بسم الله

"وما رميت إذ رميت ولكن الله رمى" تذكر أنه معك حيثما كنت، فلولاه لا حول لك ولا قوة

استعن بالله وانطلق، وستملأ الدنيا فرحًا و إنجازًا بإذنه..

Note: in this link

https://drive.google.com/open?id=0BwRHXC4PKpePTVpGeF8xNkltUWs there are *very very useful* sketchy pharm videos to watch if you have time.

CNS Pharmacolgy. Part1

Anxiolytics and Hypnotics

Benzodiazepines

- Mechanism of action:
  1- $GABA_A$ receptor has five subunits of α, β, and γ subunits (fig 1)
  2- The α subunit could be of two types: α_1 or α_2
  3- $GABA_A$ activation ↑Cl^- influx
  4- Influx of chloride= more negative resting membrane potential= HYPERpolarization.
  5- These receptors (channels) are activated by both GABA (endogenous molecule) and Benazodiazepines (the drug), but each

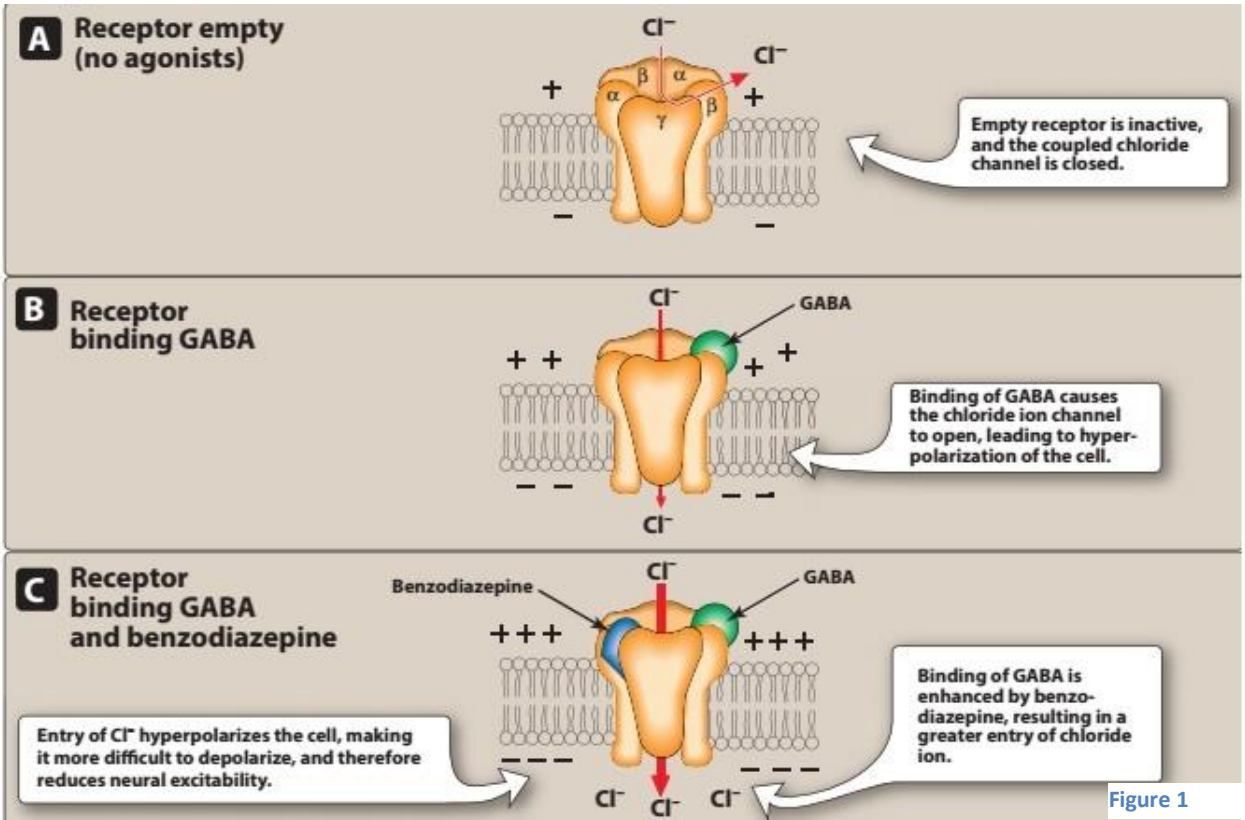

Figure 1

one binds into a DIFFERENT site

- Actions:

These drugs have anxiolytic and hypnotic effects

Generally speaking;
receptors having α_1 subunit mediate sedation (hypnosis)
Receptors having α_2 subunit mediate antianxiety and cognitive impairment functions. So let's take a closer look:

Action	α Subunit	Notes
Sedative/ Hypnotic	α_1	At higher doses
Anterograde amnesia	α_1	
Anticonvulsant	α_1	This effect is only Partially mediated by α_1-$GABA_A$ receptors
Reduction of anxiety	α_2	At low doses
Muscle relaxant	α_2	Baclofen is a muscle relaxant that acts through GABA receptors

- Uses:
  "Pam"-cake offered "all a.m."

Duration of action	Drug	Indication/ uses
Short acting	Triazolam	**Sleep disorders.** Patients with difficulty in going to sleep. **To induce Amnesia:** premedication for unpleasant procedures eg:endoscopy.
Intermediate acting	Lorazepam	
	Temazepam	**Sleep disorders.** Patients with frequent wakening.
	Alprazolam	Acute **anxiety** (eg: *Panic disorders)*
Long acting	Diazepam	**1.Anxiety** that requires prolonged treatment. **2.Seizures:** DOC in terminating **status epilepticus.** **3.**Skeletal **muscle** spasms
	Flurazepam	
	Clonazepam	Adjunct in certain types of **seizures**

- Cross tolerance exist between the benzodiazepines and ethanol.
- Benzodiazepines increase stage 2 of non-REM sleep. Both REM sleep and slow-wave sleep are decreased
- When treating insomnia, it is important to balance the sedative effect needed at bed time and the "hang-over" upon wakening.

- Pharmacokinetics
  Most benzodiazepines are metabolized by the liver into compounds that are also active.
- Dependence
  -psychological and physical dependence occur
  -Withdrawal symptoms: (CNS stimulation effects)
    - Anxiety
    - Agitation
    - Insomnia
    - Seizures
  - Benzodiazepines with short half life eg: triazolam induce more sever withdrawal reactions

- Adverse effects
  - Drowsiness and confusion
  - Ataxia (no coordinatin, can't drive a car)
  - Cognitive impairment
- ➢ Use catiously in patients with liver disease
- ➢ Avoid in acute angle closure glaucoma
- ➢ Alcohol/CNS depressents enhance the effects of benzodiazepines (concurrent use might cause life-threatening respiratory depression)

Flumazinel

A GABA receptor antagonist that is used to reverse the effects of benzodiazepines

Benzodiazepines are not necessarily the best choice for anxiety or insomnia. Antidepressants with anxiolytic actions (SSRIs) are preferred in many cases when anxiety disorders are in question.

Anticonvulsants

- Mechanism of action: بشكل عام لكن لكل دواء طريقة محددة (أو مجموعة محددة من الطرق)

- Blocking Na^{+} or Ca^{+2} channels
- ↑ inhibitory tone by enhancing GABA-ergic impulse (Remember: Hyperpolarization)
- ↓Excitatory effects of glutamate.

Antiepileptic	seizure		Other uses	MOA	Side effects
	Focal	Generalized			
Carbamazepine	✓	✓ Tonic clonic	DOC for **trigeminal neuralgia**. used in Bipolar disorder	Blocks Na^{+} channels	-Hyponatremia -Induction of CYP450 - increase absence seizures (contraindicated)
Ethosuxemide		✓ **ABSENCE**		Block T-type Ca^{+2} channels	
Gabapentin	✓		Pstherpetic neuralgia	Analog of GABA	
Lamotrigine	Used in a wide variety of types			Blocks Na^{+} channels	Rash (Stevens-Johnson syndrome. life-threatening)
Phenytoin	✓	✓ Tonic clonic And status epilepticus		Blocks Na^{+} channels in their inactivated state	-Induction of CYP450 -Nystagmus and ataxia (CNS depression) -gingival hyperplasia -osteoporosis
Valproic acid	Broad spectrum of activity against seizures			Na^{+}, Ca^{+2} and GABA	-hepatotoxic -teratogenic

Phenytoin exhibits nonlinear (zero-order) kinetics. i.e, a small increase in dose produces a large increase in plasma conc.

Status epilepticus

Two or more seizures without full recovery in between episodes. Life threatening. Management: Benzodiazepines (Diazepam) and phenytoin

Clinical vignette: *(extra. With link to pathology)*

A patient with history of epilepsy is rushed to the ER. His family reported him being unresponsive then he started vomiting and convulsing. His blood work show low serum sodium. You concluded that the cause of his condition is hyponatremia.

1. *If you were to make a guess, on which antiepileptic is that patient?*
2. *How will you manage this patient?*

Answers

1. This patient has most probably recently started on **carbamazepine.**

2. You should gradually correct his sodium levels with IV isotonic saline. Rapid correction can cause **central pontine myelinolysis**

تحذير: الرجاء التركيز

Anesthetics

Inhalation anesthetics

MAC: *minimum alveolar concentration* is the concentration of inhaled anesthetic as percentage of inspired air at which 50% of patients do not respond to a surgical stimulus. So MAC is the median effective dose (ED_{50}) of the anesthetic: a measure of **potency**

- MAC is small for potent anesthetics
- Large for less potent agents

*Nitrous oxide alone can NOT produce complete anesthesia

-The more lipid soluble the anesthetic is, the lower the MAC and the greater the potency
-MAC values are lower in the elderly

Mechanism of Action:

- Unknown. Anesthetics are chemically unrelated compounds→they do not act on a single receptor
- General anesthetics increase the sensitivity of $GABA_A$ receptors
- Others inhibit NMDA receptors

1.Halothane

- A potent anesthetic
- Hepatotoxic in adults but NOT in children
- Suitable in pediatrics
- Adverse effects:
    - Cardiac arrhythmias (sensitize the heart to effects of catecholamines)
    - Concentration-dependent hypotension; best treated with a vasoconstrictor eg. *Phenylephrine*
    - Malignant hyperthermia;
      on exposure to halogenated hydrocarbon *anesthetics* or the

neuromuscular blocker *succinylcholine.* If this reaction happened, give *dantrolene*.

2. Isoflurane

- NOT toxic to the liver
- Does NOT induce cardiac arrhythmias
- Produce dose-dependent hypotension (but less than halothane)
- Stimulate respiratory reflexes (coughing, etc)

3. Sevoflurane

DOC for inhalation induction in pediatric patients

4. Nitrous oxide "laughing gas"

- A potent analgesic but a weak general anesthetic→frequently used in combination with oxygen for analgesia esp in dentistry.
- Moderate to no effect on the cardiovascular system
- Least hepatotoxic of the inhalation agents

<u>IV Anesthetics</u>

1. **Propofol**
    - Used for <u>induction(first choice)</u> or maintenance of anesthesia
    - depresses the CNS, but is occasionally accompanied by excitatory phenomena.
    - Decreases blood pressure
    - Cause systemic vasodilation
    - Useful for surgeries in which spinal cord function is monitored
    - Has some **antiemetic effects** (lower incidence of postoperative nausea and vomiting)

Quick reminder:

Drugs that cause hypotension are:
1.Halothane,
2.Isoflurane and
3.propofol

While Ketamine cause an increase in blood pressure

2.Ketamine

- induces a dissociated state (the patient is unconscious but appears to be awake)
- cause stimulation of the heart (increase blood pressure and cardiac output)/ useful for patients with hyppovolemic or cardiogenic shock
- Bronchodilator/ useful in asthmatics
- Used mainly in children
- NOT WIDELY USED because it may induce hallucinations particularly in young adults (similar in that to *phencyclidine* (PCP))

Local anesthetics

- Mechanism:

Block sodium channels → No action potential

تحذير: الرجاء التركيز

The pH of the tissue and pKa are very important
- local anesthetics are weak bases (pKa~8)
-The physiologic pH is lower than the pKa of weak bases
- At physiologic pH, most of the drug is ionized
-Nonionized form crosses axonal membrane
-From within, the ionized form block sodium channels
-So the non-ionized form should cross the cell membrane then get ionized and block the sodium channel
-if the pH dropped (infected site), less and less of the non-ionized form will be available to cross membranes and therefore the onset will be delayed and you might need higher concentration of the drug to achieve effect.

Nerve fiber sesnsitivity:

Small unmyelinated nerve fibers for pain, temperature and autonomic activity are the most sensitive. (Motor nerve fibers are not commonly affected)

Local anesthetics include **procaine, lidocaine, tetracaine**

A vasoconstrictor (*epinephrine*) is coadministered:

- ↓local anesthetic absorption into the systemic circulation
- Prolong the duration of action
- ↓toxicity

- Side effects
  - Allergic reaction (esp *procaine*)
  - Altered mental status
  - Cardiovascular instability