Opioids

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Opioids receptors

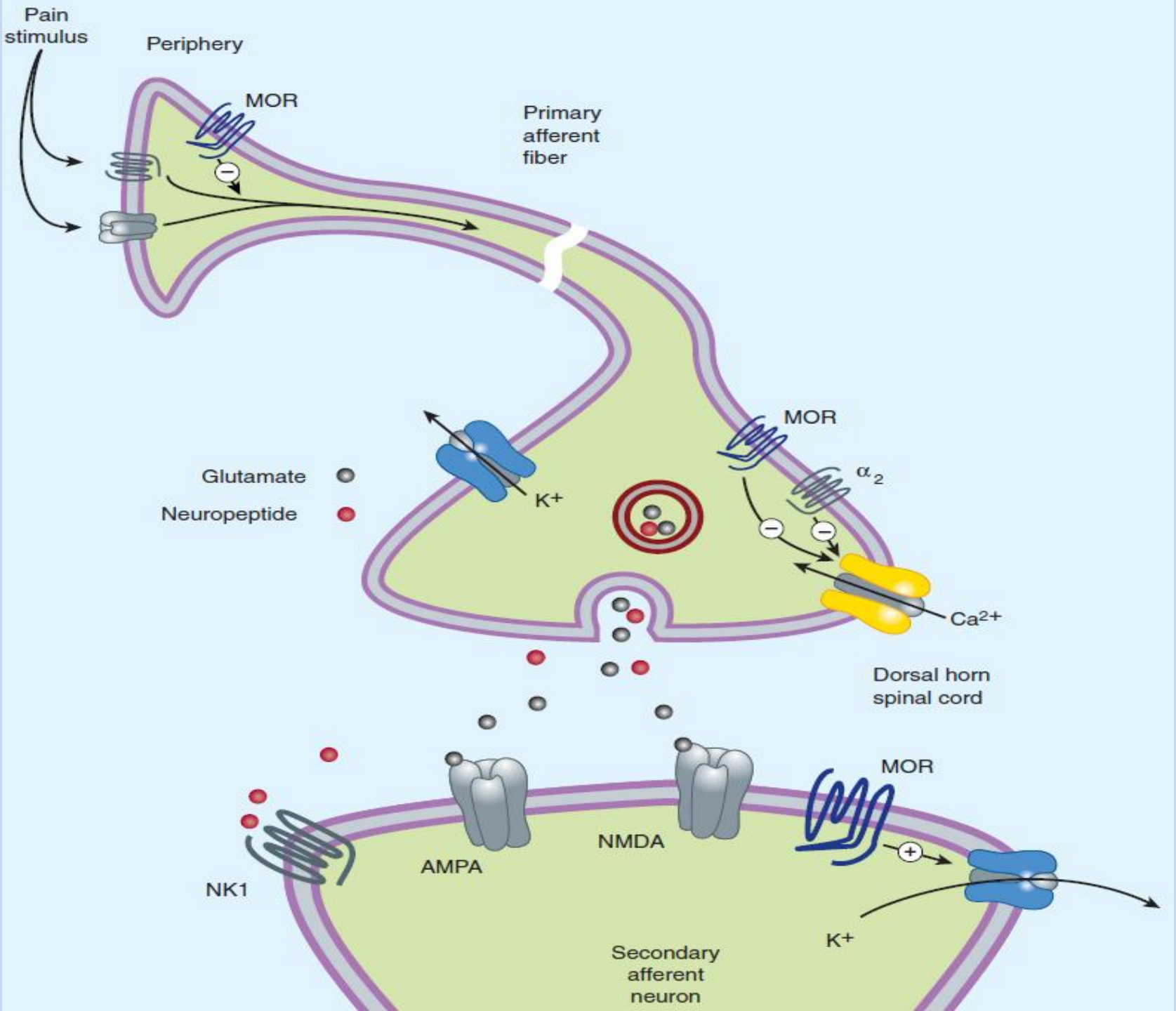
Receptor Subtype	Functions	Endogenous Opioid Peptide Affinity
μ (mu)	Supraspinal and spinal analgesia; sedation; inhibition of respiration; slowed gastrointestinal transit; modulation of hormone and neurotransmitter release	Endorphins > enkephalins > dynorphins
δ (delta)	Supraspinal and spinal analgesia; modulation of hormone and neurotransmitter release	Enkephalins > endorphins and dynorphins
κ (kappa)	Supraspinal and spinal analgesia; psychotomimetic effects; slowed gastrointestinal transit	Dynorphins > > endorphins and enkephalins

Mechanism of action

- All opioids receptors are GPCRs that inhibit AC.

- Receptor activation causes either:

1. ↑ K^+ efflux >>> hyperpolarization (post-synaptic).
2. ↓ Ca^{++} influx >>> ↓ nt. release (pre-synaptic).


Pain stimulus
Periphery
MOR
Primary afferent fiber
Glutamate
Neuropeptide
K+
MOR
α2
Ca2+
Dorsal horn spinal cord
MOR
NK1
AMPA
NMDA
K+
Secondary afferent neuron

Generic Name	Receptor Effects[1]		
	μ	δ	κ
Morphine[2]	+++		+
Hydromorphone	+++		
Oxymorphone	+++		
Methadone	+++		
Meperidine	+++		
Fentanyl	+++		
Sufentanil	+++	+	+
Alfentanil	+++		
Remifentanil	+++		
Levorphanol	+++		
Codeine	±		
Hydrocodone[5]	±		
Oxycodone[2,6]	++		
Pentazocine	±		+
Nalbuphine	—		++
Buprenorphine	±	—	—
Butorphanol	±		+++

Strong agonists

Morphine

- Inhibits release of excitatory nt. (glutamate) carrying nociceptive stimuli.

- Also acts on κ-R in the dorsal horn of spinal cord decreasing release of substance P.

Pharmacological actions

- Analgesia (↑ pain threshold, alters brain perception of pain).
- Sedation / Euphoria.
- Respiratory depression (↓ sensitivity of respiratory centers to CO_2).
- Depression of cough reflex.
- Miosis.
- GIT : emesis, ↓ GI motility, ↑ biliary pressure.
- CVS: bradycardia and hypotension.

Indications

- Analgesia.
- Pulmonary oedema.

Pharmacokinetics

- Significant 1st pass metabolism and GI absorption is erratic.
- Parenteral route is more preferred.

Adverse effects

- Dysphoria.
- Severe respiratory depression.
- Nausea and vomiting.
- Increased intracranial pressure (c.i. in head injury).

Tolerance

Degrees of tolerance that may develop to some of the effects of the opioids.

High	Moderate	Minimal or None
Analgesia	Bradycardia	Miosis
Euphoria, dysphoria		Constipation
Mental clouding		Convulsions
Sedation		
Respiratory depression		
Antidiuresis		
Nausea and vomiting		
Cough suppression		

Meperidine (Pethidine)

- Similar actions to morphine, but it causes tachycardia & pupil dilation (anti-cholinergic S/E).

- It’s used as analgesic, but it is not recommended due to metabolism to neurotoxic metabolite (nor-meperidine) and also not recommended in geriatrics / patients with renal impairment (accumulation of nor-meperidine).

Methadone

- Agonist at μ receptor and also blocks NMDA-R & monoaminergic transporters which can explain its activity against neuropathic/ cancer pain which is not relieved by morphine.

- ***Indications:*** analgesia , opioid abuse (b. it can be given orally with long $t_{1/2}$ and tolerance and physical dependence develop more slowly).

Fentanyl, Alfentanil, Remifentanil and Sufentanil

- Fentanyl has 100 analgesic potency of morphine used in analgesia / anesthesia.
- Sufentanil > fentanyl > alfentanil (Potency).
- Remifentanil has rapid onset & very short duration of action.

Heroin

- Also called diamorphine , diacetyl-morphine.
- 3 fold increase in potency as compared with morphine.
- Never used in clinical practice due to high abuse potential.

Mild-moderate agonists

- ***Codeine***: 30% analgesic efficacy as compared with morphine, used mainly as analgesic and antitussive.

- ***Dihydrocodeine, Hyrdrocodone, Prpoxyphene*** are weak agonists also used as analgesics.

- ***Diphenoxylate and Loperamide***: used for treatment of diarrhoea.

Mixed agonist-antagonist

Pentazocine

- K-R agonist, μ-R and δ-R receptor antagonist (or PA).
- Used as analgesic with less euphoria & respiratory depression as compared with morphine.
- High doses causes respiratory depression, ↑ BP and ↑ cardiac work.

- ***Nalbuphine and Butorphanol***: K-R agonist, μ-R antagonist.

- ***Buprenorphine:*** K-R antagonist, μ-R partial agonist, used in opioids abuse.

- All mixed agonist-antagonist exhibit ceiling effect for respiratory depression.

Other analgesics

Tramadol

- Activates μ-R and also inhibits reuptake of NE/ 5HT.

- Drug-drug interactions: avoid concurrent use with MAOI, SSRI and TCA.

Tapentadol

- Activates μ-R and also inhibits reuptake of NE only.

Opioids antagonist

Naloxone, Naltrexone and Nalmefene

- Higher affinity to μ-R.

- Used in acute opioids toxicity (reverses respiratory depression and coma).

Methylnaltrexone, Naloxegol and Alvimopan

- More selective to peripheral μ-R.

- Used to prevent opioids-induced constipation.

Thank you

References

-Basic & Clinical Pharmacology , Bertram G. Katzung 12th edition .

-Lippincott’s Illustrated Reviews: Pharmacology , 5th edition .

-Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th ed. .