

## OPIOID ANALGESICS AND ANTAGONISTS

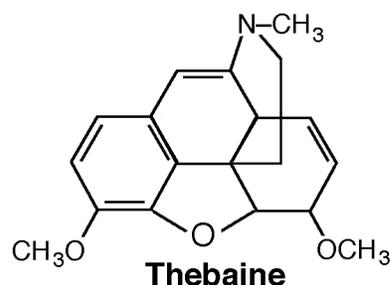
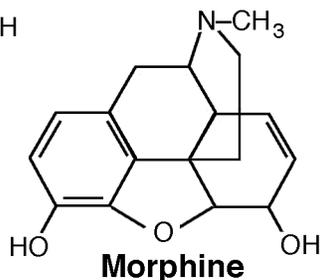
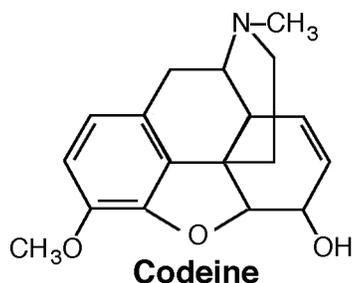
**Opiates** are drugs derived from opium and include morphine, codeine and a wide variety of semisynthetic congeners. The term **Opioid** drug is more inclusive, applying to all agonists and antagonists with activity at the mu, delta and kappa types of opioid receptor. Opioid receptors are defined as those receptors sensitive to the actions of (-) isomer of the competitive antagonist, naloxone. **Endorphin** is a generic term referring to the three families of endogenous opioid peptides: the enkephalins, the dynorphins and the beta-endorphins. The word **Narcotic** was derived from the Greek word for stupor, and it then became associated with the strong opiates, but now it is primarily a legal term referring to a wide variety of abused substances.

Opiates have been for more than 2500 years to control dysentery and pain. Opium contains more than 20 distinct alkaloids. (The principal ones are listed below). In 1806, the German chemist, Serturner first isolated a pure compound from the opium sap and called it morphine after Morpheus, the Greek god of dreams.

### Natural opium alkaloids:

These phenanthrenes are isolated from opium, which is the dried exudate from unripened seed capsules of the poppy plant *Papaver somniferum*, found in Asia Minor.

- Morphine**: 9-14% of opium by weight. This is the “gold standard” of the opiate drugs.
- Codeine**: (3-methyl morphine) (0.5% of opium) It is a less potent analgesic with much less dependence potential than morphine. It is also used as an antitussive.
- Thebaine**: (3,6-Dimethyl Morphine) (0.2% of opium) It is a non-analgesic and causes some CNS excitation. It is also a precursor for some semisynthetic opioids such as etorphine and naloxone.



## Pharmacologic Action of Morphine

*Principal uses:* control of moderate to severe pain, cough, and diarrhea

### Central Nervous System

- a. Analgesia - relief of moderate pain, intense pain becomes bearable. Effects last from 4-8 hours. A significant feature of the analgesia is that it occurs without loss of consciousness (unlike barbiturates or anesthetics).
- b. Sedation - depression, sleep-like EEG,  $\square$  anxiety.
- c. Respiratory depression: Opiates  $\uparrow$  the threshold for stimulatory effect of  $p\text{CO}_2$  on brain stem chemoreceptors. The end result is a  $\square$  respiratory drive for given level of  $p\text{CO}_2$  in plasma.
- d. Cough suppression (antitussive) – due to medullary action
- e. Mood changes – dysphoria, euphoria
- f. Mental effects – apathy, lack of concentration, unproductivity
- g. Miosis – pinpoint pupils
- h. Hypothermia –  $\uparrow$  heat loss from peripheral vasodilation and opiates affect the body temperature regulation controlled in the hypothalamus
- i. Nausea and vomiting. Morphine-like drugs directly stimulate the chemoreceptor trigger zone in the area postrema of the medulla. While a common, unpleasant side effect in many ambulatory individuals, nausea is uncommon in recumbant patients.
- j. Hypothalamic and neuroendocrine changes
  - 1) hyperglycemia – due to catecholamine release from adrenal medulla.
  - 2)  $\uparrow$  Vasopressin, Prolactin and Growth hormone release.
  - 3)  $\square$  ACTH, Luteinizing hormone (LH) and Follicle stimulating hormone (FSH). Disrupts menstrual cycles until tolerance established.
- k. Convulsions. Very high doses of morphine will cause seizures. This is a particular risk for individuals with impaired renal excretion of normeperidine (the major metabolite of meperidine).

**GI tract**      constipates — reduces peristalsis  
                     constricts sphincter of Oddi - suppressing biliary secretions)  
                     inhibition of contraction of smooth muscle by blocking Acetylcholine release

**Cardiovascular**      (peripheral vasodilation, orthostatic hypotension) Effects on the myocardium are not significant in normal individuals.

## Types of pain:

Stimulation of nociceptors causes "nociceptive pain"; damage to neural structures (nerve crush injuries) causes "neuropathic" pain. Nociceptive pain responds better to opiates than Neuropathic pain which may require substantially higher doses of opiate. Pain is often accompanied by anxiety, fear, panic and suffering which exacerbates the clinical problem; pre-emptive analgesia (e.g. give the drug before the pain) can substantially reduce the dose of opiate required.

## Therapeutic uses

- A. Severe visceral pain — A 10 mg dose of morphine relieves moderate postoperative pain in 90% of patients, and severe pain in 70%. Patients report that the pain is less-intense, less distressing, or entirely gone. Unlike local anesthetics, Opiates do not block sensation of touch, heat, or pressure.
- B. Preoperative preparation — decreases anxiety; decreases the dose required for other anesthetics. Pre-emptive analgesia reduces need for post-operative analgesics.
- C. Post operative pain — decreases pain, anxiety, shock
- D. General anesthesia — I.V. large doses
- E. Cough — antitussive (codeine is effective; the non-narcotic opiate derivative dextromethorphan has largely replaced opiates for this use)
- F. Diarrhea — morphine □ intestinal motility
- G. Terminal illness — sedation and anxiolytic effects

## Major problems

- A. Respiratory depressive effects. Death from opiate poisoning is almost always due to the respiratory depression caused by the slower rate of breathing and the reduction in the responsiveness of the brainstem centers to carbon dioxide accumulating in the blood.
- B. Muscle rigidity. High doses of opiates given during anesthesia can cause trunk rigidity and resistance to mechanical ventilation.

C. Tolerance and physical dependence

1. when repeatedly administered, tolerance develops to analgesia, resp. depression, euphoria, sedation, nausea, hypotension, hypothermia
2. less tolerance develops to miosis, CNS excitation, and constipation
3. dependence — physiologic need for continued drug administration to prevent appearance of a stereotyped withdrawal syndrome
4. characteristics of withdrawal are opposite those caused by morphine administration, e.g., □ sleep, dilated pupils, intestinal spasm and diarrhea, ↑ heart rate and blood pressure, skin resembles a plucked turkey = “cold turkey”

yawning, lacrimation, rhinorrhea, mydriasis, piloerection

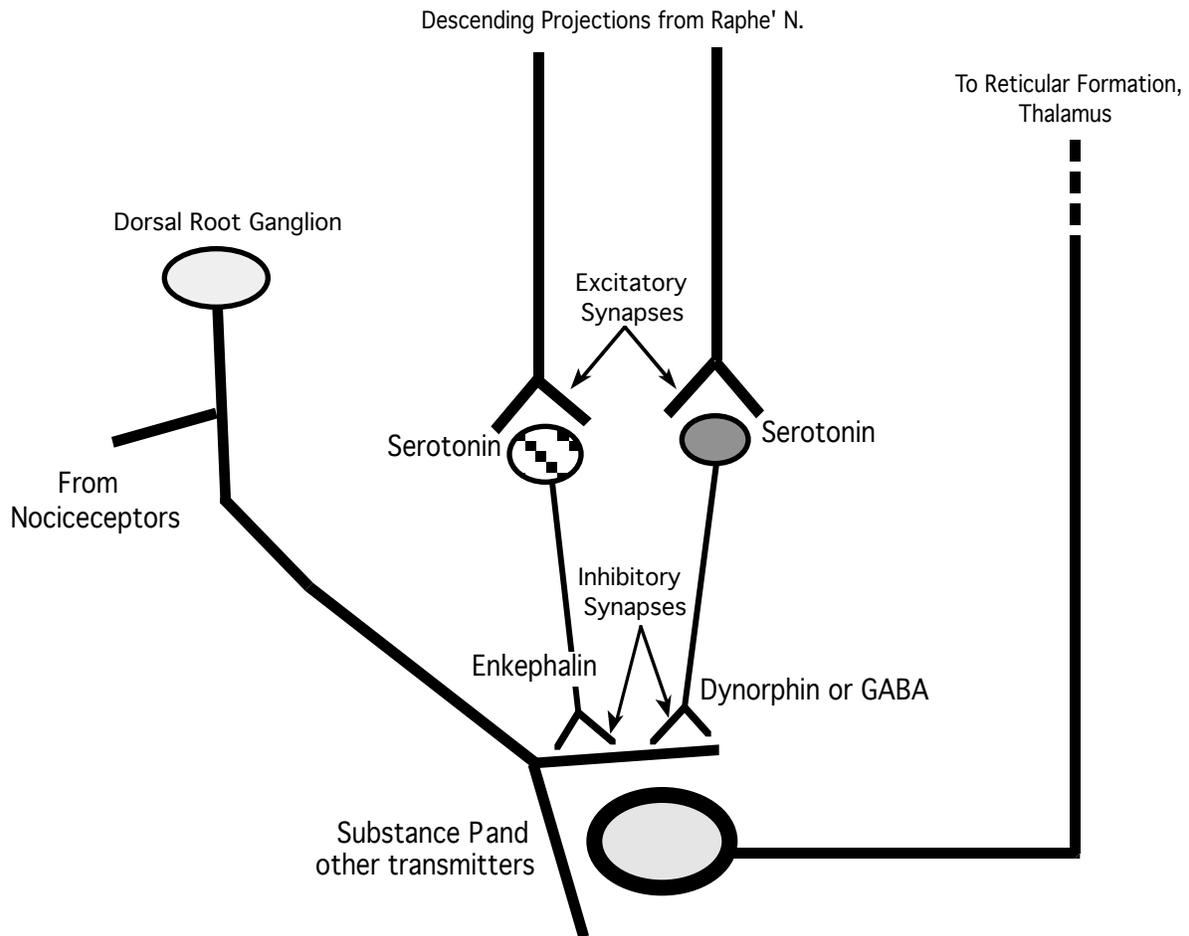
While drug abuse is a common problem with these compounds (particularly among health care workers), patients experiencing pain should not be undermedicated because of fear of drug addiction.

- D. Morphine and related alkaloids must be used with caution in patients with compromised respiratory function. Opiates can cause an increase in intracranial pressure, and cerebral edema is a serious risk for patients with head trauma.

**Mechanism of Action:**

In pain pathways, opioids selectively block nociceptive fiber (pain) transmission carried by unmyelinated C-fibers and myelinated A-delta fibers.

**Synaptic Arrangement of Dorsal Horn**



In the spinal cord, morphine produces analgesia by inhibiting transmitter release, principally glutamate and Substance P. The constipating effects in gut are produced by opioids potently inhibiting acetylcholine release and dramatically decreasing peristalsis.

## Opioid receptor subtypes

Opioid drugs act by binding to specific opioid receptors expressed on neuronal plasma membranes. With the development of mixed agonist-antagonist drugs like nalorphine which mimicked some morphine effects but were more potent than morphine in others, mu and kappa opioid receptors.

Multiple types of opioid receptors (mu and kappa), mediating different effects of opiate agonists were first postulated by Martin (1968). Delta receptors were later identified by the distinct pharmacological effects of other opioid analogues.

<b>Receptor</b>	<b>Effects <i>in vivo</i></b>
<b>Mu and Delta</b>	Analgesia (central and spinal) Respiratory depression Miosis Euphoria drowsiness, confusion, apathy nausea and vomiting Tolerance/dependence
<b>Kappa</b>	Analgesia (spinal level) Sedation Miosis Dysphoria Diuresis Tolerance/dependence

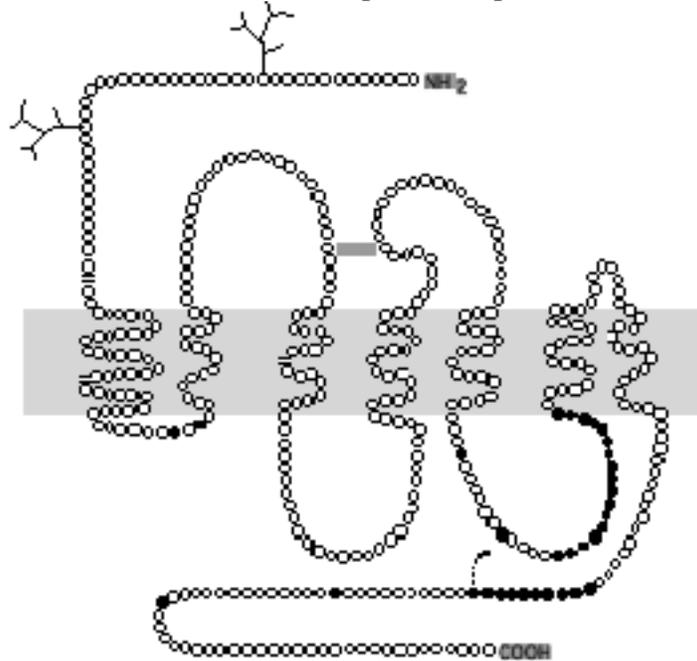
Stereospecific opiate receptors with the pharmacologic specificity of  $\mu$ ,  $\kappa$ , and  $\delta$  types have been identified in various regions of the brain and in the gut. In the brain they are found in high density in the thalamus, amygdala, caudate, hypothalamus, periaqueductal gray and the gray matter of the spinal cord.

The opioid receptors are structurally distinct and the selective agonists do not produce cross-tolerance.

Other opioid receptor types (epsilon, mu1 and mu2, kappa3, sigma) have been proposed. But a critical reading of the literature has failed to find sufficient evidence supporting the proposed existence of these other types.

## Cellular mechanism of action:

### Model of the opioid receptor



Mu, delta, or kappa receptor activation each result in the catalytic conversion of the pertussis toxin sensitive G-proteins ( $G_i/o$ ) from the GDP bound form to the GTP bound form.  $G_i \cdot GTP$  inhibits adenylate cyclase, and  $G_o$  regulates the conductance of calcium and potassium channels in the neuronal membrane. Calcium conductance is reduced and potassium conductance is increased. Both effects reduce the excitability of neurons and block neurotransmitter release.

### *Categories of Opioids: (partial listing)*

Opioid drugs are selected for specific therapeutic uses based on pharmacodynamic (selectivity, efficacy, affinity) and pharmacokinetic (distribution and metabolism) properties. A large number of analogues have been developed with the hope that a compound having less risk of respiratory depression or lower addictive liability could be found.

The principal differences between the available drugs are in opiate receptor specificity, analgesic efficacy and duration of action.

### **mu-receptor agonists**

**morphine** (described above). Readily absorbed from gut and sites of injection. Hydrophilic compound that slowly passes into the CNS. A major metabolite, Morphine-6-glucuronide is active and has effects that are indistinguishable from morphine.

**one idiosyncratic property of morphine is its ability to produce an intense itching reaction caused by a naloxone-insensitive, direct release of histamine from mast cells. Morphine has the potential to precipitate or exacerbate asthmatic attacks. (fentanyl derivatives are a better choice for analgesia with history of asthma).**

**heroin** (Diacetyl morphine) - not used clinically, but widely abused

1. more lipid soluble than morphine and penetrates CNS more rapidly
2. hydrolysed to morphine and its effects are the same

**codeine**

1. less potent analgesic (low affinity and low efficacy), but also antitussive
2. Codeine is metabolized by CYP2D6 to morphine; 10% of Caucasians and many Chinese lack the P450 isozyme that converts codeine to morphine, thus are unresponsive to codeine.

**Tramadol** (FDA approved 1995) is a **synthetic codeine analog**

Partial mu agonist

Inhibits reuptake of NE and 5HT (use caution with antidepressants, particularly MAO inhibitors)

Analgesia

Lower risk of respiratory depression than with full agonists

Unlike morphine, does not cause histamine release (pruritis)

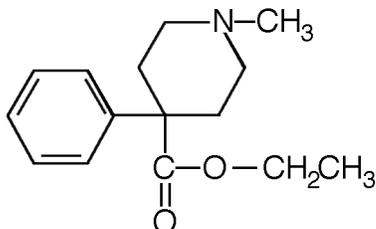
Can precipitate withdrawal in opiate dependent individuals

Active metabolite (desmethyl-tramadol)

Adverse effects: dizziness, somnolence, nausea, constipation

Seizures (not blocked by naloxone)

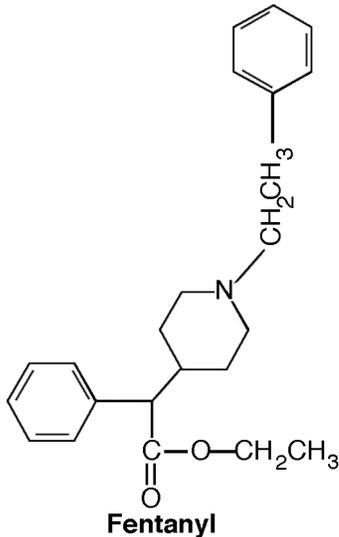
**meperidine** (phenylpiperidine) (Demerol®)



**Meperidine**

1. qualitatively identical effects to morphine (including histamine release risk), but 10 times less potent
2. shorter duration of action: < 4 hr
3. greater abuse potential because it is orally active.
4. metabolite (normeperidine) is renally excreted, and its accumulation in the blood can cause CNS arousal and seizures. Use only for acute pain.

## Fentanyl (Sublimaze®)

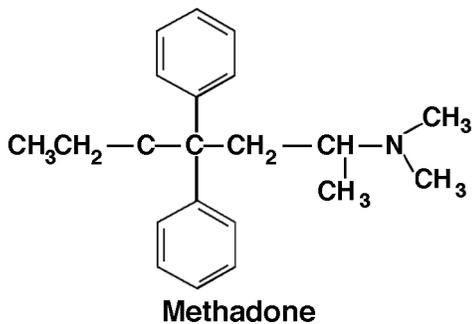


1. structural relative of meperidine
2. 100 x more potent than morphine, short duration of action (app. 1-2 hrs)
3. available in a transdermal 'patch' to provide slow release, sustained >48hr dosing.
4. widely used during anesthesia and to control post-operative pain.

## Remifentanyl (FDA approved 1996)

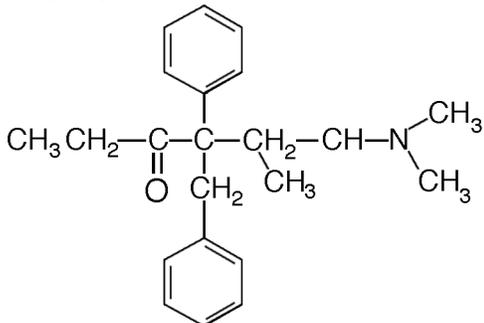
Very short acting mu opioid agonist; rapid onset - rapid offset effects are gone 5-10 min after discontinuation: thus, not desirable if post-operative analgesia is required.  
i.v. use only

## Methadone



1. orally active, long acting opiate
2. abstinence syndrome takes longer to develop with methadone
3. effect and toxicity similar to morphine; used in opiate addiction treatment

**propoxyphene (Darvon<sup>®</sup>)**



**Propoxyphene**

1. It is a structural congener of methadone;
2. weak analgesic = codeine, rather potent respiratory depressant, can cause CNS excitation, convulsions.

**oxycodone**

1. slightly more potent than morphine
2. combined with aspirin (Percodan) or acetaminophen (Percocet)

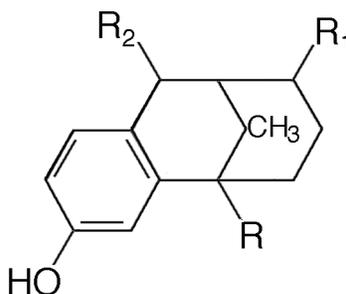
**diphenoxylate (Lomotil<sup>®</sup>)**

1. high gut activity, low abuse potential
2. used with atropine in diarrhea

**loperamide (Immodium<sup>®</sup>)**

1. not well absorbed, poorly soluble
2. low abuse potential

***kappa-receptor agonists***



**pentazocine (Talwin<sup>®</sup>)** (R=CH<sub>3</sub>, R<sub>1</sub>=CH<sub>2</sub>CH-(CH<sub>3</sub>)<sub>2</sub>, R<sub>2</sub>=H)  
(benzomorphan, like cyclazocine)

1. kappa agonist with weak mu antagonist potency
2. when given with morphine it will antagonize morphine effects
3. tolerance/dependence does develop slowly and withdrawal mild
4. Talwin-NX (pentazocine + naloxone) when taken orally, the naloxone is metabolized, when injected the naloxone precipitates withdrawal.

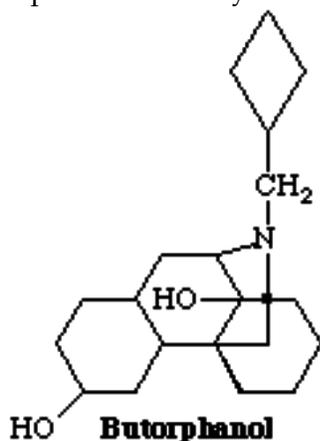
## Mixed Agonists-Antagonists

**buprenorphine** (Temgesic<sup>®</sup>) (mu partial agonist and kappa antagonist)

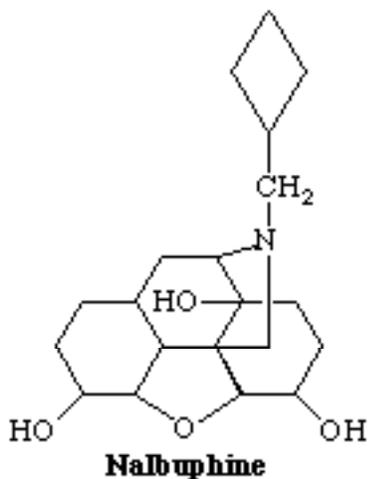
This is a lipophilic Thebaine derivative with 20-30 times morphine's analgesic potency. It has a low respiratory depression activity and some antagonist activity at the  $\kappa$  receptor. It can precipitate withdrawal. It has very mild dependence potential and appears to be a partial agonist at the  $\mu$  receptor. It may also have  $\kappa$  receptor antagonist activity.

**butorphanol** (Stadol<sup>®</sup>): (kappa agonist and mu partial agonist)

It has analgesic potency 30 times that of morphine. It has low respiratory depressant activity.



**nalbuphine** (Nubain<sup>®</sup>): effects similar to pentazocine, but 10 times more potent mu antagonist



## Antagonists

### naloxone (Narcan®)

potent competitive antagonist of the effects of morphine and its congeners and derives from N-allyl substitution of the agonist configuration, e.g. oxymorphone – Naloxone

### naltrexone (10x more potent than naloxone)

#### Postulated Effects of Agents At Three (3) Types of Opiate Receptors

	□	□	□
Morphine	++	+	+
Fentanyl	+++	+	+
Pentazocine	-	++	NA
Cyclazocine (Ethylketocyclazocine)	-	+++	NA
Nalorphine	---	-	-
Nalbuphine	-	+	NA
Butorphanol	-	++	NA
Buprenorphine	PA,-	- (weak)	NA

NA = data not available    PA = partial agonist    - = Antagonist    + = Agonist

Analgesic Used	Trade Name	Duration of Action (hours)	Doses (Mg)	
			IM, SC	Oral
<i>Morphine-like</i>				
Methadone	DOLOPHINE	4-6+	2.5-10	10
Levorphanol	LEVO-DROMORAN	4-6+	1-2	2-4
Codeine		4-5	10-30	15-60*
Oxymorphone	NUMORPHAN	4-5	1	NA
Morphine		4-5	8-10	60+
Meperidine	DEMEROL	2-4	75-100	300+
Fentanyl	SUBLIMAZE	< 1	0.05-01 (IV)	NA
Sufentanil	SUFENTA	< 1	< 1 (IV)	NA
Alfentanil	ALFENTA	< 1	< 1 (IV)	NA
<i>Selected Opioid Combination Oral Products</i>				
Codeine	Many products with aspirin and with acetaminophen		NA	7.5-60
Oxycodone	PERCODAN with aspirin		NA	5-10
	PERCOCET with acetaminophen		NA	
Hydrocodone	HYCODAN with homatropine methylbromide		NA	10
	LORCET 10/650 with 650 mg of acetaminophen		NA	10

\*Lower doses used for cough suppression (e.g., 10-20 mg for codeine), less constipation.

IM = intramuscular; IV = intravenous; NA = not applicable

## Endogenous opioid peptides

Three classes of endogenous peptide ligands for opioid receptors have been identified:

### 1. Enkephalins

- A. Methionine and leucine enkephalin  
H – Tyr Gly Gly Phe Met – OH  
H – Try Gly Gly Phe Leu – OH

Originally isolated from brain extracts. Enkephalins are biosynthesized from a 267 amino acid precursor (Proenkephalin A) containing met and leu enkephalin and C-terminally extended versions of met-enkephalin.



- ME = met enkephalin  
LE = Leu enkephalin  
ME\* = extended ME = ME + Arg Gly Leu  
ME\*\* = extended ME = ME + Arg Phe

These peptides are cleaved from the precursor by a trypsin-like enzyme

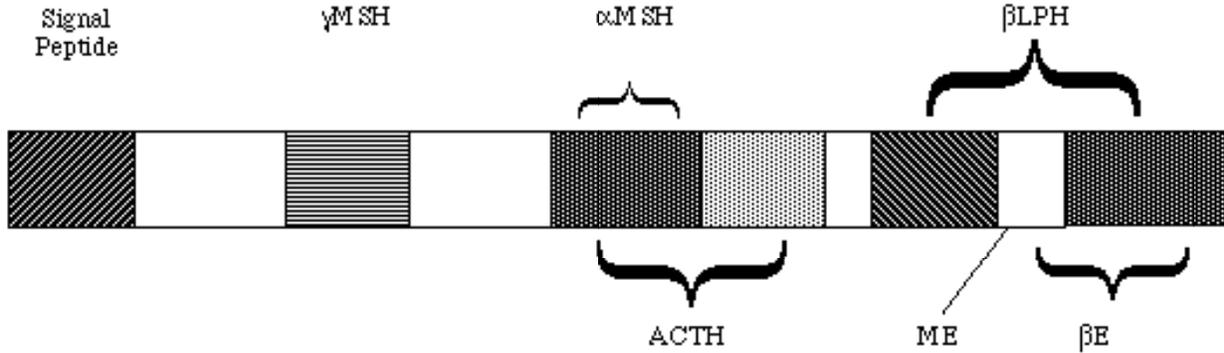
- B. Delta receptors (d = deferens)

Binding sites in gut and brain have been identified which have a higher affinity for enkephalins than morphine. They are present in greatest number in the mouse vas deferens preparation, therefore called "d" (for deferens) receptors." The  $\delta$  receptor has recently been cloned and shown to be a member of the seven transmembrane domain family.

### 2. Endorphins

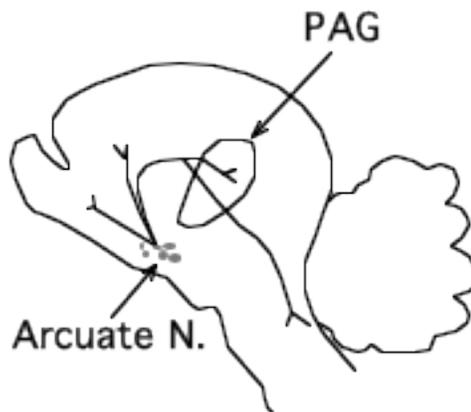
- A. Endorphins begin with Met-enkephalin sequence.  
 $\beta$ -endorphin is a 31 amino acid peptide isolated from pituitary and later brain. It is a potent analgesic and has other opiate-like effects some 1000x those of morphine's. The effects last 2-8 hours after intracranial injection. It is also not peripherally active.
- B. It is synthesized and secreted by cells of the anterior and intermediate lobes of the pituitary and the neurons of the brain. Endorphin-containing neurons have cell bodies in medial basal hypothalamus.  $\beta$ -endorphin is synthesized from a 264 amino acid precursor which also contains other neuropeptides.

Pro-opiomelanocortin (POMC)



- ME = Met enkephalin
- βE = β-endorphin
- ACTH = Adreno corticotropic hormone
- γMSH = Melanocyte stimulating hormone
- αMSH = gamma melanocyte stimulating hormone
- βLPH = β-Lipotrophin

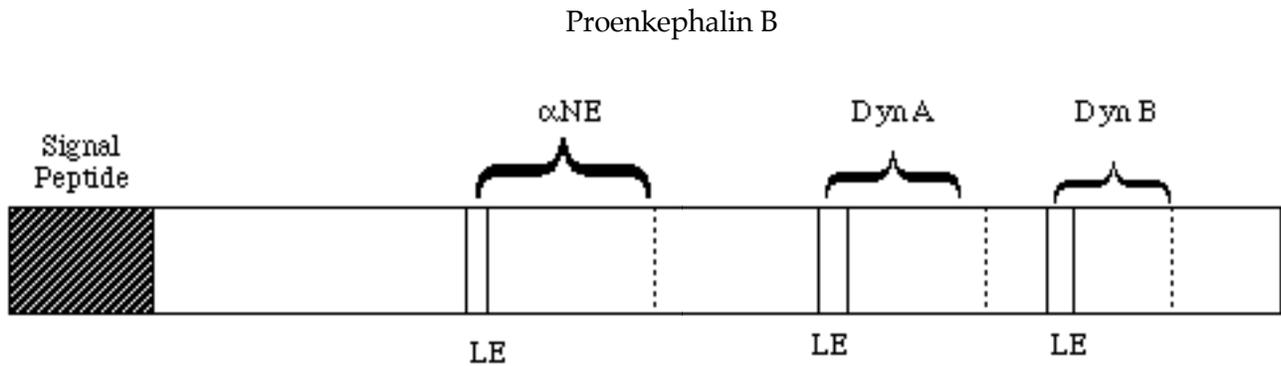
- C. Physiologically thought to act in periaqueductal gray/thalamus to block transmission in 2° and 3° pain pathways.
- D. POMC neuronal cell bodies reside in the hypothalamus



PAG = Periaqueductal Gray (Central Gray)

### 3. Dynorphin/ $\kappa$ -neo endorphin

- A. Originally isolated from posterior pituitary. In contrast to  $\mu$ -endorphin, these two peptides begin with the leu-enkephalin sequence. Dynorphin and  $\kappa$ -neo endorphin are co-synthesized in a common precursor which is distinct from Proenkephalin A and pro-opiomelanocortin precursor, called Proenkephalin B.



LE = leucine enkephalin

$\kappa$ -NE =  $\kappa$ -neo endorphin

**H Tyr Gly Gly Phe Leu Arg Lys Pro Lys - OH (10aa)**

Dyn A = Dynorphin A

**H Tyr Gly Gly Phe Leu Arg Arg Ile Arg Pro Lys Leu Lys Trp Asp Asn  
Gln - OH (17aa)**

DynB = Dynorphin B

**H Tyr Gly Gly Phe Leu Arg Arg Gln Phe Lys Val Val Thr - OH (13aa)**

- B. All these are very potent (1-10 nM kappa receptor affinity), but they are not potent analgesics when given centrally, and may be rapidly degraded. They induce kappa type analgesia (may be at the spinal level). This class of opiate peptides are the endogenous ligands for the kappa type opioid receptor. They are synthesized in neurons present throughout the brain and spinal cord.

#### *other topics of interest*

stress induced analgesia