Analgesic opioids
HISTORY:

Theophrastus (botanist) III a.c.

Arabia and use against dysentery

Morphine 1806 (Sertturner) Codeine 1832 (Robiquet)
Papaverine 1848 (Merck)

Opioid receptors (1972-73)

Different receptor types (1976)

Opioid peptides (1975)
In 1973, Martin and Snyder begin binding studies that will lead to the cloning of three main types of opioid receptors in the central nervous system: μ, δ and κ.

In 1975 Hughes and Kosterliz isolated, purified and sequenced the first two endogenous peptides with morphine-like activity called enkephalin (from brain).

Soon after, two other classes of endogenous opioid peptides, the dynorphins and the endorphins, were isolated.

In 1994 the nociceptin / orphanin FQ receptor was cloned.

In 2000, the commission of the International Union of Pharmacology adopted the terms MOP, DOP, and KOP to indicate the receptors of the opioid peptides μ, δ and κ, respectively. The commission also recommended the NOP terms for the N / OFQ receptor.
ENDOGENOUS OPIOID SYSTEM

Control and modulatory functions:

- **sensory role:** prominent in the inhibition of pain stimuli (posterior spinal cord horns, periaqueductal gray, thalamus)

- **modulatory role:** in gastrointestinal, endocrine and autonomic functions (ventral part of the brainstem, hypothalamus)

- **emotional role:** evident in the powerful reward and addictive properties of opioids (hippocampus, amygdala, limbic structures)

- **cognitive role:** in modulation of learning and memory
<table>
<thead>
<tr>
<th><strong>OPPIO ENDOGENI</strong></th>
<th><strong>STRUTTURA AMINOACIDICA</strong></th>
<th><strong>ATTIVITÀ RECETTORIALE</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Endomorfina 1</td>
<td>Tyr-Pro-Trp-Phe</td>
<td>+++</td>
</tr>
<tr>
<td>Endomorfina 2</td>
<td>Tyr-Pro-Phe-Phe</td>
<td>+++</td>
</tr>
<tr>
<td>[Leu(^5)]encefalina</td>
<td>Tyr-Gly-Gly-Phe-Leu</td>
<td>++  +++</td>
</tr>
<tr>
<td>[Met(^5)]encefalina</td>
<td>Tyr-Gly-Gly-Phe-Met</td>
<td>++  +++</td>
</tr>
<tr>
<td>Dinorfina B</td>
<td>Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Gln-Phe-Lys-Val-Val-Tyr</td>
<td>+   +        +++</td>
</tr>
<tr>
<td>b-endorfina</td>
<td>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</td>
<td>+++  +++</td>
</tr>
<tr>
<td>a-Neoendorfina</td>
<td>Tyr-Gly-Gly-Phe-Leu-Arg-Lys-Tyr-Pro-Lys</td>
<td>+   +        +++</td>
</tr>
<tr>
<td>b-Neoendorfina</td>
<td>Tyr-Gly-Gly-Phe-Leu-Arg-Lys-Tyr-Pro</td>
<td>++  +        ++</td>
</tr>
<tr>
<td>Nocicettina/Orfanina FQ</td>
<td>Phe-Gly-Gly-Phe-Thr-Gly-Ala-Arg</td>
<td>+++</td>
</tr>
</tbody>
</table>
Opioids actions
Central nervous system

Hormonal actions Increased prolactin secretion and inhibition of GHRH, CRF, ACTH, FSH, LH. Decreased release of β-endorphin

Depressive actions on the immune system

Respiratory System
Slight bronchoconstriction. Respiratory depression

Cardiovascular System
Cutaneous vasodilation and itching (histamine release). Vasodilation of the capacitance and resistance vessels: orthostatic hypotension

Gastrointestinal System
Decreased gastrointestinal secretion, decreased gastric motility. Constipation and antidiarrheal effect. Hypertonus of the sphincter of Oddi

Toxicogenic action
Tolerance. Psychic physical addiction with withdrawal syndrome
Therapeutic uses of opioids

Analgesia (eg surgery, cancer) *

Treatment of diarrhea

Treatment of cough (reflex)

Treatment of acute pulmonary edema

* Neuropatic pain
Hydrophilic

- Propoxifene
- Morphine
- Codeine
- Hydrocodone
- Methadone

Lipophilic

- Fentanyl
- Alfentanil
- Sufentanil
- Remifentanil
- Carfentanil
- Lofentanil
Treatment of pain based on severity of pain

1. Slight
   - Aspirine
   - Paracetamole
   - NSAD
   ±Adiuvants

2. Moderate
   - Codeine
   - Idrossicodone
   - Ossicodone
   - Tramadole
   - Tapentadolo
   ±Adiuvants

3. Severe
   - Morphine
   - Hydromorphone
   - Methadone
   - Levorfanolo
   - Fentanyl
   ±Adiuvants
   ±Adiuvants
Opioid Receptors
ENDOGENOUS OPIOID SYSTEM

LOCAL OPIOID RECEPTORS IN THE CNS AND INTESTINAL AND BLADDER PLEXUS
OPIOID RECEPTOR MECHANISMS

OPIOID RECEPTOR ➔ G PROTEIN

- **adenylate cyclase inhibition**
- **$K^+$ channel receptor-regulated**
- **Inhibition of Ca$^{++}$ current voltage-dependent**

- **Hyperpolarization of cell membrane**
- **Limitation of Ca$^{++}$ ions entrance**

**Inhibition of neurotransmitter release involved in pain transmission**
Mechanism of action of $\mu$ receptor agonists

Activation of $\mu$, $k$ and $\delta$ receptors on presynaptic terminals of nociceptive afferent fibers reduces the release of excitatory transmitters involved in pain (glutamate, substance P, etc.).

The activation of the $\mu$-receptors in the postsynaptic sites increases the conductance to K+ determining the onset of postsynaptic inhibitory potentials (IPSP) and consequent reduction of the discharge of neurons directed to the higher centers.
Tabella 25.2. Effetti attribuiti ai 4 recettori del gruppo oppioide e localizzazioni centrali e periferiche degli stessi recettori.

<table>
<thead>
<tr>
<th>Effetto</th>
<th>Tipi di Recettore</th>
<th>Sede</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MOP</td>
<td>DOP</td>
</tr>
<tr>
<td>Analgesia S.S.</td>
<td>+++</td>
<td>–</td>
</tr>
<tr>
<td>Analgesia S.</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Analgesia P.</td>
<td>+?</td>
<td>–</td>
</tr>
<tr>
<td>Euforia</td>
<td>+++</td>
<td>–</td>
</tr>
<tr>
<td>Dipendenza</td>
<td>+++</td>
<td>–</td>
</tr>
<tr>
<td>Disforia</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Sedazione</td>
<td>++</td>
<td>–</td>
</tr>
<tr>
<td>Memoria</td>
<td>+++</td>
<td>–</td>
</tr>
<tr>
<td>Nausea, vomito</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Depressione respiratoria</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Ipotesione, Bradicardia</td>
<td>++</td>
<td>–</td>
</tr>
<tr>
<td>Miosi</td>
<td>++</td>
<td>–</td>
</tr>
<tr>
<td>Diuresi</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Stipsi</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>ADH, Prolattina</td>
<td>+++</td>
<td>–</td>
</tr>
<tr>
<td>ACTH, LH, FSH</td>
<td>+++</td>
<td>–</td>
</tr>
<tr>
<td>Immunodepressione</td>
<td>+++</td>
<td>–</td>
</tr>
</tbody>
</table>
Localization and mechanisms of opioid receptor transduction

**Trunk and brain bulb:** breathing (CO2 center), nausea, vomiting, blood pressure, pupil diameter, stomach secretion

**Medial thalamus:** affective component

**Hypothalamus:** neuroendocrine secretion (GHRH, CRH, LH, FSH, ACTH, prolactin)

**Limbic system** (Hippo. Amyg. Ctx. N. accumbens): emotional component, gratification (dopamine)

**Spinal cord, trigeminal nerve, PAG:** pain sensorial stimuli

**Periphery:** sensory nerve endings

**Immune cells:** indeterminate role
Opioids-mediated Analgesia
1) Spinoparabrachial pathway (red), spinothalamic pathway (blue) areas concerned with both discrimination and affect

From amygdala and hypothalamus terminate in PAG. From PAG to the lower brainstem control many of the antinociceptive and autonomic responses that follow noxious stimulation

PB: nucleo parabrachiale
VMH: ipotalamo
Ce: amigdala
1) Spinoparabrachial pathway (red), spinothalamic pathway (blue) areas concerned with both discrimination and affect.

2) From amygdala and hypothalamus terminate in PAG. From PAG to the lower brainstem control many of the antinociceptive and autonomic responses that follow noxious stimulation.
Opioid Drugs
<table>
<thead>
<tr>
<th>Farmaco</th>
<th>Potenza</th>
<th>Via di somministrazione</th>
<th>Uso terapeutico</th>
<th>Effetti Collaterali</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morfina</td>
<td>++</td>
<td>i.t., i.v., s.c., p.o.?</td>
<td>Dolore Acuto e Cronico</td>
<td>Sedazione, depr. respiratoria, nausea, vomito, stipsi, euforia, tolleranza, dipendenza, prurito</td>
</tr>
<tr>
<td>Idromorfone</td>
<td>+++</td>
<td>p.o., i.m., i.v.</td>
<td>Dolore Acuto e Cronico</td>
<td>Come Morfina</td>
</tr>
<tr>
<td>Codeina</td>
<td>+</td>
<td>p.o., i.m.</td>
<td>Dolore moderato, Tossie</td>
<td>Poco sensibile a naloxone, non provoca dipendenza</td>
</tr>
<tr>
<td>Petidina Meperidina</td>
<td>+</td>
<td>p.o., i.m.</td>
<td>Dolore acuto</td>
<td>Analgesico con effetti anticolinergici; può causare eccitazione convulsioni dovute a Norpetidina</td>
</tr>
<tr>
<td>Fentanile</td>
<td>+++</td>
<td>i.v., i.t., cerotto</td>
<td>Dolore Acuto, Anestesia</td>
<td>Come Morfina, non libera istamina</td>
</tr>
<tr>
<td>Remifentanile</td>
<td>+++++</td>
<td>i.v.</td>
<td>Anestesia di breve durata</td>
<td>Come Fentanile</td>
</tr>
<tr>
<td>Metadone</td>
<td>++</td>
<td>p.o., i.m., s.c.</td>
<td>Dolore Cronico, Disintossicazione</td>
<td>Come Morfina, blando euforizzante, dipendenza diversa</td>
</tr>
<tr>
<td>Dextro propossifene</td>
<td>+</td>
<td>p.o.</td>
<td>Dolori Acuti e Cronici moderati</td>
<td>Depr. respiratoria, convulsioni dovute a Norpropossifene</td>
</tr>
<tr>
<td>Tramadolo</td>
<td>+</td>
<td>p.o., i.v.</td>
<td>Dolore Acuto postoperatorio e Cronico</td>
<td>Convulsioni, perdita di equilibrio; non causa a) depressione respiratoria; b) dipendenza; c) tolleranza</td>
</tr>
<tr>
<td>Loperamide</td>
<td>+++</td>
<td>p.o.</td>
<td>Diarrea</td>
<td>Ipertensione, tachicardia</td>
</tr>
<tr>
<td>Pentazocina</td>
<td>+</td>
<td>i.m.</td>
<td>Dolore Acuto</td>
<td>Depr. respiratoria insensibile a Naloxone</td>
</tr>
<tr>
<td>Buprenorfina</td>
<td>++++</td>
<td>i.m., sublinguale, i.t.</td>
<td>Dolore Acuto e Cronico, Disintossicazione</td>
<td>Rimbalzo da Morfina ed Eroina</td>
</tr>
<tr>
<td>Naloxone</td>
<td>+++</td>
<td>i.v., i.m.</td>
<td>Iperdosaggio, effetti collaterali di oppioidi</td>
<td>MOP, DOP, KOP</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>++</td>
<td>p.o., s.c., i.v., i.m.</td>
<td>Iperdosaggio, effetti collaterali di oppioidi</td>
<td>MOP, DOP, KOP</td>
</tr>
</tbody>
</table>
MORPHINE

PHARMACOKINETICS

Administration:
Morphine sulphate / hydrochloride
Oral; IM; SC, EV, Epidural; Intrathecal; Intraarticular

Absorption:
Oral bioavailability 25%

Distribution:
Protein binding: 30%
Cross the BBB and placenta. Plasma half-life: 2 - 3 hours

Metabolism:
Hepatic: Glucuronidation → morphine-6-glucuronide (active metabolite) → Morphine-3-glucuronide

Elimination:
Renal: metabolites (morphine-3-glucuronide)
Biliary, fecal: glucuronides (10%)
Actions of morphine

- The main pharmacological effects are:
  - analgesia. Infarto, edema polmonare,
  - euphoria and sedation
  - respiratory depression and suppression of cough
  - nausea and vomiting
  - pupillary constriction
  - reduced gastrointestinal motility, causing constipation. Motilità vie biliari
  - histamine release, causing bronchoconstriction and hypotension.
- The most troublesome unwanted effects are constipation and respiratory depression.
- Morphine may be given by injection (intravenous or intramuscular) or by mouth, often as slow-release tablets.
- Acute overdosage with morphine produces coma and respiratory depression.
- Morphine is metabolised to morphine 6-glucuronide (M6G), which is more potent as an analgesic.
- Morphine and M6G, are the active metabolites of diamorphine and codeine.
Pump for erogation of morphine
Morphine Metabolism

- Codeine
- Norcodeine
- Morphine
- Normorphine
- Morphine-3-glucuronide
- Morphine-6-glucuronide
- Codeine-6-glucuronide

Enzymes involved:
- CYP2D6
- CYP2D7
- UGT2B7
- UGT1A1
- UGT2B7

Elimination via bile and urine

UGT: UDP-glucuronosyl-transferase
Strengthening of parasympathetic eye stimulation caused by morphine
Drugs that interact with opioid analgesics

* Meperidine or pethidine blocks reuptake 5HT (pyrexia), intravenously decreases peripheral resistance and increases blood flow, dilates cerebral vessels such as morphine, does not contrast cough and diarrhea is used in obstetrics (for its brief action is used in childbirth and labor). Effective orally (as opposed to morphine) and intramuscularly
Other Opioids
Codeine

Dextromethorphan (5HT)
CODEINE PHOSPHATE (metabolite: → morphine)
Indications: Cough suppression (dry or painful cough)
Not recommended for children; Asthma; alterations of the hepatic and renal function

CHLORIDATED LOPERAMIDE (Imodium®)
Indications: Symptomatic treatment of acute diarrhea in addition to rehydration
FENTANIL  (Fentanest®)

Synthetic opioid, derived from pethidine. Receptor agonist μ

Pharmacokinetics
Administration: Citrate injectable solution. 5 mg / ml EV, IM, EPI, Transdermal Absorption: rapid
Distribution: Binding to protein: 80% Plasma half-life: 4 hours
Metabolism: Hepatic: dealkylation, hydroxylation
Elimination: Renal: (85% met. 8% no mod.) Fecal: biliary

INDICATIONS
Preoperative medication. Chronic intractable pain (transdermal systems 25-100 mg / hour)

TOXICITY
Respiratory depression, dizziness, tremors, myoclonus, convulsions. Nausea, vomiting, constipation. Pharmacodynamic interaction with BZD.
Induction and inhibition of the metabolism of other drugs
METADONE  (Eptadone®)
Syntetic Opioid, long acting

PHARMACOKINETICS

Administration: Oral 2.5-10mg - 40mg / day (drug addiction)
Absorption: rapid
Distribution: Protein binding: 70-80% Plasma half-life: 23 hours
Metabolism: Hepatic demethylation - conjugation
Elimination: Renal 21% unchanged Fecal: biliary

INDICATIONS

Treatment of acute and chronic pain. Treatment of opioid addiction

TOXICITY

Respiratory depression, nausea, vomiting
Stabilizing effect of methadone
TRAMADOL (Contramal®)

Synthetic opioid

Low binding $\mu$ receptors- inhibits NA and 5-HT reuptake

**PHARMACOKINETICS**

Administration: IM 50-100 mg x4 / day Oral, EV Absorption: large (2 h)

Distribution: Protein binding 20% Plasma half-life 6 hours

Metabolism: Hepatic conjugation demethylation

Elimination: Renal 60% met 30% immod Fecal 10%

**INDICATIONS**

Postoperative pain treatment. Obstetric analgesia. Neoplastic pain. It is NOT indicated as an analgesic in balanced anesthesia for intraoperative consciousness increase

**TOXICITY**

Low incidence of respiratory and cardiac depression and low potential for addiction
Antagonists of opioid receptors
NALOXONE  (Narcan®)  Direct Antagonist

PHARMACOKINETICS

Administration: EV 0.4-2 mg up to a maximum of 10 mg  
Absorption: Bioavailability oral low  
Distribution: Plasma half-life 30-80 min  
Metabolism: Hepatic large Glucuronidation  
Elimination: Renal glucuronides  

INDICATIONS  

Diagnosis and treatment of opioid overdose  

TOXICITY  

Hypotension, hypertension, cardiac arrhythmias. Pulmonary edema. Opioid withdrawal symptoms
NALTREXONE (Antaxone®, Nalorex®, Narcoral®) Antagonist

PHARMACOKINETICS

Administration: Oral 50 mg / 100 mg
Absorption: Bioavailability oral 40%
Distribution: Protein binding 21% Half-life 4 h
Hepatic metabolism: extensive conjugation
Elimination: Renal 60% conjugated. Fecal 3%

INDICATIONS

Treatment of opioid addiction

TOXICITY

Nausea, vomiting, abdominal pain. Constipation. Anxiety, nervousness, irritability
Withdrawal Syndrome

8-12 hrs
- lachrymation
- rhinorrhea
- yawning
- sweating
- mydriasis
- anorexia
- restlessness
- irritability
- tremor

24-72 hrs
- pupillary dilation,
- tremor
- anorexia
- intestinal spasms,
- vomiting, diarrhea, weight
- loss, chills, skin redness,
- abdominal cramps, bone
- and muscle pain

7-10 days
- Lack of food intake; vomiting, sweating, and diarrhea
- cause dehydration; ketosis, acid-base balance disturbance
- insomnia, increased arterial blood pressure and body
- temperature
Opioid dependence and abuse
Definition of “Abuse”

Non-therapeutic use of the substance

Self-administration of a substance in ways that deviate from shared medical and social norms
Definition of “DRUG ADDICTION”

Pathological condition characterized by loss of control of consumption behavior and serious consequences on the social life of the individual.
DRUG ADDICTION IS RELATED TO THREE FACTORS

1) The substance of abuse

2) The consumer

3) The social environment in which the meeting between the substance and the consumer takes place
Drug addiction must be considered as a "chronic disease" of a recurring nature and development.

A drug addict is an individual who, as a result of repeated administration of a substance of abuse, becomes:

1) Dependent on the effects of the substance taken

2) Has an uncontrollable desire to continue taking it (CRAVING)

3) It shows a marked tendency to increase the dose
Opioids Tolerance
Opioids Tolerance

Hypothesized Mechanisms

- **Short term:** reduction of the coupling between the opioid receptor and the G protein, with loss of the ability to exchange GDP with GTP.

- **Long-term:** receptor desensitization, receptor internalization, phosphorylation of the intracellular receptor loops and reduction of the opioid agonist's efficacy

- **Reduction in intracellular sodium levels with reduced activity of Na/K-ATPase**
OVERDOSE

SYMPTOMS

Pupil miosis with non reactive pupils to a light stimulus
Superficial respiration with 2/3 breaths / min

Body temperature: hypothermia
Reduced or absent osteo-tendon reflexes
Rhabdomyolysis
Acute cyanosis
Cardiovascular system bradycardia / severe hypotension
Central nervous system severe respiratory depression
absence of response to external stimuli; brain anoxia

EVOLUTION

acute cardiorespiratory failure
coma - death

THERAPY

Opioid antagonists maintenance of airway patency
(assisted ventilation, oxygen) maintenance of
circulation, contrast of convulsions
Weaning
<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substitution, to alleviate withdrawal symptoms</td>
<td>Methadone, used short-term to blunt opiate withdrawal Buprenorphine</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-term substitution</td>
<td>Methadone substitution for opiate addiction Buprenorphine, levo-acetilmetadolo LAAM,</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Blocking response</td>
<td>Naltrexone to block opiate effects</td>
</tr>
<tr>
<td>Modification of craving</td>
<td>Bupropion (antidepressant) Naltrexone (blocks opiate receptors—also of value in treating other addictions) Clonidine (α2-adrenoceptor agonist) Acamprosat (GABA)</td>
</tr>
</tbody>
</table>
Effects of *buprenorfina* vs placebo