Neuroscience system

Opioid Analgesics

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ILOs:

1-Identify opioid receptors.

2-Recognize the uses, adverse effects and contraindications of morphine.

3-Describe the manifestation and the management of morphine toxicity.

4-Know classification of opioids.

5-Distinguish the mechanism of action of opioids.

Definition:

- Opioid analgesics are drugs which, while providing relief from pain, *produce drowsiness, changes in mood and mental clouding.*
- Opiates are drugs *derived from opium*, a natural product derived from *Papaver Somniferum* plant; and include the natural products morphine, codeine, and thebaine, and many semisynthetic derivatives.

Classification of opioids:

I-Morphine and related opioids:

Morphine Codeine Tramadol Heroin Levorphanol

II-Meperidine and congeners:

Meperidine Fentanyl Diphenoxylate Loperamide

III-Methadone and congeners:

Methadone Propoxyphene

IV-Mixed Agonist-Antagonists and Partial Agonists:

Pentazocine Butorphanol Nalbuphine Buprenorphine

Opioid Receptors:

These receptors and the corresponding actions include:

1-μ (mu):

- μ_1 : supraspinal analgesia
- μ_2 : spinal analgesia, respiratory depression, sedation, euphoria, miosis and decreased GIT motility.

2-κ (Kappa): spinal analgesia, dysphoria, hallucinations, less intense miosis and respiratory depression than do μ receptors.

3-δ (delta): the effects in human beings are unclear although they may produce analgesia at both spinal and supraspinal levels

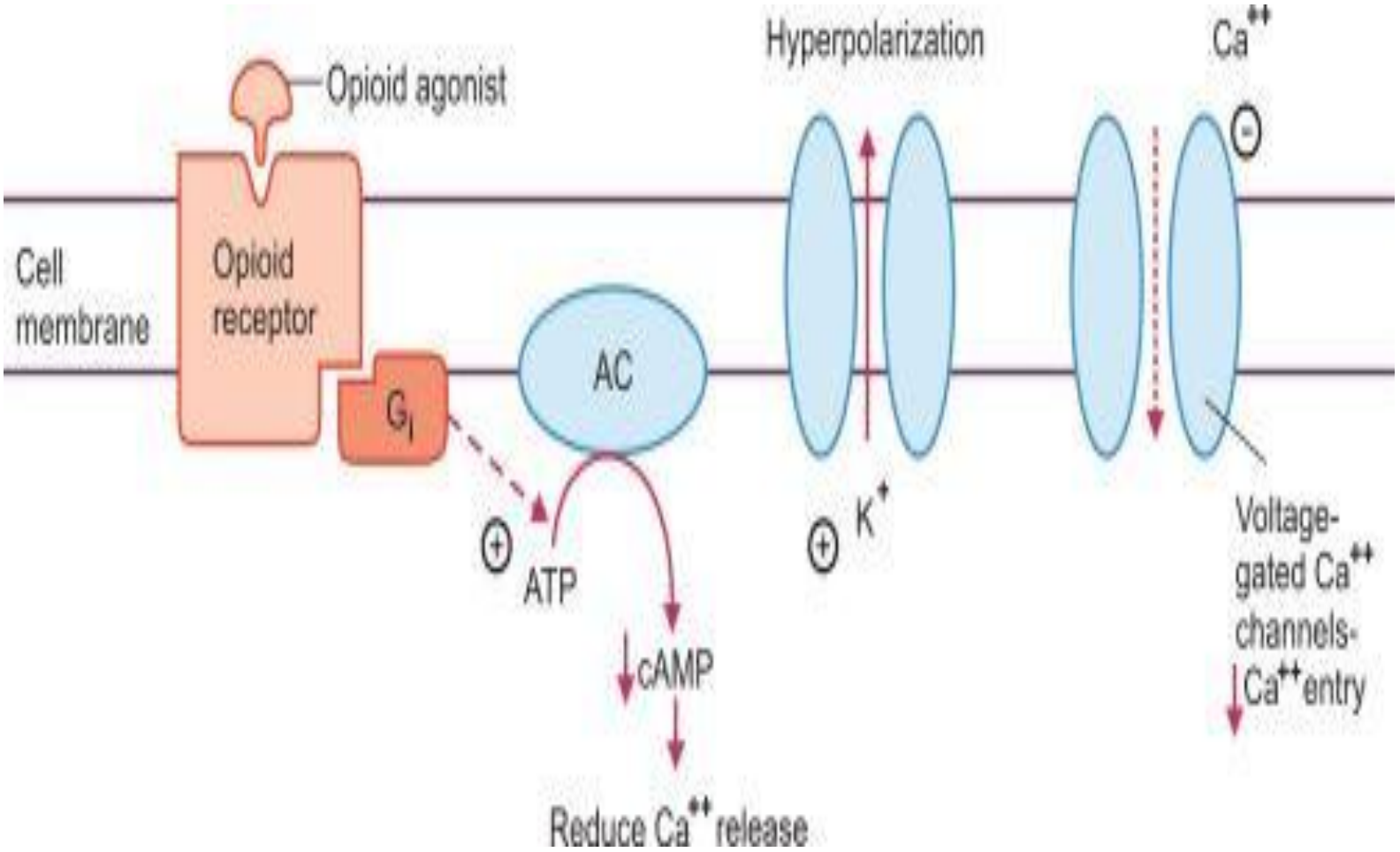
Mechanism of Action:

- Opioid agonists produce analgesia by *binding to specific G protein-coupled receptors* that are located in CNS and other tissues.
- These receptors are present in high concentrations in the limbic system, thalamus, hypothalamus, corpus striatum, brainstem and spinal cord.

A-The opioids have two well-established direct G protein-coupled actions on neurons:

(1) *They close voltage-gated Ca^{2+} channels* on presynaptic nerve terminals and thereby *reduce transmitter release.*

(2) *They hyperpolarize* and thus inhibit postsynaptic neurons by *opening K^{+} channels*.


Opioid agonist
Cell membrane
Opioid receptor
G_i
AC
ATP
cAMP
Reduce Ca^{++} release
Hyperpolarization
K^+
Ca^{++}
Voltage-gated Ca^{++} channels-
Ca^{++} entry

- The presynaptic action (depressed transmitter release) has been demonstrated for *release of a large number of neurotransmitters including* glutamate, the principle excitatory amino acid released from nociceptive nerve terminals, as well as acetylcholine, norepinephrine, serotonin, and substance P.

B-Opioid receptors also regulate the activity of certain enzymes (inhibit adenyl cyclase and reduce the intracellular cAMP content).

Therapeutic uses:

1-Analgesia:

- *Severe, constant or acute* (lasting hours to days) *pain* is usually relieved with opioid analgesics; whereas sharp, intermittent pain does not appear to be as effectively controlled. Also, chronic pain (lasting weeks to months) is not very satisfactorily managed with opioids.

- *For relief of sudden agonizing pain*, morphine is usually *given IV* to produce immediate relief and minimizes shock.
- *Extensive use* of morphine in *postoperative analgesia should be avoided* as it may produce respiratory depression, urinary retention and constipation, it may mask the signs of recovery and prevent the early recognition of complications.

2-Cardiac asthma with Pulmonary Edema:

- The relief produced by intravenous morphine in dyspnea from pulmonary edema associated with left ventricular heart failure is remarkable.
- Proposed mechanisms include *reduced anxiety* (*perception* of shortness of breath), *decrease respiratory effort* and *reduced cardiac preload* (reduced venous tone) *and afterload* (decreased peripheral resistance).

NB:

- If *respiratory depression* is a problem, *furosemide* may be *preferred* for the treatment of pulmonary edema.
- On the other hand, morphine can be *particularly useful* when treating painful *myocardial ischemia with pulmonary edema*. Nitroglycerin is *superior* to morphine in this condition.

3-Cough:

- Suppression of cough (useful in dry non-productive cough) can be obtained at *doses lower than those needed for analgesia* eg, codeine .
- However, *in recent years* the use of opioid analgesics to suppress cough has diminished largely because *a number of effective synthetic compounds* have been developed that are *neither analgesic nor addictive*.

4-Diarrhea:

- Diarrhea *from almost any cause* can be controlled with the opioid analgesics, but if diarrhea is associated with infection such use must not substitute for *appropriate chemotherapy.*
- Now *synthetic surrogates* with *more selective gastrointestinal effects* and *few or no CNS effects*, eg, diphenoxylate or loperamide, are used.

5-Shivering:

- Although all opioid agonists can reduce shivering, meperidine is reported to have the most pronounced anti-shivering properties.
- Meperidine apparently blocks shivering mainly through an action on subtypes of *the* α_2 *adrenoceptor*.

6-Applications in Anesthesia:

- The opioids are frequently used as *premedicant* drugs before anesthesia and surgery because of their sedative, anxiolytic, and analgesic properties.
- They are also used *intraoperatively* both as *adjuvants* to other anesthetic agents and, in high doses (eg, fentanyl), as a *primary component* of the anesthetic regimen.

- Opioids are most commonly used in *cardiovascular surgery and other types of high-risk surgery* in which a primary goal is to *minimize cardiovascular depression* (eg. Fentanyl or sufentanil). In such situations, mechanical respiratory assistance must be provided.
- Opioids can also be used as regional analgesics by administration into the epidural or subarachnoid spaces of the spinal column.

Adverse effects:

1-Direct toxic effects of the opioid analgesics:

Which are extensions of their acute pharmacologic actions and include:

- Respiratory depression, nausea, vomiting, constipation (may be serious in old people and precipitate intestinal obstruction), increased intracranial pressure, postural hypotension accentuated by hypovolemia.

- Urinary retention, increased pressure in the biliary tract, dizziness, mental clouding, itching around nose, urticaria (more frequent with parenteral and spinal administration) and, behavioral restlessness, tremulousness, hyperactivity (in dysphoric reactions).

2-Tolerance and dependence:

A-Tolerance:

- Although development of tolerance begins with the first dose of an opioid, tolerance generally does not become clinically manifest until after 2–3 weeks of frequent exposure to ordinary therapeutic doses.
- Tolerance develops most readily when large doses are given at short intervals and is minimized by giving small amounts of drug with longer intervals between doses.

- ***Degrees of Tolerance:***

High: Analgesia, euphoria, dysphoria, mental clouding, sedation, respiratory depression, antidiuresis, nausea, vomiting and Cough suppression.

Moderate: Bradycardia

Minimal or None: Miosis, constipation and convulsions.

- *Cross-tolerance* is an extremely important characteristic of the opioids, not only with respect to their analgesic actions but also to their euphoriant, sedative, and respiratory effects.
- Tolerance to morphine is attributed to adaptation of cells in the nervous system to the drug action (*pharmacodynamics tolerance*).
- Tolerance can be reversed by NMDA receptor antagonist and nitric acid synthase inhibitors.

B-Dependence:

1-Physical dependence:

- The development of physical dependence is usually associated with *tolerance* to repeated administration of an opioid of the μ type.
- Failure to continue administering the drug results in a *characteristic withdrawal or abstinence syndrome* that reflects an exaggerated rebound from the acute pharmacologic effects of the opioid.

- *The signs and symptoms* of withdrawal include rhinorrhea, lacrimation, yawning, chills, piloerection, hyperventilation, hyperthermia, mydriasis, muscular aches, vomiting, diarrhea, anxiety, and aggression.
- With morphine, withdrawal signs usually start within 6–10 hours after the last dose. Peak effects are seen at 36–48 hours. By 5 days, most of the effects have disappeared, but some may persist for months.

Symptoms of Opioid Withdrawal

Nausea and cramping

Anxiety

Vomiting

Insomnia

Irritability

Muscle aches and joint pain

verywell

❖ Abstinence Syndrome:

- Results not only from *drug withdrawal* but also ***antagonist-precipitated withdrawal*** which can be induced in a subject physically dependent on opioids by administering naloxone or or another antagonist.
- Within 3 minutes after injection of the antagonist, signs and symptoms similar to those seen after abrupt discontinuance appear, peaking in 10–20 minutes and continues until the antagonist is eliminated.

❖Treatment of morphine addiction:

Consists of its replacement by another narcotic analgesic that shows *cross dependence* with morphine and its *withdrawal syndrome is mild*.

Methadone orally is used. Once the patient is stabilized on methadone, its dose is gradually reduced by 20% daily.

Buprenorphine (a partial agonist) is as effective as methadone.

Levo-α-acetylmethadol (μ full agonist) also used.

- *Another approach* is to use:

Clonidine, an α_2 adrenergic agonist which is effective in *suppressing autonomic hyperactivity* manifestations observed in abstinence syndrome.

Lofexidine, a similar drug with *greater affinity* for α_2 receptors and *less hypotension* that limits usefulness of clonidine.

2-Psychologic Dependence:

- The *euphoria*, *indifference to stimuli*, and *sedation* usually caused by the opioid analgesics, especially when injected intravenously, tend to promote their compulsive use.
- These factors constitute the *primary reasons for opioid abuse* liability and are strongly reinforced by the development of *physical dependence.*

Contraindications and Cautions in Therapy:

1-Use in asthmatic patients:

- Is hazardous as it *depresses the respiratory center and cough reflex*, *releases histamine* and tends to *dry secretions*, so if used, should be with extreme caution.

2-Use in Patients with Head Injuries:

- Carbon dioxide retention caused by respiratory depression results in cerebral vasodilation.
- In patients with elevated intracranial pressure, this may lead to *lethal alterations in brain function*.
- Morphine also produces *miosis* and *mental clouding* that may interfere with the diagnosis.

3-Use during Pregnancy and labor:

- *In pregnant women who are chronically using opioids*, the *fetus* may become *physically dependent* in utero and manifest withdrawal symptoms in the early postpartum period including irritability, shrill crying, diarrhea, or even seizures.
- When morphine is administered to the *mother during labor*, it crosses the placental barrier and the fetus may exhibit (*asphyxia neonatorum*). So morphine *should be avoided if delivery is expected within 4-5 hours*.

4-Use in Patients with Impaired Pulmonary Function:

- In patients with *borderline respiratory reserve* as in emphysema, kyphoscolioisis, severe obesity and chronic corpulmonale, the *depressant properties* of the opioid analgesics *may lead to acute respiratory failure*.

5-Use in Acute Abdomen:

- *Pain* is a chief diagnostic symptom and its total *abolition* may *interfere with the diagnosis*.

6-Use in Patients with Impaired Hepatic or Renal Function:

- Because morphine and its congeners are *metabolized primarily in the liver*, patients with *hepatic dysfunction* are not able to tolerate morphine.
- Half-life is prolonged in patients with *impaired renal function*, and morphine and its active glucuronide *metabolite may accumulate*; dosage can often be reduced in such patients.

7-Use in Patients with Endocrine Disease:

- Patients with *adrenal insufficiency* (Addison's disease) and those with *hypothyroidism* (myxedema) may have prolonged and *exaggerated responses* to opioids.

8-Use in Patients with Reduced Blood Volume:

- Are more susceptible to the *hypotensive effect* of morphine and therefore should be used with caution in any type of *heamorrhage*.

9-Use of Pure Agonists with Weak Partial Agonists:

- When a *weak partial agonist* such as pentazocine is *given* to a patient also receiving a *full agonist* (eg, morphine), there is a risk of diminishing analgesia or even inducing a state of withdrawal; combining full agonist with partial agonist opioids should be avoided.

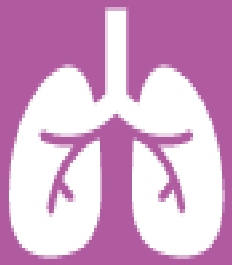
ACUTE OPIOID TOXICITY:

- Acute opioid toxicity may *result from clinical overdosage*, *accidental overdosage in addicts*, or *attempts at suicide*.
- It is difficult to define the exact amount of any opioid that is toxic or lethal to humans but in a normal pain free adult, a dose of 60 mg of morphine is usually toxic and a dose of 200mg is usually fatal.

Symptoms and diagnosis:

- The triad of *coma*, *pinpoint pupils*, and *depressed respiration* strongly suggests opioid poisoning.
- Urine formation is depressed, body temperature falls, and the skin becomes cold and clammy. The skeletal muscles are flaccid, the jaw is relaxed, and the tongue may obstruct the airway. Frank convulsions occasionally occur in infants and children.

During an Emergency Overdose Look For:



Respiratory Depression

Pinpoint Pupils

Unconsciousness

THE FOLLOWING SIGNS AND SYMPTOMS MAY INDICATE AN OPIOID OVERDOSE EMERGENCY:

UNUSUAL SLEEPINESS OR NOT ABLE TO AWAKEN

BREATHING WILL BE SLOW OR ABSENT

SLOW HEARTBEAT OR LOW BLOOD PRESSURE

SKIN FEELS COLD AND CLAMMY

PUPILS ARE TINY

NAILS AND LIPS ARE BLUE

- When death ensues, it is nearly always from respiratory failure.
- Even if respiration is restored, death still may occur as a result of complications that develop during the period of coma, such as pneumonia or shock.
- Noncardiogenic pulmonary edema is seen commonly with opioid poisoning.

Treatment:

- *Opioid antagonists* can produce dramatic reversal of the severe respiratory depression; naloxone is the treatment of choice but should be used with care as it *may produce severe withdrawal syndrome* which is sometimes more life threatening than the respiratory depression itself.

Opioid Antagonists

The antagonism is *competitive* in nature

❖Naloxone:

1-It has a *pure* antagonistic activity by binding to opioid receptors.

2-Usually given by *injection* and has a *short duration* of action.

Uses:

1-Treatment of *acute opioid poisoning*.

2-To counteract neonatal opioid-induced *fetal asphyxia*.

3-Diagnosis of *opioid addiction*.

❖Naltrexone:

1-It is a *pure* antagonist with high oral efficacy (given orally).

2-It is *more potent* than naloxone and has *longer duration* of action (about 24 hours).

Uses:

1-It can be used in ***ex abusers*** to opioids who are fully withdrawn as it will block the effects of self administered opioids.

2-It is approved for *treatment of alcoholism*.