Practical Clinical Toxicology

Toxicity of Opioids

Lab.8
5th Year

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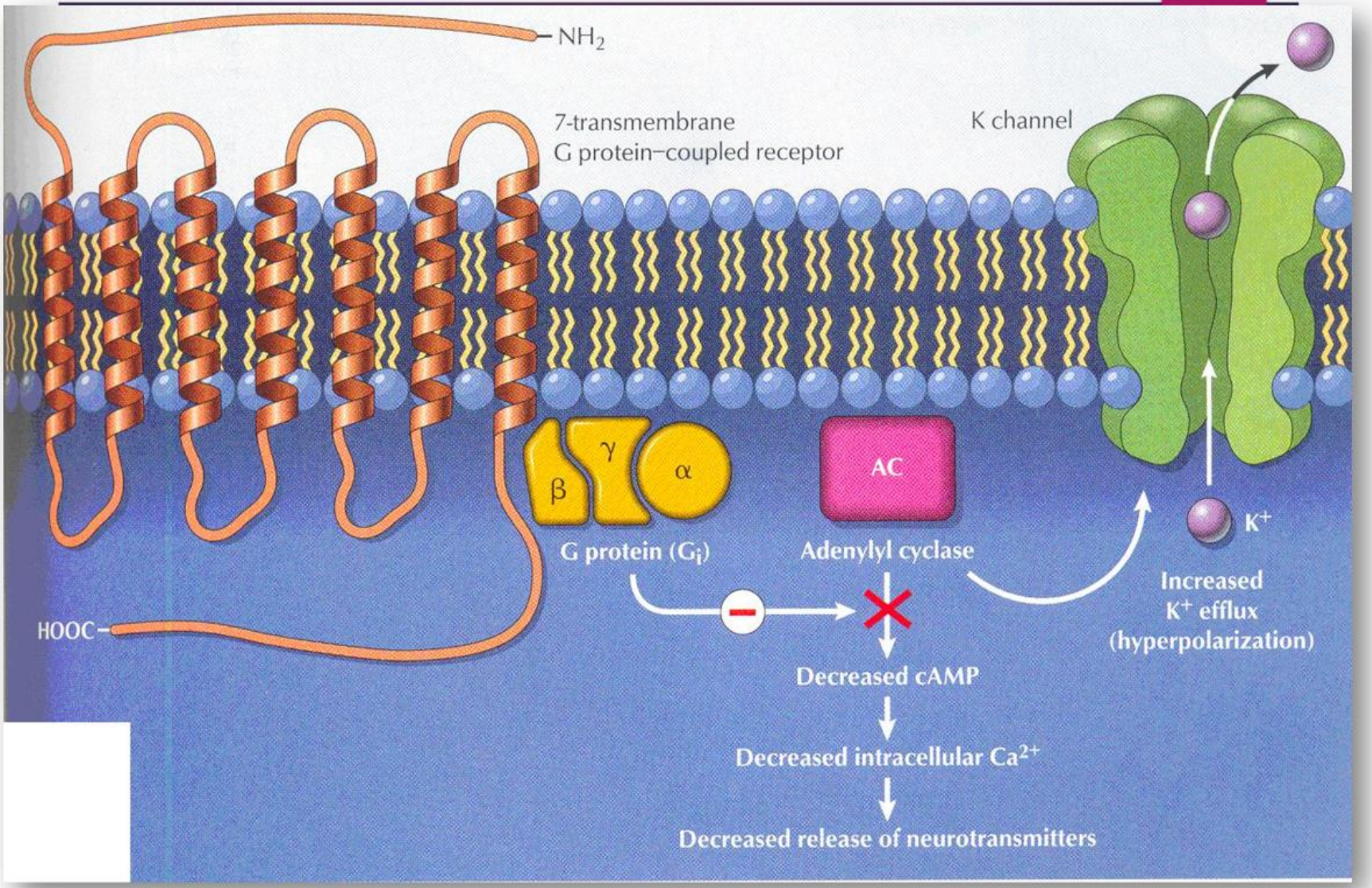
- Opiates are medications derived from the opium poppy.
- The most widely used and effective narcotic analgesics are derived from opium alkaloids.
- Opioids are all substances that bind to the opioid receptors.
- They include endogenous substances as well as all exogenous opium-derived and synthetic drugs that interact with opioid receptors

- Opioids are used to treat acute pain and palliative care to alleviate the severe, chronic, disabling pain of terminal conditions such as cancer, and degenerative conditions such as rheumatoid arthritis
- Opioids are used to treat moderate to severe pain (particularly of visceral origin) that may not respond well to other pain medications
- Induce reduction in response to a noxious (painful) stimulus.


NH2
7-transmembrane
G protein–coupled receptor
K channel
γ
β
α
AC
G protein (Gi)
Adenylyl cyclase
K+
Increased
K+ efflux
(hyperpolarization)
HOOC
Decreased cAMP
Decreased intracellular Ca2+
Decreased release of neurotransmitters

The main opioid receptors that mediate the effects of opioids are mu, kappa, and delta.

Mu receptors mediate analgesia, euphoria, sedation, respiratory depression, gastrointestinal dysmotility, and physical dependence.

Kappa receptors mediate analgesia, diuresis, miosis, and dysphoria.

Delta receptors mediate analgesia, inhibition of dopamine release, and cough suppression.

Opioids pharmacology

Gastrointestinal System

- Stimulation of the chemoreceptor trigger zone causes nausea and vomiting
- Smooth muscle tone is increased but motility is decreased resulting in delayed absorption, and constipation

Central Nervous System

- Analgesia
- Sedation: Drowsiness
- Euphoria and dysphoria
- Hallucination
- Tolerance
- Dependence

Respiratory System

- Respiratory depression: Opioids suppress cough

Cardiovascular System

- Mild bradycardia: a direct effect on (SA) node
- Vasodilatation: histamine release
- reduced sympathetic drive

- Endocrine System: Inhibit ACTH, prolactin and gonadotrophic hormone is inhibited. Increase ADH
- Ocular effects: Miosis
- Immunity: depress the immune system after long-term opioid abuse

Toxicity

1. Nausea and vomiting
2. Drowsiness or sedation
3. Skin changes: allergic reaction, causes a skin rash characterized by red, itchy, raised bumps, This is caused by the release of histamine in response to opioid
4. Constipation
5. Respiratory depression
6. Psychological effects: Opioids give rise to a sense of euphoria and may also lead to hallucinations, delirium, dizziness and confusion
7. Changes in heart rate
8. Spasms: urinary retention or biliary
9. Dependence and likelihood of abuse

Treatment / Management

If the patient is comatose and in respiratory distress, airway control must be obtained.

Endotracheal intubation is highly recommended for all patients who are unable to protect their airways. naloxone should be administered to reverse the respiratory depression.

However, one should be aware that naloxone can also cause agitation and aggression when it reverses the opiate. If the individual is a drug abuser, the lowest dose of naloxone to reverse respiratory apnea should be administered.

Naloxone is a pure competitive antagonist of opiate receptors and has no agonistic activity.
For patients overdosed on diphenoxylate, methadone, butorphanol, nalbuphine, and pentazocine, higher doses of naloxone are required.
Besides naloxone, the 2 new agents on the market to reverse opiate toxicity are nalmefene and naltrexone.
Nalmefene has a half-life of 4 to 8 hours, whereas naltrexone has a half-life of 8 to 12 hours.
However, the routine use of these longer-acting opiate antagonists is not recommended because of the fear of precipitating a prolonged period of opiate withdrawal.

In patients who have taken large doses of propoxyphene, methadone, diphenoxylate/atropine or fentanyl, much larger doses of naloxone are usually required to reverse the toxicity.

If the patient is alert at the time of admission, activated charcoal can be used within 1 hour of ingestion of a drug to be effective, with opiates, there is slowing of gastric motility, and hence, activated charcoal can be given as late as 2 to 3 hours after ingestion

- **Naloxone and naltrexone**
  - **Commonly used opioid antagonist**
  - **Partial inverse agonist**
  - **Competitive antagonists that bind to the opioid receptors with higher affinity than agonists**
  - **Antidote drug for treating opioid overdose**
- **nalorphine and levallorphan**
  - **Partial agonist effects**
  - **Produce limited analgesic effects when administered in high doses.**
  - **Buprenorphine in combination with naloxone is widely available and is used to treat opiate use disorder. This formula has also been used in narcotic overdose. The big advantage of using this combination is that it reduces withdrawal symptoms for 24 to 36 hours**

Case 1:

A 19-year-old woman with a history of psychiatric illness, weighing 70 kg, ingested 200 tablets which contained a total dose of 2.3 g codeine base & and 1.7 g phenobarbital. She arrived at an emergency facility in a deep coma with miotic pupils & and shallow respirations.

The patient was given two intravenous injections of **naloxone,** 0.4 mg each dose, after which there was significant improvement in her respiratory status & and slight dilation of the pupils. The gastric contents were found to contain large amounts of codeine.

The patient was further treated with a continuous drip of nalorphine, 0.7 μg/kg/min, but after 36 hr there was no improvement in neurologic status.
Naloxone was not available in the hospital in sufficient quantity, which accounted for the change in medication. A 6-hour hemodialysis was unsuccessfully tried.

The nalorphine drip was discontinued 5 days later & the patient's respiratory condition remained satisfactory. There were signs of brainstem damage. The patient died suddenly during a convulsive crisis 10 days after admission.