King Saud University

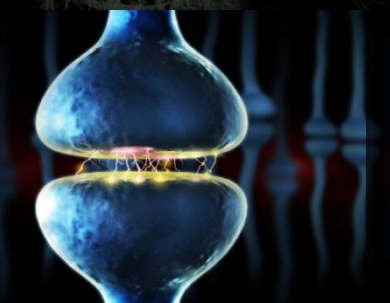
College of Medicine

2nd Year, 1st Block

PHARMACOLOGY 433

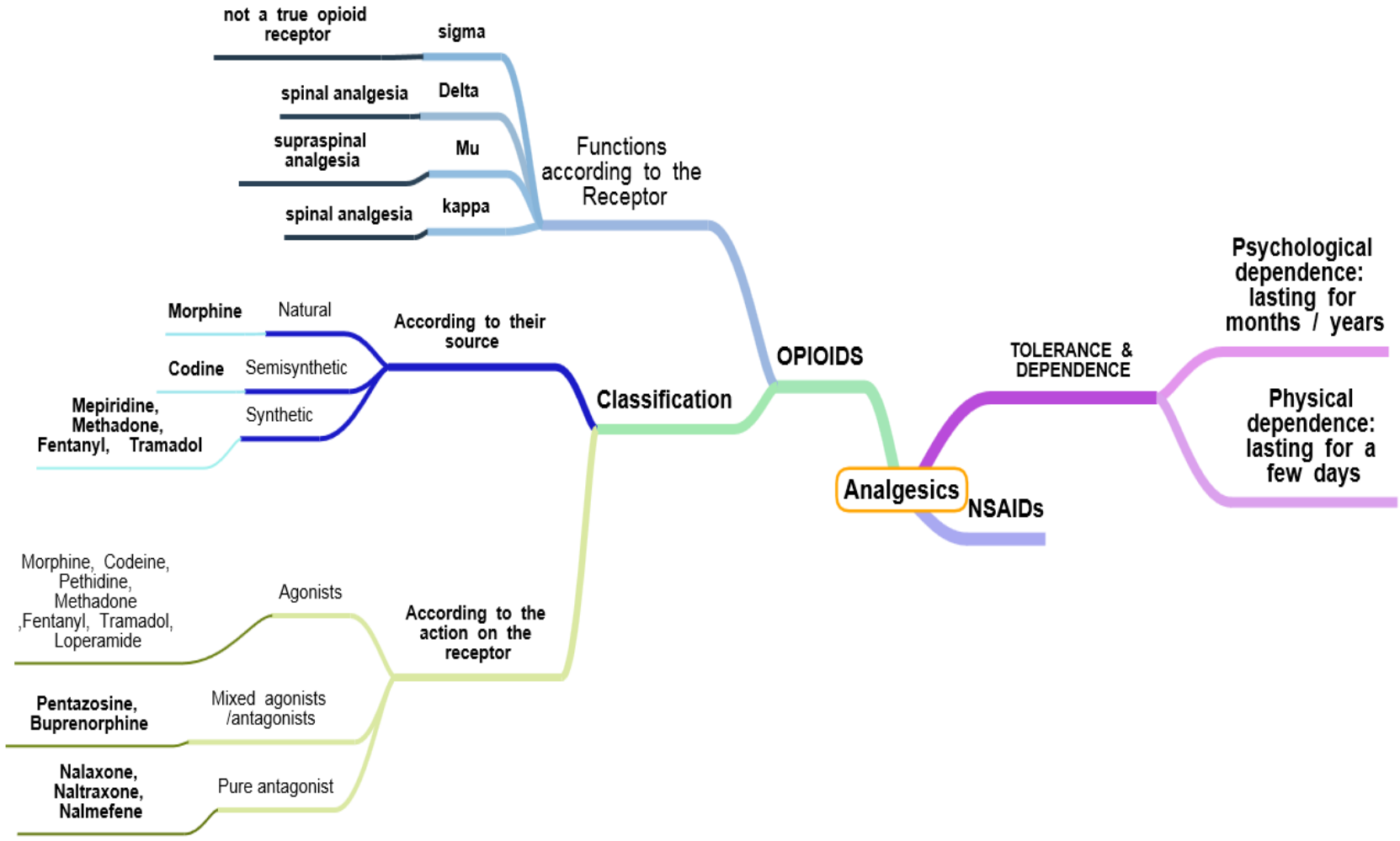
MED 433 Teams

L4: Drugs used in management of pain



CNS Block

Mind Map


Analgesics
NSAIDs
OPIOIDS
TOLERANCE & DEPENDENCE
Psychological dependence: lasting for months / years
Physical dependence: lasting for a few days
Classification
According to their source
Morphine
Natural
Codine
Semisynthetic
Mepiridine, Methadone, Fentanyl, Tramadol
Synthetic
According to the action on the receptor
Morphine, Codeine, Pethidine, Methadone ,Fentanyl, Tramadol, Loperamide
Agonists
Pentazosine, Buprenorphine
Mixed agonists /antagonists
Nalaxone, Naltraxone, Nalmefene
Pure antagonist
Functions according to the Receptor
not a true opioid receptor
sigma
spinal analgesia
Delta
supraspinal analgesia
Mu
spinal analgesia
kappa

Pain can produce by

Activation of nocicereceptors

e.g

opreation , Crash injury, Ischemic, Inflammation….

Nuropathic

e.g cancer pain, Low back pain

Analgesics ➔ used to induce analgesia

What is analgesic ??

It is a state in which a painful stimuli is modulated; though perceived but felt no more painful.

Treatment of pain

Non-OPIOIDS

NSAIDs

For Mild To Moderate Dull Aching

e.g: gout

OPIOIDS

For Moderate To Severe pain

*** In case of acute pain the purpose of treatment is to control the pain gate (substantia gelatinosa, periaqueductal gray matter).**

*** In case of chronic pain we have to treat the symptoms beside the pain, e.g : using psychiatric therapy in treating chronic pain because most of chronic pain are accompanied with bad psychological conditions.**

Classification Of OPIOIDS Analgesics

According to their source

- Natural (Morphine)
- Semisynthetic (Codine)
- Synthetic (Mepiridine, Methadone Fentanyl Tramadol)

According to agonistic/antagonistic actions at receptors:

- Agonists
  - Morphine
  - Codeine
  - Pethidine
  - Methadone
  - Fentanyl
  - Tramadol
  - Loperamide [no BBB ➔ diarrhea]
- Mixed agonists /antagonists
  - Pentazosine
  - Buprenorphine
- Pure antagonist
  - Nalaxone
  - Naltraxone
  - Nalmefene

OPIOIDS

It contains a mixture of alkaloids, the principal components being

morphine, codeine & papaverine

Mimic action of endogenous opioids :

Endorphins, Dynorphins,Enkephalins

Act on endogenous opioid receptors

mu, delta, kappa, sigma

This means that these drugs are acting similarly to natural substances in our body that relief the pain.

Functions mediated by endogenous OPIOIDS RECEPTORS

Receptors	Functions
μ	supraspinal analgesia, respiratory depression, euphoria, physical dependence
δ	spinal analgesia, respiratory depression, ↓GIT motility
k	spinal analgesia, sedation, pupil constriction, dysphoria All of them typical G-protein coupled receptors.
σ	not a true opioid any more

Important

How can OPIOIDS induce analgesic effect ?

Important

1 Presynaptic(قادم من مكان الألم)

Drug Binding to presynaptic opioid receptors coupled to Gi → ↓ AC & cAMP → ↓ voltage-gated Ca^{2+} channels → ↓ excitatory transmitter

2 postsynaptic

Drug Binding to postsynaptic → ↑ opening of K channels → ↓ neuronal excitability

↓ firing of nociceptive pathways converging at Periaqueductal GM

→ to allow for inhibitory firing along the descending pathway returning to dorsal horn → ↓ pain

Also inhibit pain transmission by acting directly on the dorsal horn, and by ↓ excitation of peripheral nociceptive afferent neurones.

AC = adenylyl cyclase

This mechanism occurs in periaqueductal gray matter, dorsal horn cell

Tolerance & Dependence

Psychological dependence

With repeated prescribing of some opioid drugs, the patient is going to be addicted to it (craving), and in case of stopping the drug the patient will develop a physical dependence.

Physical dependence = Withdrawal manifestations

Withdrawal manifestations develops upon stoppage the drug. lasting for a few days in form of

Withdrawal manifestations

You have to know them

- ↑ body ache
- insomnia
- diarrhea
- goose flesh
- lacrimation

During addiction treatment course we will be able to solve the withdrawal manifestation problem, but the pscycological problem needs a **psychiatric therapy.**

Morphine

Pharmacokinetics

* t ½ is 2-3h

*It is slowly & erratically absorbed orally.

*Medically given by IM or IV injection .

*It should be repeated if sustained effect is needed

*Undergoes enterohepatic recycling

crosses placenta → Contrindications in case of PREGNANCY

*crosses BBB

Pharmacodynamic

Good action

1- Analgesia [in acute & chronic pain]

2- Euphoria → powerful sense of contentment & well being

3- Depression of cough reflexes

Side effects

4- Effects on GIT:-↑in tone ↓motility → severe constipation

5-↓LH, FSH, ACTH , testosterone↑Prolactin, GH, ADH → urine retention

6- Releases histamine from mast cells → Contrindications in case of bronchial asthma or impaired pulmonary function

7- Nausea & vomiting → ↑CRTZ

8- Respiratory depression→↑pCO2

9- ↑pressure in the biliary tract + constriction of biliary sphincter →contraction of gall bladder

10- Pin point pupil:- due to stimulation of occulomotor center by m, k (effects. Diagnostic)

Pin point pupil characteristic of OPIOIDS toxicity

That means if a patient is having a pin point pupil as a manifestation it means (opioid toxicity) and we should treat him with a drug the antagonize the action of opioids **(Naloxone) will be discussed later.**

Clinical Indications

In severe case

1- control pain cancer pain, severe burns, trauma severe visceral pain (not renal/biliary colic, acute pancreatitis)

2- diarrhea

3-cough

4- acute pulmonary oedema

5- myocardial ischemia

6-non painful conditions Heart Failure to relieve distress

7- pre-anaesthetic medication (The patient should take an opioid drug preoperatively, the best drug for pre-anesthetic conditions is Pethidine " will be discussed later")

Side effects

*Sedation

*Respiratory depression.

*Constipation

*Euphoria.

* Itching → histamine release

*Tolerance; not to meiosis, convulsion or constipation

*Dependence.

*Nausea & vomiting.

Contraindications

1. HEAD INJURY*
2. PREGNANCY

Never give morphine

3. bronchial asthma or impaired pulmonary function
4. Liver & Kidney diseases (including renal& biliary colics)
5. Endocrine diseases (myxedema & adrenal insufficiency)
6. Elderly are more sensitive;↓metabolism, lean body mass & renal function
7. Not given infants, neonates or during child birth➔

↓conjugating capacity ➔ accumulate ➔ ↓ respiratory

8. With MAOIs

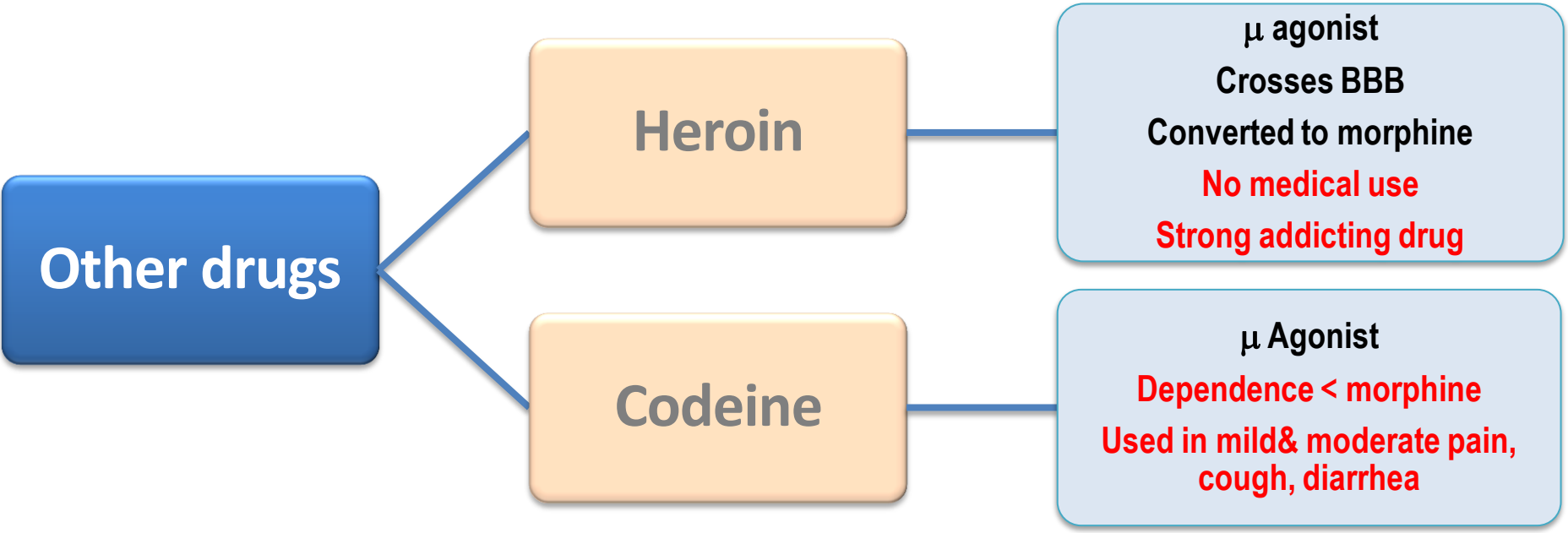
Important

Could be asked as a Scenario

*if we give morphine in this case, that will lead to increase the intracranial pressure.

Drug	Action	Indications	Side effects
Meperidine Or Pethidine	1- k agonism → spinal analgesia 2- Has atropine –like action + Smooth muscle relaxant 3-No cough suppressant effect	1- Used in obstetric analgesia (PREGNANCY) 2- renal & biliary colics 3- preanaesthetic medication	*Addiction *atropine –like action (Tremors, Convulsions, Hyperthermia, Hypotension Burred vision, Dry mouth, Urine retention Tolerance & Addiction)
TRAMADOL	μ agonist , ↓ potent given orally	Mild pain e.g : tooth extraction Or if someone is using NSAIDs usually, and its not effective anymore we can prescribe TRAMADOL + during labor	Seizures (not in epileptics), Nausea , Dry mouth, Dizziness , Sedation Less adverse effects on respiratory & C.V.S
Fentanyl	μ agonism ↑potency	1- Commonest analgesic supplement during anesthesia, IV 2- In combination with droperidol as Neuroleptanalgesia 3-In cancer pain → in form of transdermal patch	Mimic opioid agonists / respiratory depression most serious / CV effects are less. Bradycardia may still occur
METHADONE	μ- Weaker Agonist t½ 55 h	Used to treat opioid withdrawal , Firm occupancy of opioid receptors by methadone ↓ desire for other opioid intake (↓ craving)	In non addicts, it causes tolerance & dependence

Other drugs can be used as analgesics



Antagonizing Acute Opioid Toxicity

the next table illustrate the drugs the antagonize opioids action (Antagonizing Acute Opioid Toxicity) :

Drug	Action	Indications	Side effects
Naloxone	Pure opioid antagonist	1-Used to treat respiratory depression (in adult as well as new born baby) 2- Acute Opioid Toxicity	**Precipitates withdrawal syndrome in addicts**
Naltrexone	Very similar to naloxone but with longer duration of action [t½=10h		

Naloxone used for <u>Acute</u> Opioid Toxicity

<u>But !!</u>

<u>Chronic</u> Opioid Toxicity this happened mainly with addicted and we don't give addicted this drug

Scenario

A patient came to the ER suffering from acute pulmonary oedema or myocardial ischemia or Heart Failure, the best drug in this case is ?

Morphine

The same previous scenario but in a pregnant lady, the best drug is ?

Meperidine Or Pethidine

A patient came to the ER complaining from renal & biliary colics the best drug is ?

Meperidine Or Pethidine

If someone is suffering from gout and the NSAIDs are not effective anymore, or if someone is going to extract a teeth, the best drug is ?

TRAMADOL

A patient with cancer pain , the best drug is ?

Fentanyl

A patient suffering from Psychological problem and he was using droperidol, and he has pain the best drug is ?

Fentanyl

Scenario

The best drug to treat addiction ?

METHADONE

if a patient developed respiratory depression in the OR, or a women was giving birth and the new born baby developed respiratory depression?

Naloxone

A patient came to the ER, on examination the physician found that he has Pin point pupil (Acute opioid toxicity)?

Naloxone

If a patient came to ER and he was addicted (Chronic Opioid Toxicity) we should avoid using what ?

Naloxone

why we should avoid using naloxone in addicted patients ?

He will develop Withdrawal manifestation

summary

Drugs	Indication	Side effect	Contraindication
Morphine	control pain &non painful condition diarrhea, cough, acute pulmonary edema, myocardial ischemia	Sedation, Respiratory depression Constipation, Nausea & vomiting ,Itching Euphoria,Tolerance Dependence	Head injury, pregnancy, , asthma, Liver & Kidney diseases , Endocrine diseases ,elderly and infant , with MAOI
Meperidine (pethidine)	As in morphine but not in cough & diarrhea • Used in severe visceral pain; renal & biliary colics • Used in obstetric analgesia (No ↓ resp.) • Preanaesthetic medication (better)	Tremors, Convulsions, Hyperthermia, Hypotension Burred vision, Dry mouth, Urine retention Tolerance & Addiction	-
Tramadol	Mild - moderate acute & chronic visceral pain & during labor	Seizures ,Nausea , Dry mouth, Dizziness, Sedation ,Less adverse effects on respiratory & C.V.S	-

summary

	Indication	Side effect
Fentanyl	*Commonest analgesic during anesthesia , *In combination with droperidol as neuroleptanalgesia *In cancer pain transdermal patch changed	Mimic opioid agonists / respiratory depression most serious / CV effects are less. Bradycardia may still occur
Methadone	Used to treat opioid withdrawal.	-
naloxon	Pure opioid antagonist. Used to treat **respiratory depression** caused by opioid overdose	-

Quiz yourself

1.Drugs acting on δ receptors are considered as :

A.spinal analgesia
B.supraspinal analgesia
C.infraspinal analgesia

2.According to opoids sources, Fentanyl considered as :

A.natural opoids
B.synthetic opoids
C.semisynthetic opoids

3.Ache, insomnia, diarrhea are manifestations of :

A.Physical dependence
B.Psychological dependence
C. Both

4. A pregnant lady has severe visceral pain, the physician prescribed an analgesic to relief it which one of the following is indicated?
A.heroin
B.morphine
C.Meperidine

5.Heroin Acts on :

A.m receptor
B. δ receptor
C. k receptor

6.A patient has an acute pulmonary oedema, the physician prescribed an analgesic. later, the patient developed Itching due to histamine release, the drug is :
A.paracitamol
B. Morphine
C. Fentanyl

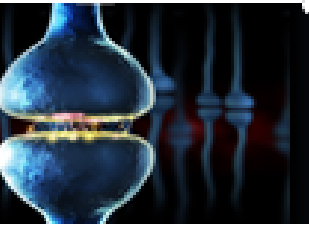
7.A drug used to treat respiratory depression caused by opioid :

A.paracetamol
B. Beta blockers
C.Naloxone

8.Which one is used For Mild To Moderate Dull Aching :

A.morphine
B. Meperidine
C.NSAIDs

Answers: 1.A 2. B 3.A 4.C 5.A 6.B 7.C 8.C



CNS Block

PHARMACOLOGY 433

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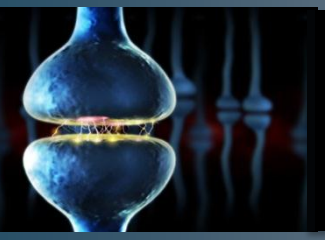
We hope that we made this lecture easier for you
Good Luck !



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