

## 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

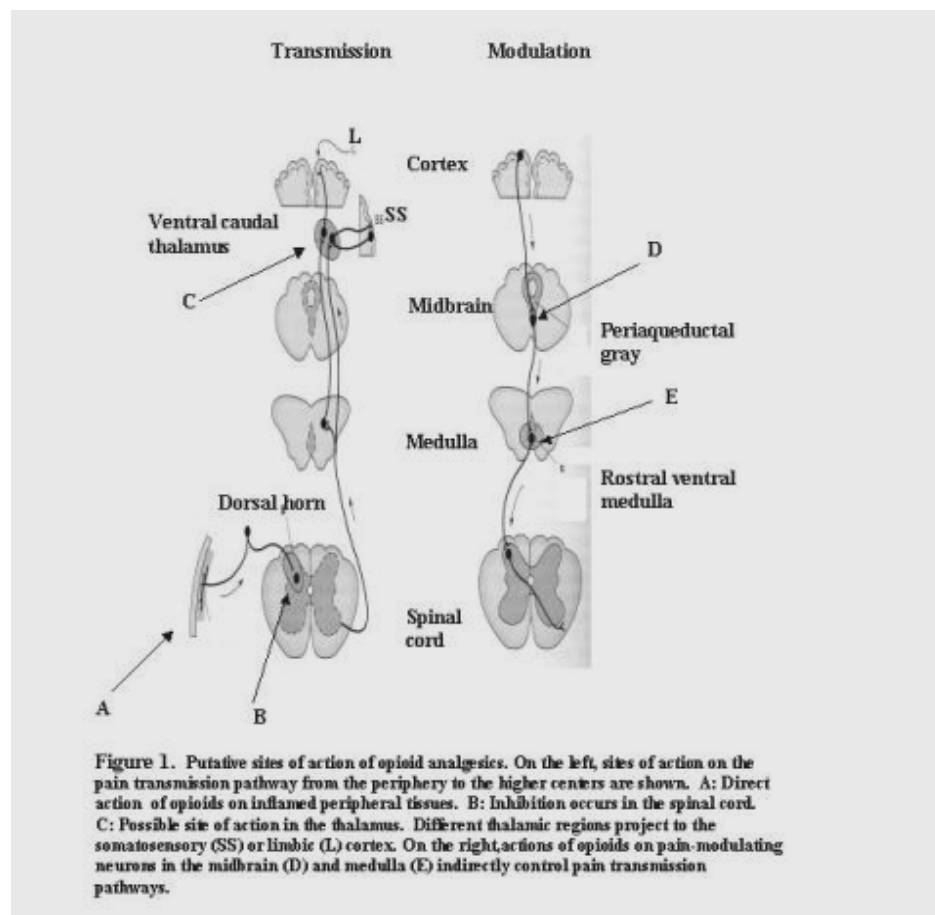
C: thalamus

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



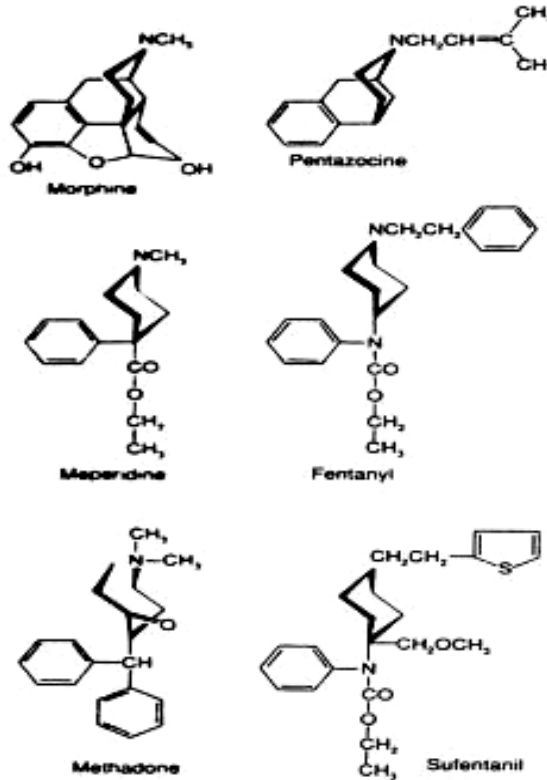
### 3. Opioid Analgesic Drugs

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**.

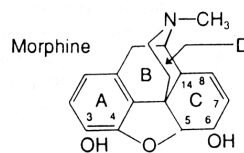
Examples: Opiates: morphine, codeine

Opiate-Like: fentanyl, meperidine, methadone

See below the structures of some opioid analgesic drugs and derivatives

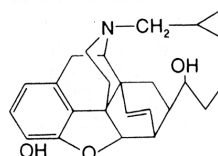


#### Morphine analogues



Drug	Substituents			
	3	6	N	14
Morphine	—OH	—OH	—CH <sub>3</sub>	—H
Heroin	—OCO · CH <sub>3</sub>	—OCO · CH <sub>3</sub>	—CH <sub>3</sub>	—H
Codeine	—OCH <sub>3</sub>	—OH	—CH <sub>3</sub>	—H
Levorphanol	—OH	—H	—CH <sub>3</sub>	—H (lacks —O— at C <sub>4</sub> —C <sub>5</sub> )
Dihydrocodeine	—OCH <sub>3</sub>	—OH	—CH <sub>3</sub>	—H (lacks double bond C <sub>7</sub> —C <sub>8</sub> )
Nalorphine	—OH	—OH	—CH <sub>2</sub> CH=CH <sub>2</sub>	—H
Nalbuphine	—OH	—OH	—CH <sub>2</sub> —cyclobutyl	—OH (lacks double bond C <sub>7</sub> —C <sub>8</sub> )
Butorphanol	—OH	—H	—CH <sub>2</sub> —cyclobutyl	—H (lacks —O— at C <sub>4</sub> —C <sub>5</sub> & double bond C <sub>7</sub> —C <sub>8</sub> )
Naloxone	—OH	=O	—CH <sub>2</sub> CH=CH <sub>2</sub>	—HO (lacks double bond C <sub>7</sub> —C <sub>8</sub> )

Buprenorphine



## 4. Endogenous Opioids:

### Enkepalins , Endorphins, Dynorphins, Endomorphins

#### Enkepalins:

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

#### Endorphins:

$\alpha$ -neoendorphin	<b>Tyr-Gly-Gly-Phe-Leu-Arg-Lys-Tyr-Pro-Lys</b>
$\beta$ -neoendorphin	<b>Tyr-Gly-Gly-Phe-Leu-Arg-Lys-Tyr-Pro</b>
$\beta$ h-endorphin	<b>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)</b>

#### Dynorphins:

Dynorphin A	<b>Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys-Trp-Asp-Asn-Gln</b>
Dynorphin B	<b>Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Gln-Phe-Lys-Val-Val-Thr</b>

#### Endomorphins:

Endomorphin 1	Tyr-Pro-Trp-Phe-NH <sub>2</sub>
Endomorphin 2	Tyr-Pro-Phe- Phe-NH <sub>2</sub>

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

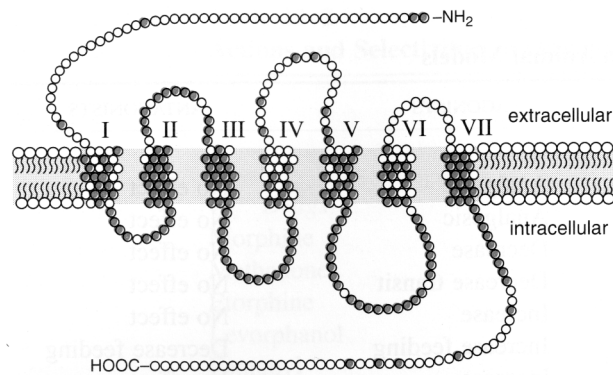
## 5. Selected Synthetic Opioid Peptides:

<b>DAMGO</b>	[D-Ala <sup>2</sup> , MePhe <sup>4</sup> , Gly(ol) <sup>5</sup> ] enkephalin
<b>DPDPE</b>	[D-Pen <sup>2</sup> , D-Pen <sup>5</sup> ] enkephalin
<b>DSLET</b>	[D-Ser <sup>2</sup> , Leu <sup>5</sup> ] enkephalin-Thr <sup>6</sup>
<b>DADL</b>	[D-Ala <sup>2</sup> , D-leu <sup>5</sup> ] enkephalin
<b>CTOP</b>	D-Phe-Cys-Tyr-D-Trp-Orn-Pen-Thr-NH <sub>2</sub>
<b>FK-33824</b>	[D-Ala <sup>2</sup> , N-MePhe <sup>4</sup> , Met(O) <sup>5</sup> -ol] enkephalin
<b>[D-Ala<sup>2</sup>] Deltorphan I</b>	Tyr-D-Ala-Phe-Asp-Val-Val-Gly-NH <sub>2</sub>
<b>[D-Ala<sup>2</sup>, Glu<sup>4</sup>] Deltorphan II</b>	Tyr-D-Ala-Phe-Glu-Val-Val-Gly-NH <sub>2</sub>
<b>Morphiceptin</b>	Tyr-Pro-Phe-Pro-NH <sub>2</sub>
<b>PL-017</b>	Tyr-Pro-MePhe-D-Pro-NH <sub>2</sub>
<b>DALCE</b>	[D-Ala <sup>2</sup> , Leu <sup>5</sup> , Cys <sup>6</sup> ] enkephalin

## 6. OPIOID RECEPTORS

Opioids bind to specific receptor molecule that mediates its effects. Several opioid specific receptors have been cloned: Mu ( $\mu$ ), Kappa ( $\kappa$ ), and Delta ( $\delta$ ) 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:



$\mu$ ,  $\delta$ , and  $\kappa$  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.
- Hyperpolarization 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

<p><math>\mu</math> receptor</p>	<p>periaqueductal gray, spinal trigeminal nucleus, cuneate and gracile nuclei, thalamus regions</p> <p>nucleus of solittract, nucleus ambiguus</p> <p>parabrachial nucleus</p> <p>neurons of the postrema</p>	<p>Pain perception (morphine analgesia)</p> <p>Morphine-control respiration</p> <p>Morphine- depress respiration</p> <p>Nauesea and vomiting</p>
<p><math>\kappa</math> receptor</p>	<p>hyphothalamic region</p>	<p>Neuroendocrine effects</p>
<p><math>\delta</math> receptor</p>	<p>dorsal horn of the spinal cord</p>	

## 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  $\kappa$  receptor and weak antagonist at  $\mu$  and  $\delta$  receptor

Nalbuphine- similar to Pentazocine but potent antagonist at  $\mu$  receptor

Buprenorphine- lipophilic, about 0.4 mg equivalent to 10 mg morphine, partial  $\mu$  agonist receptor, antagonist at  $\kappa$  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  $\mu$ ,  $\kappa$ , and  $\delta$  receptors with a 10-fold higher affinity for  $\mu$  receptor than for  $\kappa$ .

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

Compound	$\mu$	$\delta$	$\kappa$
<b>Agonists</b>			
Morphine	+++		+
Methadone	+++		+
Meperidine	++	+	+
Codeine	+	+	+
Etorphine	+++	+++	+++
Fentanyl	+++		
Sufentanil	+++	+	+
<b>Endogenous Peptides</b>			
Met-enkephalin	++	+++	
Leu-enkephalin	++	+++	
$\beta$ -Endorphin	+++	+++	
$\alpha$ -Neoendorphin	+	+	+++
Dynorphin A	++		+++
<b>Antagonists</b>			
Naloxone	---	-	--
Naltrexone	---	-	--
<b>Mixed agonists/antagonists</b>			
Pentazocine	-		+
Nalbuphine	--		++
Buprenorphine	++		--
<b>Synthetic opioid peptides</b>			
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<sub>2</sub> (i.e., depress CO<sub>2</sub> 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 retention  
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 (yep)

48 – 72 hrs:                 symptoms peak, dilated 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  $\mu$ ,  $\kappa$ , and  $\delta$ ; 10-fold higher affinity for  $\mu$  than for  $\kappa$  [This may explain why naloxone readily reverses respiratory depression with only minimal reversal of analgesia that results from agonist stimulation of  $\kappa$  receptors in the spinal cord

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