PHARMACOLOGY TEAM

Lecture : 4

Drugs Related To Balance

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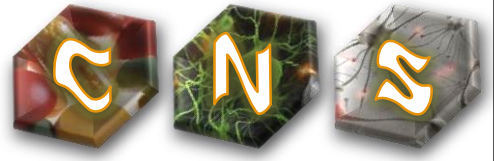
OBJECTIVES

- Recognize causes and symptoms of balance disorders.
- Identify the transmitters involved in vestibular transmission
- Segregate classes of drugs used in the management protocols to control or prevent vertigo
- Identify drugs that can precipitate vertigo

Mind Map



GENERAL CONCEPTS

drugs for vertigo

- **vestibular suppressants**
  - **Drugs that ↓Spinning**
    - **Benzodiazepines**
      - Lorazepam, Clonazepam & Diazepam
    - **Betahistine**
  - **Drugs that ↓emesis**
    - **H_1 antagonist**
      - Meclizine
      - Dimenhydrinate
    - **Phenothiazines**
      - Prochlorperazine
      - Promethazine
    - **Dopamine Antagonists**
      - Metoclopramide
      - Domperidone
- **Drugs that prevent recurrence**
  - **L-type Ca Channel Blockers**
  - **Corticosteroids**
  - **Diuretics**

Drugs inducing vertigo

- **VESTIBULOTOXINS** — Most of them functional
- **MIXED OTOTOXINS** — Functional or structural

Pathway of Balance Control

Fluid in the semi-circular canal → stimulating nerve endings → firing impulses along the vestibular nerve

↘

TO vestibular nuclei (relay stations)

↘

The processed output goes Conscious brain

↘

- sense of position in space
- Eye muscles to stabilize
- Neck spine & limbs to control posture and movement

NOTE :This slide and the next two are from Dr.Osama's Slides Only

Transmitters Involved In Vestibular Firing

Main Transmitters

- Glutamates
- Acetylcholine
- Glycine
- GABA

Modulatory Transmitters

- Histamine
- Noradrenaline

What is Vertigo ???

It is a type of dizziness that creates the sense that you or your environment is **SPINNING**.

- It Causes ALSO, Nausea or vomiting
- sweating
- abnormal eye movements (nystagmus)

General Concepts

CNS

Impact on vestibular nuclei , afferent inputs or efferent outputs

Causes

Inner ear (Ménière's disease)

Vestibular hair cell stimulation unrelated to head and body motions

↑endolymphatic pressure → microscopice breaks (often with vestibular hair loss)→ depolarization and functional loss.

Others

Low tolerance for vehicular motion such as cars, boats, cruise ships, and airplanes that cause MOTION SICKNESS

Ménière's disease is a disorder of the inner ear that can affect hearing and balance.

It is characterized by episodes of vertigo, tinnitus and progressive hearing loss .

Vertigo (Therapeutic Management)

Vestibular Suppressants

This group is further Disused

Intend to dull brain response to vestibular signals from inner ear — suppress firing+symptoms — act on CRTZ

↓Spinning

↓Emesis

Could be managed centrally or locally (GIT)

Prevent Recurrence

Intend to suppress acute attacks

[tame vertigo episodes]

Diuretics <u>but not loop diuretics</u> (they cause vertigo)	(↓ fluid retention)
Corticosteroids (in endolymph)	(↓inflammation)
L-type Ca Channel Blockers. E.g.: cinnarazine, flunnarazine, verapamil (not dihydroperidine)	(↑ vasodilatation)

vasodilation effect): shunt blood to other vasodilator areas to lower excessive vasodilation and pressure in the inner ear

NB. If migraine is also present

→ add on its treatment

Vestibular Suppressants
(Decrease The Spinning)

Drugs	Their mechanism of action
Benzodiazepines (Lorazepam, Clonazepam & Diazepam)	promote & facilitate central vestibular compensation via GABA modulation GABA is an inhibiter.
Betahistine ,fast in action (this drug is discussed in the next slides).	H_1 agonists ,as a vasodilators H_3 antagonists

Histamine works as a mediator and neurotransmitte

H3 is found in brain ,pre and Postsynaptic membranes.
If we activate H3 in presynaptic, it inhibits the release of histamine

Betahistine

Mechanism of actions

Weak agonist
at H_1 receptors

regulates inner ear
fluid homeostasis
(labyrinthine circulation)

inducing vaso-dilatation
in middle ear

relieves pressure
in inner ear

Strong antagonism
of H_3 autoreceptors

↑ augmenting effects
on H_1 receptors in the brain

- ↑ H synthesis in tuberomammillary nuclei of the posterior hypothalamus to promote & facilitate central vestibular compensation

- ↑ H release in vestibular nuclei

↑levels of neurotransmitters such as 5HT in the brainstem, which inhibits the activity of vestibular nuclei.

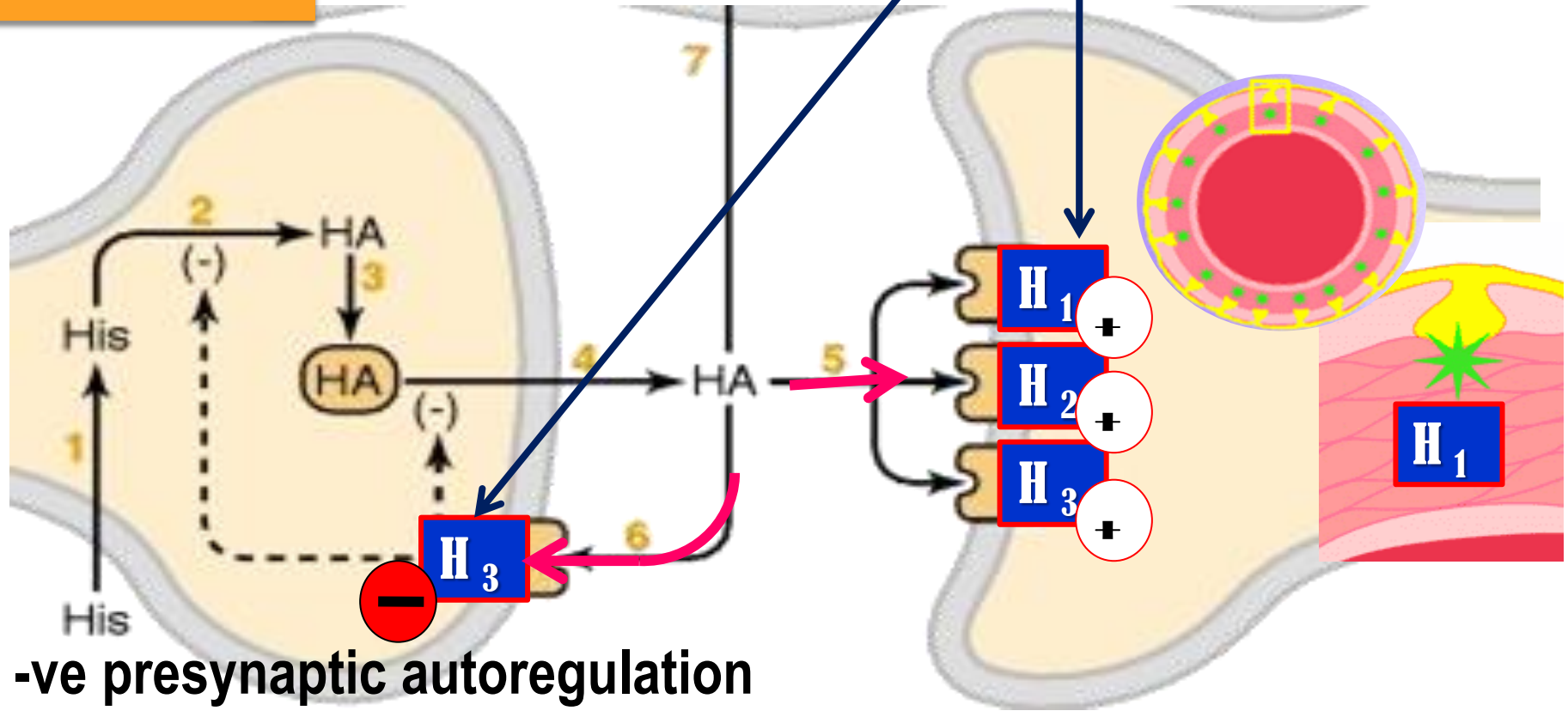
Mechanism of action (cont.)

Histamine → **Mediator**

Neurotransmitter

- CNS
- ANS

Betahistine



-ve presynaptic autoregulation

Slides | Important | Doctor's Notes | Explanation

Betahistine

Pharmacokinetics	*Tablet form, rapidly & completely absorbed *Partially metabolized (active) & excreted in urine *$t_{1/2}$=2-3h
ADRs	Headach,Nausea,Gastric effects (H2 gastric acid secretion) &↓ appetite and weight loss
Contraindications	Peptic ulcer ,Bronchial asthma (allergy) Pheocromocytoma (one of the signals that release adrenaline from adrenal medulla)

Vestibular Suppressants : Antiemetic

is a drug that is effective against vomiting or **emesis** and nausea.

Drug family	Mechanism	example
H_1 antagonist histamine reacts with gastric acid to cause emesis	*Antihistamine	Meclizine
	*Anticholinergic	Dimenhydrinate ☑
Phenothiazines (not selective) Work indirectly on dopamine	**Dopamine antagonists + Sedation** Sedation is good because if the patient (with vertigo) tries to stand he'll fall down hurting himself	Prochlorperazine ☑ Promethazine Drugs highlighted in red are further Disused →
Dopamine Antagonists Work directly on dopamine	**Dopamine Antagonist + Gastroprokinetic** i.e. enhance gastric emptying from stomach to duodenum(thus, decrease vomiting)	Metoclopramide☑ (crosses BBB) not good in long use because it will cause extra pyramidal manifestations like Parkinson)
		Domperidone ➜ doesn't cross BBB

Vestibular Suppressants : Antiemetic (cont.)

Drug	Mechanism of action	Indications	Adverse effects
DIMENHYDRINATE (Dramamine) more antiemetic less sedative than Meclizine **so more effective in vertigo than meclizine**	•**Antiemetic:** Block H1 receptors in CRTZ •**Sedative effects:Weak anticholinergic effects**	•in vertigo •In control of MOTION SICKNESS by ↓ excitability in the labyrinth & blocking conduction in vestibular-cerebellar pathways.	•Sedation •Dizziness •Anticholinergic side effects **Contraindications** •Glaucoma •Prostatic enlargement
PROCHORPERAZINE (A Piperazine Phenothiazines)	Antipsychotic , some sedation + antiemetic effects: it Blocks dopamine receptors at CRTZ	•One of the best antiemetics in vertigo •(sedating & has some vestibular suppressant action	—
METOCLOPRAMIDE	•A potent central antiemetic acting on CRTZ •Has some sedating action •Has potent gastroprokinetic effect	**In vertigo Cross BBB Work Centrally in verigo** CRTZ: chemoreceptor trigger zone	•Restlessness or drowsiness •Extrapyramidal manifestations on prolonged use

Slides Important Doctor's Notes Explanation

DRUGS INDUCING VERTIGO

Are those drugs (or chemicals) producing destructive damaging effects on structure or function of labyrinthine hair cells &/ or their neuronal connections

VESTIBULOTOXINS

Affecting only the balance

FUNCTIONAL derangement

(most of the vestibulotoxins are drugs that cause functional derangement)

Drugs altering fluid & electrolyte •
- Diuretics
- Antihypertensives ….

Drugs altering vestibular firing•
- Anticonvulsants
- Antidepressants
- Sedative hypnotics
- Alcohol
- Cocaine

MIXED OTOTOXINS

Affecting the balance &hearing

STRUCTURAL derangement

•Aminoglycoside antibiotics;
gentamycin, kanamycin, neomycin, streptomycin, tobramycin, netlimycin
•Fluroquinolines, Vancomycin, Polymixin
•Nitrogen mustard (cancer chemotherapy drug)

How structural derangement is induced by these drugs?

❖Neomycin → activate caspases → Death Receptor Pathway→ Apoptosis.

❖Gentamycin → evoke free radicals → Mitochondrial Pathway → Apoptosis.

FUNCTIONAL derangement

Quinine, chloroquine, quinidine causes vertigo+tinnutus
Loop diuretics,NSAIDs, Tobacco•

How functional derangement is induced by these drugs?

↓local blood flow → biochemical changes → alter electromechanical transduction →Firing of impulses

QUESTIONS

Note :
drug that induces functional damage is better than drug induces structural damage
Because after stopping the drug the function will become normal

1) Sara, 40 years old female noticed that she gets a virtigo for the day before her period for the last 4 months. the doctor prescribed her a drug to prevent futher primenustrual virtigo. The drug is:
   A) Furosemide
   B) Cinnarazine
   C) Meclizine

2) Abdullah, 50 years old male. He is traveling from Jeddah to Egypt by ferry and suddenly he feel nauseous and dizzy. Which one of the folowing can stop his symptoms:
   A) Dimenhydrinate
   B) Betahistine
   C) Quinine

3) **Neomycin can promote apoptosis by:**
   A) Activating caspases
   B) Evoking free radicals
   C) Both A & B

1)B 2)A 3)A

THE END

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