pin point pupils are characteristics of morphine overdose. There is very little tolerance to this effect.

B. GASTROINTESTINAL TRACT

Decreases GI motility
Increases GI tone
Produces constipation (Diphenoxylate-meperidine derivative [Lomotil])
GI spasms can be controlled by atropine (acetyl choline receptor antagonist)
Biliary tract spasm. Opioids can exacerbate biliary colic

C. CARIOVASCULAR SYSTEM

No prominent effects
Peripheral vasodilation most prominent effect due to histamine release and decreased adrenergic tone
Very high doses may produce bradycardia
Orthostatic hypotension

D. URINARY TRACT

Opioids produce urinary retension
Increase tone of urinary sphincter
Decrease urine production (increased ADH secretion)

E. UTERUS

Duration of labor may be prolonged

F. BRONCHIAL SMOOTH MUSCLE

Therapeutic doses have no effect
High doses produce constriction (can aggravate asthma)

10. PHARMACOKINETICS

i. Absorption

Readily absorbed from all sites of administration

ii. Distribution

Distributed to all tissues
Morphine is poorly transported across the blood-brain barrier

iii. Metabolism

The major mechanism is conjugated with glucuronic acid in the liver. **Morphine** and **naloxone** are subject to significant "first-pass" metabolism in the liver, but **naltrexone** is not.

iv. Excretion

Free and conjugated morphine are excreted in the urine

11. THERAPEUTIC INDICATIONS

PAIN

i. Chronic pain (only under some circumstances)

Most chronic pain states are not relieved by opioid drugs:

central pain
trigeminal neuralgia (tic douloureux)
causalgia
phantom limb pain
cancer pain
lower back pain

These pain states require continuous medication
Therapy limited by tolerance and physical dependence

Chronic pain arising from terminal illness can be relieved by opioid drugs

ii. **Acute Pain**

postoperative pain
diagnostic procedures
orthopedic manipulations
myocardial infarction

iii. **Preanesthetic medication** (fentanyl-derivatives)
iv. **Dyspnea**
v. **Cough Suppression** (codeine, dextromethorphan)
vi. **Diarrhea and dysentery**

12. CONTRAINDICATIONS

i. **Decreased respiratory reserve**
emphysema
severe obesity
asthma

ii. Biliary colic
iii. Head injury
iv. Reduced blood volume
v. Hepatic insufficiency
vi. Convulsant states

13. ACUTE TOXICITY

i. **Severe Toxicity**
Estimates: 30 to 120 mg (oral) of morphine

ii. **Lethal dose**
Highly variable: > 120 mg (oral) may be lethal

iii. **Symptoms**
Profound coma
Depressed respiration (2 to 4/min)
Cyanosis
Low blood pressure
Pinpoint pupils
Decreased urine formation
Low body temperature
Flaccid muscles

iv. **Treatment**
Ventilation (do not give 100% oxygen because it can induce apnea)
Naloxone (Narcan) will reverse toxic signs
Naltrexone has a longer duration of action

14. CHRONIC TOXICITY

Tolerance and physical dependence are manifestations of chronic toxicity

i. Tolerance

Tolerance develops to:
Analgesia
Euphoria
Sedation

Lethal dose
Nausea

Tolerance **DOES NOT** develop to:
Respiratory depression (partial)
Miosis
Constipation

Cross –tolerance develops to other opioids

ii. PHYSICAL DEPENDENCE

Abnormal physical state in which the drug must be administered to maintain "normal" function. Physical dependence is manifested by "withdrawal symptoms" when administration of the drug is stopped. Physical dependence is a powerful reinforcement for continued drug taking behavior

Symptoms:

8 - 12 hrs:	lacrimation, rhinorrhea, yawning, sweating
12 – 14 hrs:	restless sleep (yen)
48 – 72 hrs:	symptoms peak, dialted pupils, anorexia, gooseflesh (cold turkey), restlessness, irritability, tremor, nausea/vomiting, intestinal spasm and diarrhea, muscle spasm

7 – 10 days symptoms end

15. OTHER OPIOIDS

Codeine –
less potent than morphine
mainly used as antitussive

Meperidine –
less potent than morphine
high doses produce excitation and convulsions
less smooth muscle spasm and miosis than morphine
little antitussive action

Diphenoxylate (Lomotil) –
meperidine derivative used to treat diarrhea

Methadone –
long duration of action (24 hr)
withdrawal protracted and attenuated
used to treat addiction

Propoxyphene (Darvon) –
mild analgesic action

16. OPIOIDS WITH AGONIST/ANTAGONIST PROPERTIES

Pentazocine (Talwin) –

less potent than morphine
will precipitate withdrawal in dependent individuals
may produce dysphoria
may be orally

Nalbuphine (Nubain) –

similar to pentazocine
not effective orally

Butorphanol (Stadol) -

similar to pentazocine
not effective orally

17. ANTAGONISTS

Naloxone –

Eliminated first pass metabolism (half life 60 to 100 min)
Readily reverses the coma and respiratory depression of opioid overdose
Rapidly displaces all receptor bound opioid molecules; therefore it is very effective reversing heroin overdose
Competitive antagonist for μ, κ, and δ; 10-fold higher affinity for μ than for κ [This may explain why naloxone readily reverses respiratory depression with only minimal reversal of analgesia that results from agonist stimulation of κ receptors in the spinal cord

Naltrexone – longer duration of action (up to 48 hrs)