# Opioids

# Overview

- Management of pain is one of clinical medicine's greatest challenges
- Pain is defined as an unpleasant sensation that can be either acute or chronic and is a consequence of complex neurochemical processes in the peripheral and central nervous systems (CNS)
- The type of pain affects the drug used
- Nociceptive pain (NSAID's) or Neuropathic pain (antiepileptics, SNRIs) →opioids may be used
- Management of severe or chronic malignant or nonmalignant pain (relieving of intense pain) → opioids

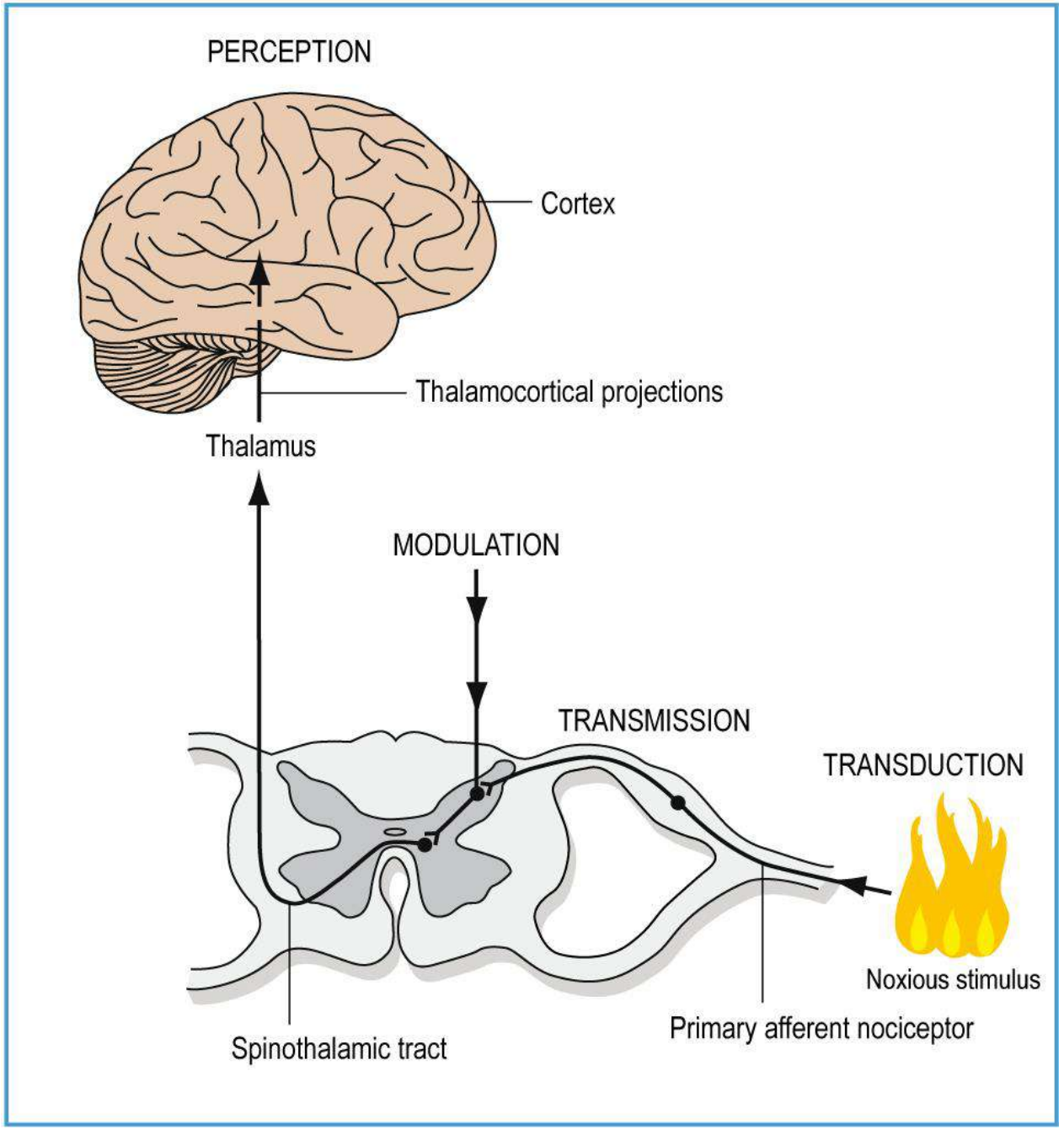
# Overview

- Opioids, sometimes called narcotics, are a group of drugs that act on the central nervous system to produce morphine-like effects such as pain relief and **euphoria (abuse)**
- All opioids act by binding to specific opioid receptors in the CNS to produce effects that mimic the action of endogenous peptide neurotransmitters (for example, endorphins, enkephalins, and dynorphins) which are the normal way our bodies deal with intense pain
- primary use is to relieve intense pain, whether that pain results from surgery, injury, or chronic disease.
- widespread availability of opioids has led to abuse of those agents with euphoric properties.
- Antagonists that reverse the actions of opioids are also clinically important for use in cases of overdose

# Pain transmission and perception

- Pain → complex neurochemical processes in the peripheral and central nervous systems (CNS)

- Signal starts in Nociceptors = branches of sensory (1st order) neurons
- 2nd order neurons in spinal cord (dorsal horn)
- The pain signal = series of action potential between neurons
- The intensity of the firing of neurons depends on the severity of the pain



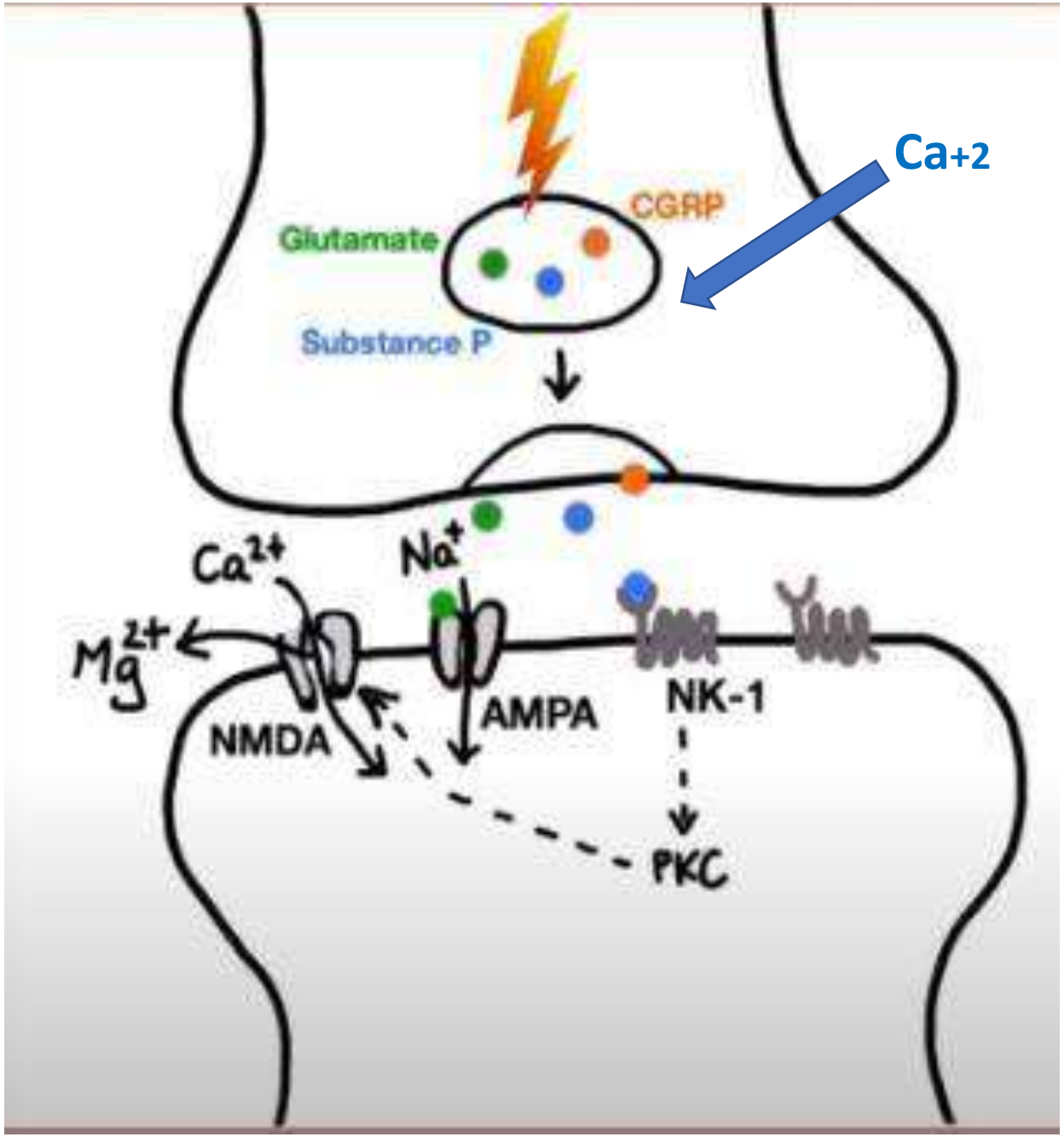
# Pain mediators

- Excitatory neurotransmitters and neuromodulators aid with the intense firing of neurons (pain)

- **Glutamate and substance P** (released due to calcium influx)
- **Glutamate**: activates AMPA and NMDA receptors → Na and Ca influx

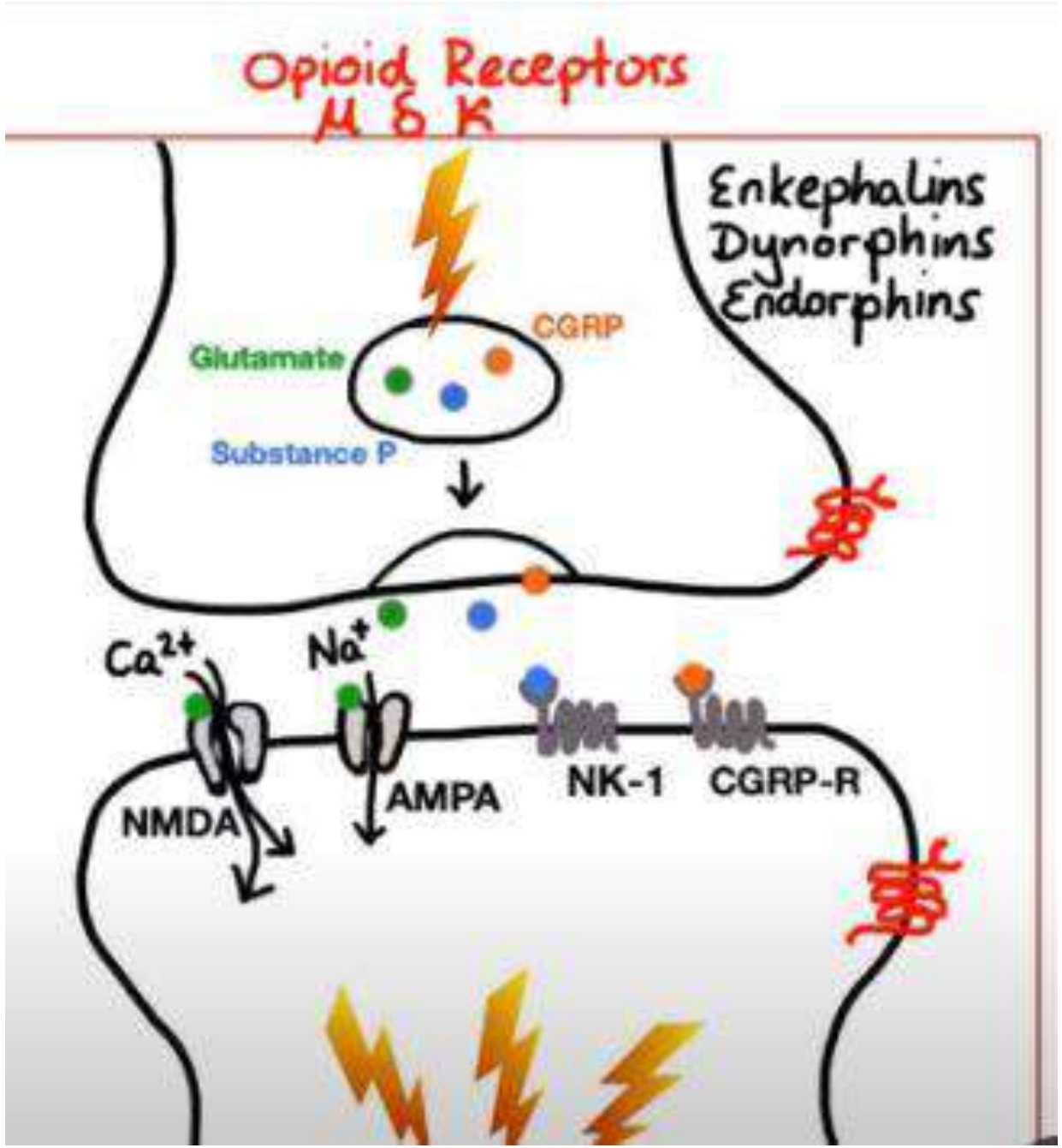
- **Substance P**: activates Neurokinin-1 receptors (NK-1)

- Excitation → pain



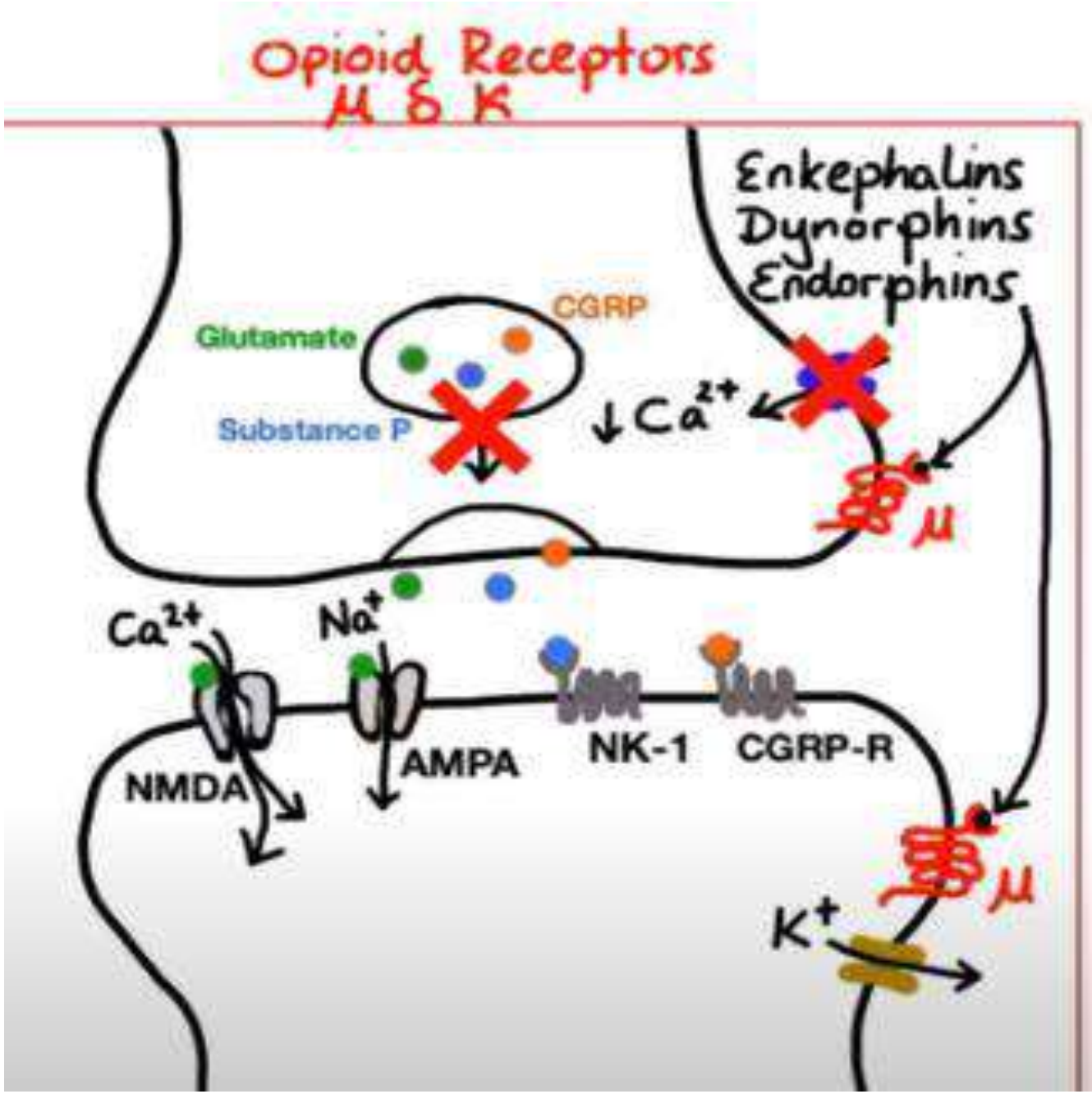
# opioid receptors

- Opioid receptors μ (mu), κ (kappa), and δ (delta) → dorsal horn of the spinal cord
- The analgesic properties of the opioids are primarily mediated by the μ receptors
- Endogenous opioids bind to the Gi-protein coupled μ receptors

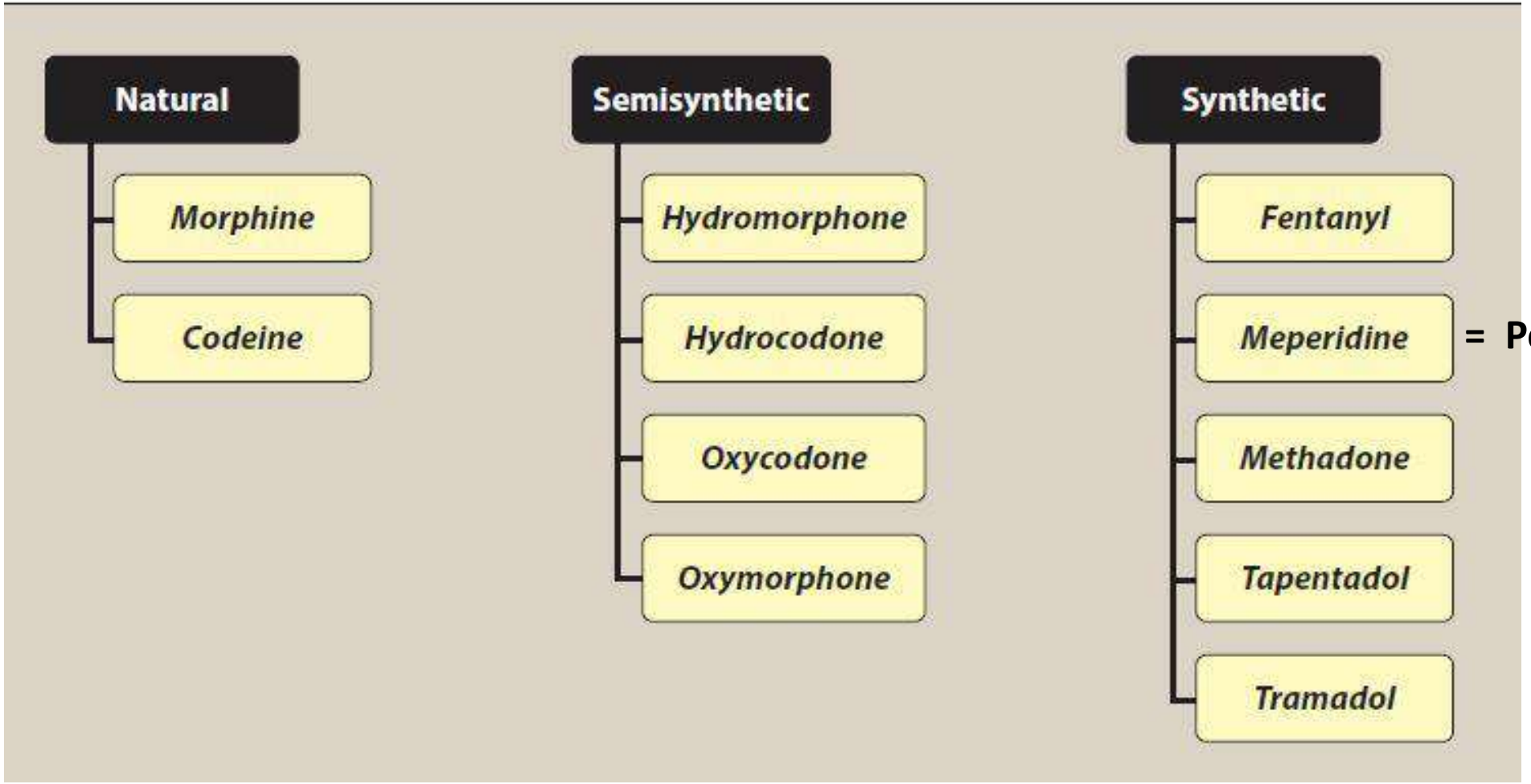


# Mechanism of action

- Gi coupled receptors → inhibits adenylyl cyclase
- They are also associated with ion channels, increasing postsynaptic K+ efflux (hyperpolarization)
- Reducing presynaptic Ca2+ influx, thus inhibiting neuronal firing and transmitter release
- Decreased release of both substance P and glutamate (controlling the pain)



# Opioid Agonists




= Pethidine

# Actions of opioids (Morphine)

- **Analgesia**:
- relief of pain without the loss of consciousness
- The relieve of pain is both by raising the pain threshold at the spinal cord level and by altering the brain's perception of pain → Patients treated with opioids are still aware of the presence of pain, but the sensation is not unpleasant

- **Depression of cough reflex:**
  **Morphine and Codeine** (weak analgesic but good antitussive) → used as a cough suppressant
- Morphine does suppress the cough reflex, but codeine is more commonly used

- **Miosis:** pinpoint pupil is a hallmark sign in morphine abusers
- Direct stimulation of μ and κ receptors

# Actions of opioids (Morphine)

- **Euphoria**:
- GABA suppression and thus increase dopamine release and activity (reward system)

- **Dose dependent Respiratory depression**:
- decreasing sensitivity of respiratory center in brain to carbon dioxide
- Respiratory depression is the most common cause of death in acute opioid overdoses

# Actions of opioids (Morphine)

- **Nausea and Emesis:**
- direct stimulation of chemoreceptor trigger zone (CTZ)

- **Constipation\ antidiarrheal effect**:
- relieves diarrhea by decreasing GI motility and increasing the tone of the intestinal circular smooth muscle
- Opioid-induced constipation

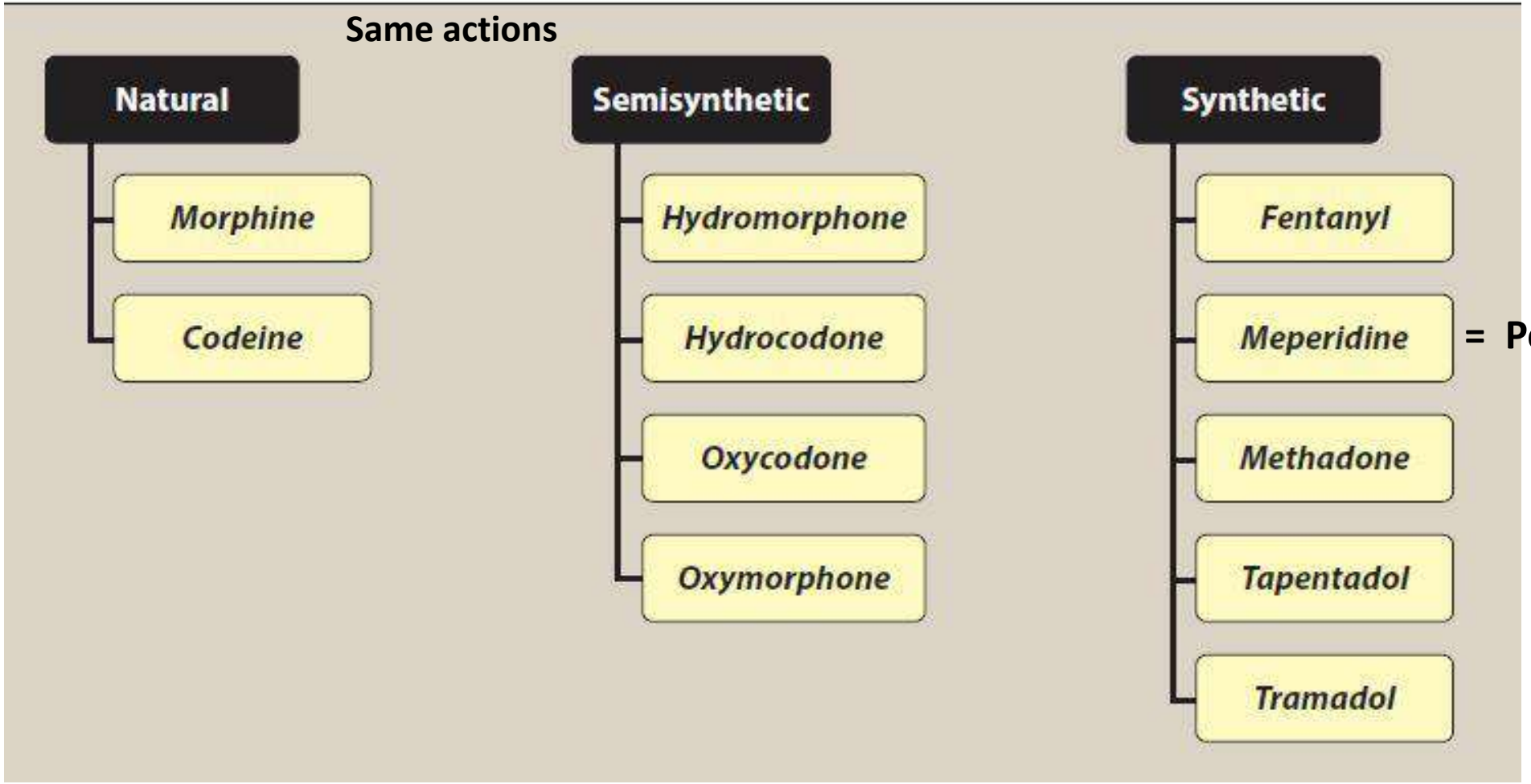
- **Cardiovascular:**
- all opioids in large doses cause bradycardia and hypotension except Meperidine (pethidine) → it causes tachycardia

# Actions of opioids (Morphine)

- **Histamine release**:
- **Morphine and Meperidine** provoke the release of histamine → vasodilation and hypotension , may cause bronchoconstriction
- Used with caution in asthma patients

- **Tolerance and physical\psychological dependence:**
- Repeated use produces tolerance to the respiratory depressant, analgesic, euphoric, and sedative effects of morphine
- potential for addiction (dependence) and withdrawal symptoms (Anxiety, insomnia, hypertension, tachycardia, muscle spasms, diarrhea, tremors, fever….)

# Opioid Agonists




= Pethidine

# Fentanyl (alfentanil: synthetic related to fentanyl)

- A synthetic opioid
- It has 100-fold the analgesic potency of morphine and is used for analgesia and anesthesia
- The drug is highly lipophilic and has a rapid onset and short duration of action (15 to 30 minutes)
- It is usually administered IV, epidurally, or intrathecally.
- Fentanyl is combined with local anesthetics to provide epidural analgesia for labor and postoperative pain.
- IV fentanyl is used in anesthesia for its analgesic and sedative effects

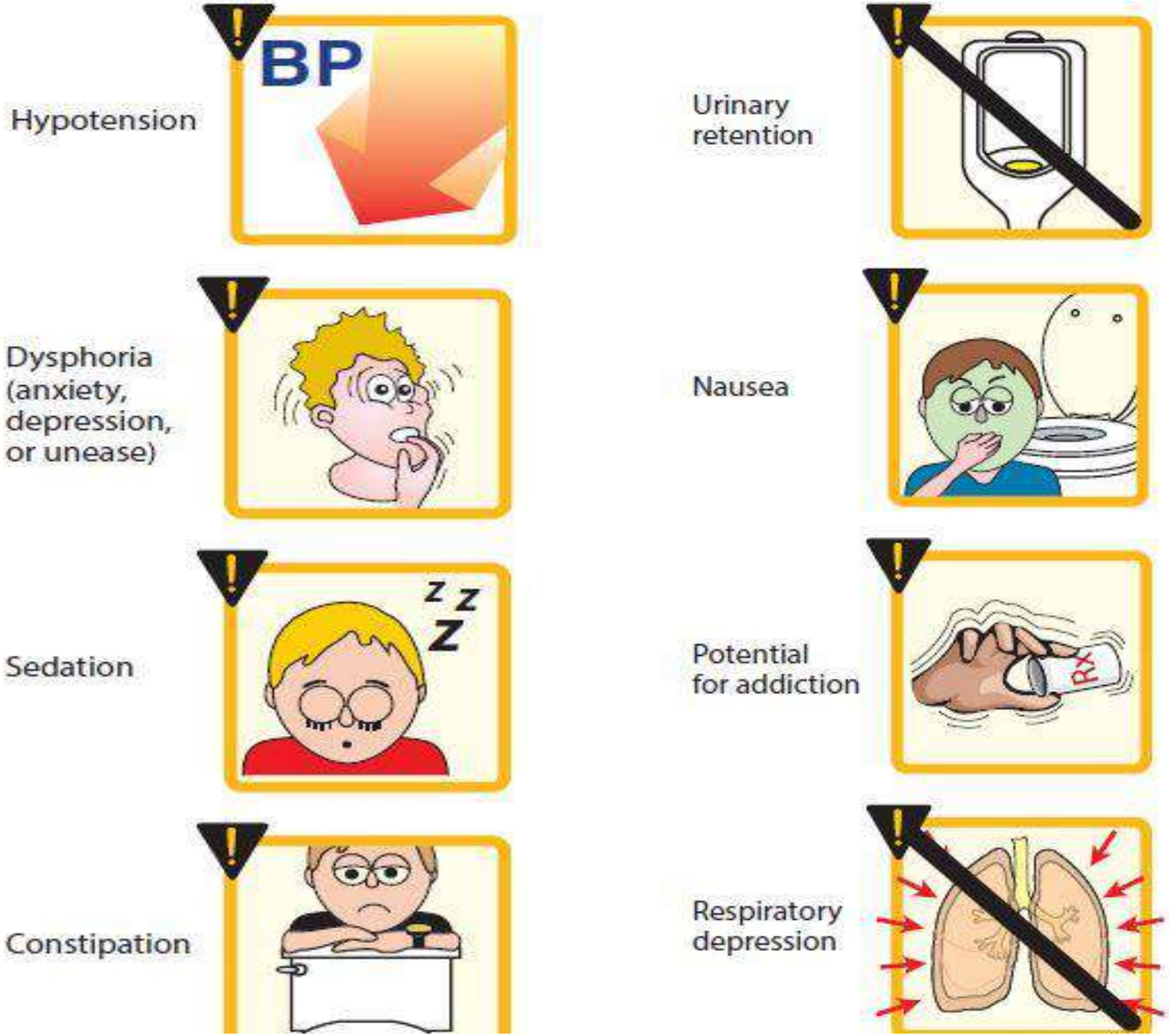
# Methadone

- The actions of methadone are mediated by μ receptors.
- It is also an antagonist of the N-methyl-d-aspartate (NMDA) receptor and a norepinephrine and serotonin reuptake inhibitor.
- Thus, it has efficacy in the treatment of both nociceptive and neuropathic pain

# Meperidine

- Aka Pethidine
- It is used for acute pain and acts primarily as a κ agonist, with some μ agonist activity
- Meperidine is very lipophilic and has anticholinergic effects, resulting in an increased incidence of delirium as compared to other opioids

**Figure 14.9: Adverse effects in people treated with opioids**



# Other analgesics

## ❖Tapentadol:

- a centrally acting analgesic
- an agonist at the μ opioid receptor and an inhibitor of norepinephrine reuptake
- It has been used to manage moderate to severe pain, both chronic and acute

# Other analgesics

## ❖Tramadol

- centrally acting analgesic that binds to the μ opioid receptor.
- The drug undergoes extensive hepatic metabolism → leading to an active metabolite with a much higher affinity for the μ receptor than the parent compound.
- weakly inhibits reuptake of norepinephrine and serotonin.
- It is used to manage moderate to moderately severe pain.
- respiratory depressant activity is less than that of morphine.
- As with other agents that bind the μ opioid receptor, tramadol has been associated with misuse and abuse.

# Opioid antagonists (antidotes)

- Antagonists that reverse the actions of opioids are clinically important for use in cases of overdose

- **Naloxone & Naltrexone**
- Naloxone (common) is used to reverse the coma and respiratory depression of opioid overdose (Within 30 seconds of IV injection)
- It is a competitive antagonist at μ, κ, and δ receptors, with a 10-fold higher affinity for μ than for κ receptors
- It rapidly displaces all receptor-bound opioid molecules.

# Opioid antagonists (antidotes)

- Naloxone has a short DOA → patient who has been treated and recovered may lapse back into respiratory depression
- Naltrexone is similar to naloxone but with a longer duration of action but not preferred because it may cause hepatotoxicity
- Naloxone can only **partially** reverse the analgesia produced by tramadol or its active metabolite