PHARMACOLOGY TEAM

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!!!! Imp. Hint :

- This team work is a combination between male and female lectures ; cause there is a slight different between them .

- at the end there are some MCQs + their answer

- Team note : red color

Parkinson`s disease

ILOs

- At the end of this lecture you will be able to:-

- Recognize the symptoms and pathophysiology of parkinsonism.

- Understand the pharmacology of drugs used for treatment of parkinsonism

pathophysiology

1- Degenerative damage to dopamenergic neurons in pars compacta of substantia negra

2- Loss of inhibitory effect on ACh excitatory neurons

3- Increase excitation of inhibitory GABAergic inhibitory neurons in corpus striatum

4- Increase Inhibitory effect on the inhibitory GABAergic neurons in pars reticulata of substantia negra.

5- This will lead to loss of restraint on the thalamus and cortex which will result in rigidity and limited mobility [hypokinesia]

So, there's imbalance between dopamine and Ach [↓dopamine & ↑ACh]

Therefore, treatment is by reversing this.

Drugs of treatment

- levodopa. :

is used with **dopa decarboxylase inhibitors**

e.g.**carbidopa , benserazide**

they prevent peripheral degradation of L-DOPA

lead to decrease the dose + side effect .

or **COMT inhibitor** e.g. **entacapone.**

- [dopamine agonists] Drugs that mimic the effects of dopamine at D2 & D3- receptors e.g. **bromocriptine, pramipexole and ropinirole**.
- MAO-B inhibitors (Inhibition metabolism of dopamine in the brain) e.g. **selegiline**
- Drugs that release dopamine e.g. **amantadine**
- Muscarinic acetylcholine antagonists ↓ ACh e.g. **benzatropine, trihexphenidyl and procyclidine.**

Note: MonoAmine Oxidase

MAO $_A$: metabolize norepinephrine **+** serotonin

MAO $_B$: metabolize dopamine

LEVODOPA :

- First -line treatment , combined with peripheral dopa decarboxylase inhibitor.
- Short duration of action t½= 1-2 h *(fluctuation of plasma concentration).*
- Absorbed from the small intestine
- by active transport,
- All types of parkinsonism except
- those associated with antipsychotic
- drug therapy.

Levodopa is an immediate precursor of dopamine that is metabolized to dopamine after crossing BBB.
Cause Administering dopamine has no effect cause it can't cross blood brain barrier.

Clinical problems with L.Dopa:

- **Wearing-off effect**.

gradual decrease in improvement after using the drug for years. That's why doctors spare the use of L.Dopa for advanced cases of Parkinsonism.

- **On-off effect**.

fluctuation of response. [sudden worsening when ↓ plasma levels of drug]

- progression of the disease and the loss of striatal dopamine nerve terminals.
- **dyskinesias** [**involuntary movements occurs in 40 to 90% of patients**]

  → due to fluctuating plasma levels of levodopa and the presence of hypersensitive dopamine receptors.

  The dyskinesias can be reduced by lowering the dosage; however, the symptoms of parkinsonism may then reappear.

** ADRs:-

** Peripheral side effects are:

- anorexia, nausea, and vomiting (due to stimulation of the CTZ).
- Orthostatic hypotension , **Mydriasis,**Cardiac arrhythmias occur in some patients.

** CNS adverse effects of levodopa therapy include vivid dreams, delusions, hallucinations, confusion , **dyskinesia** and sleep disturbances.

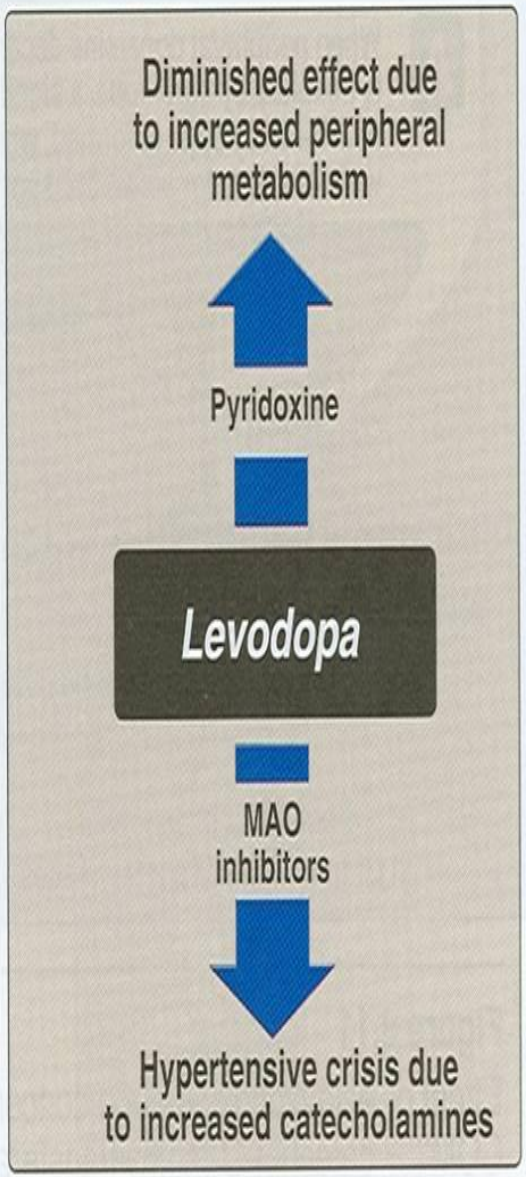


Figure 8.9
Some drug interactions observed with *levodopa*.

Interactions:-

- Proteins ingested with meals. ***(prefer to taken on empty stomach).***
- Nonselective MAO inhibitors (phenelzine, tranylcypromine).

dopamine will be transformed into epinephrine [peripherally] causing hypertensive crisis.

- Pharmacologic doses of pyridoxine. [vit. B6] it ↑ metabolism of L-DOPA.

contraindecation

- Psychotic patient. b/c anti psychotic drug decrease dopamine in the brain .
- Angle closure glaucoma. b/c it's increase intraocular press .
- With caution to patients with active ulcer.
- Patients with history of melanoma. **dopamine is a precursor for melanin**

Dopamine receptor agonists :

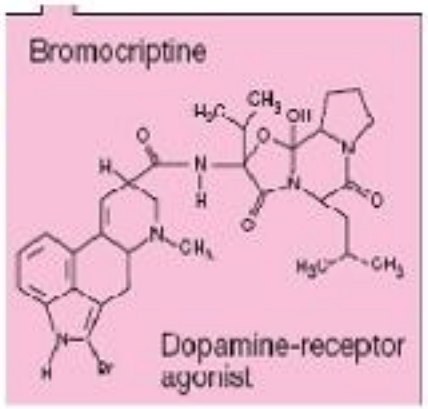
- long duration of action , less likely to cause dyskinesias than levodopa.
- As monotherapy, the dopamine agonists are less effective than levodopa.
- When used as an adjunct to levodopa in advanced stages, they may contribute to clinical improvement and reduce levodopa dosage needs.
- Examples ,bromocriptine.

Team note

Dopamine receptor agonist Compared to L.Dopa, it has:

1) less efficacy.
2) longer duration of action = ↓ clinical problems
3) more psychiatric adverse effects.
4) used with L.Dopa to decrease L.Dopa's dose. Lead to decrease the ADRs of L-DOPA

Bromocriptine



- Bromocriptine, an ergot derivative, is an agonist at the D2-receptors and a partial D1-antagonist.
- Bromocriptine is absorbed to a variable extent from the GIT ; peak plasma levels are reached within 1-2 hours after an oral dose.
- It is excreted in the bile and feces.
- Used for hyperprolactinemia. ***(galactorrhea).***

ADRs:-

- Postural hypotension, nausea, somnolence (Sleepiness)
- Dyskinesias. (*less prominent*).
- Confusion, hallucinations, delusions,
- in order to minimize adverse effects, the dose is built up slowly over 2 or 3 months.

contraindication

- In patients with a history of psychotic illness .
- Recent myocardial infarction,
- Active peptic ulceration.
- The ergot-derived dopamine agonists are best avoided in patients with peripheral vascular disease. Bromocriptine Causes peripheral vasoconstriction

Amantadine

- originally introduced as an antiviral.
- modestly effective in treating symptoms of parkinsonism.
- Useful in the early stages of parkinsonism or as an adjunct to levodopa therapy.

- **Amantadine affects dopamine release and reuptake.**
- **antagonist at muscarinic and NMDA receptors.**
- **Peak plasma concentrations of are reached 1-4 hours after an oral dose.**
- **t½=2-4h, most of the drug being excreted unchanged in the urine.**

Amantadine is Antiviral drug that has moderate antiparkinsonism and anticholenergic effect.

Adverse effects include:-

- **nausea, dizziness, insomnia, confusion, hallucinations,**
- **ankle edema, and livedo reticularis.**

livedo reticularis : a persistent purplish network-patterned discoloration of the skin caused by dilation of capillaries and venules due to stasis or changes in underlying blood vessels

- **Amantadine and the anticholinergics may exert additive effects on mental functioning.**
- **Should be used with caution in patients with a history of seizures or heart failure.**

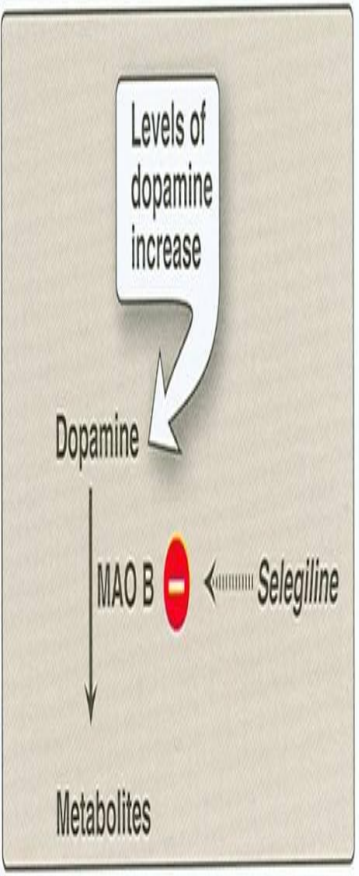


Figure 8.10
Action of selegiline (deprenyl) in dopamine metabolism. MAO = monoamine oxidase.

MAO $_B$ inhibitors:

E.g : Selegiline :

- is an irreversible inhibitor of MAO_B, an important enzyme in the metabolism of dopamine.
- Blockade of dopamine metabolism makes more dopamine available for stimulation of its receptors.
- is also used in conjunction with levodopa-carbidopa in later- stage parkinsonism to:-

- reduce levodopa dosage requirements
- and to minimize or delay the onset of dyskinesias and motor fluctuations that usually accompany long-term treatment with L-DOPA.

- Selegiline may slow the progression of the disease by reducing the formation of toxic free radicals produced during the metabolism of dopamine.
- Metabolized to desmethylselegiline, Which is antiapoptotic. effect against neurodegeneration
- It enhances the actions of endogenous dopamine.

** ADRs:-

- at higher doses Selegiline may inhibit MAO-A. ***(hypertensive crises).***
- Selegiline may cause insomnia when taken later during the day. .
- Selegiline should not be coadministered with TCA, meperidine or SSRIs. (may cause hyperpyrexia, agitation, delirium, coma).

** Anticholinergic Drugs :

- The efficacy of anticholinergic drugs in parkinsonism is due to their ability to block muscarinic receptors in the striatum.
- They exert only modest antiparkinsonian actions , used during the early stages of the disease or as an adjunct to levodopa therapy.
- Anticholinergics can provide benefit in drug- induced parkinsonism.

(they are effective when parkinsonism is due to drugs)

e.g. **1- Benztropine,**

2- Trihexyphenidyl , **>>>> Drug of choice in drug-induced Parkinsonism**

- They're effective in relieving the tremor not the hypokinesia.
- Not all patients respond well to them.

ADR:

- cycloplegia, dry mouth, urinary retention, and constipation.
- Confusion, delirium, and hallucinations may occur at higher doses.
- Trihexyphenidyl may cause withdrawal symptoms in patients receiving large doses.

Contraindications:

- **Prostatic hypertrophy**
- **Glaucoma**
- **Intestinal obstruction**

Summary

- Levodopa and carbidopa is the main treatment
- All other medications are adjuncts to levodopa therapy
- Levodopa, bromocriptine, selegiline drugs are contraindicated to be combined with antipsychotic drugs.

MCQ

1- All of the following are neurological characteristics of Parkinsonism except:

a) Tremors

b) Postural disturbances

c) Hyperkinesia

d) Rigidity

2- Crbidopa is useful in treatment of Parkinsonism because:

a) It is a precursor for Levodopa

b) It prevents peripheral biotransformation of L.dopa.

c) It prevents the breakdown of dopamine

d) It has an anti-apoptic effect.

3- Which statement about Bromocriptine is accurate?

a) It is contraindicated with psychotic patients.

b) Should not be administered with high protein meals.

c) It has an adverse effect of ankle edema

d) It is the drug of choice in drug-induced Parkinsonism

4- Which one of the following drugs is used in treatment of extrapyramidal side effects caused by neuroleptic drugs?

a)L.dopa

b) Trihexyphenidyl

c) Selegiline

d) Amantadine

5- Which one of the following drugs is contraindicated in prostatic hypertrophy and GIT block?

a) L.dopa
b) Carbidopa
c) Bromocriptine
d) Benzotropine

Answers

1	c
2	b
3	a
4	b
5	d