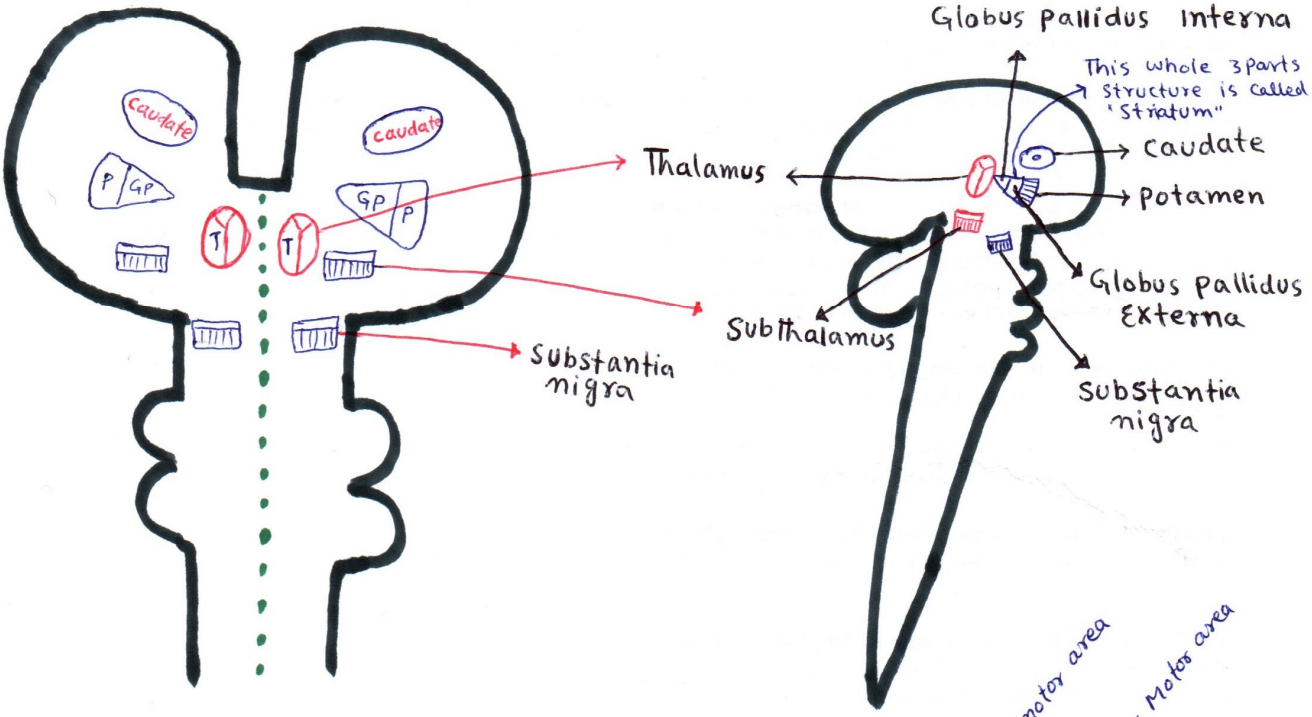
DRUGS USED IN PARKINSON'S & Alzheimers Disease

By: Zakir ullah Yousufzai



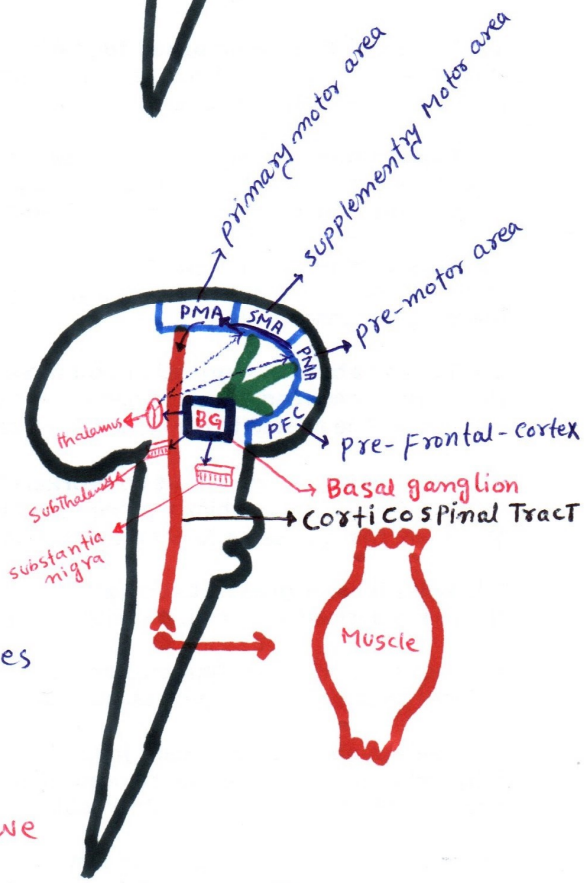
➡ Pre frontal Cortex is Concerned with:
* Thoughts & personality

When we decide to initiate a movement signal pass from:

- SMA
- Pre-MA &
- PFC

to basal ganglia, b/c Motor programes for movement are present in Basal ganglia.

E.g: A child can't write or type, but we can, b/c of training.
This training develop a circuit in Basal ganglia.



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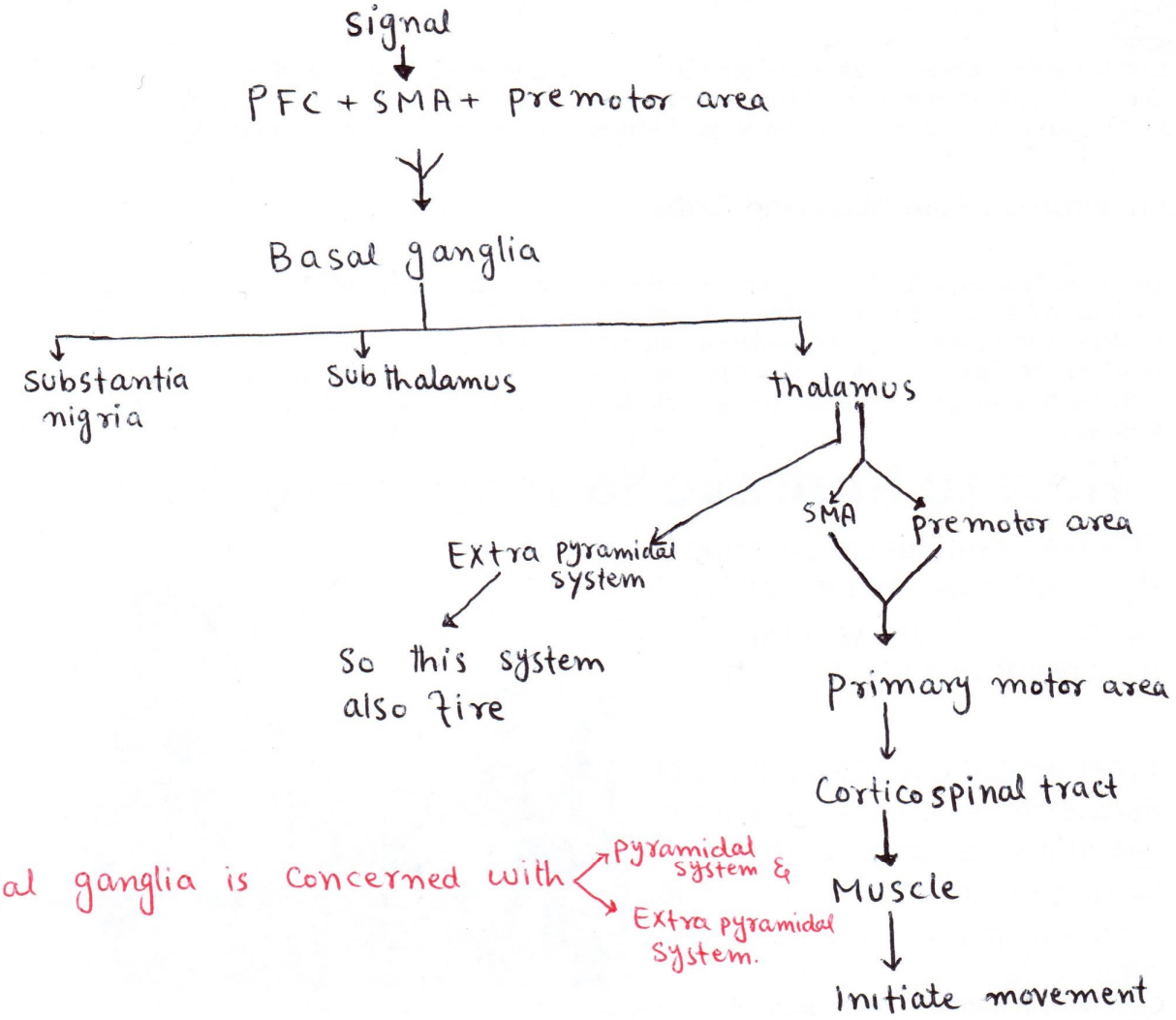
So when we initiate a movement, movement programs from, motor cortexes come to basal ganglia & program is activated.



*** Pyramidal system is concerned with:**

- final voluntry movements

*** Extrapyramidal system is concerned with:**

- Tone
- Posture
- initiation of purposeful movements

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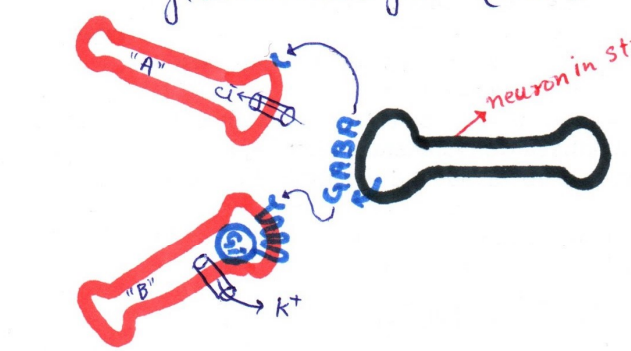
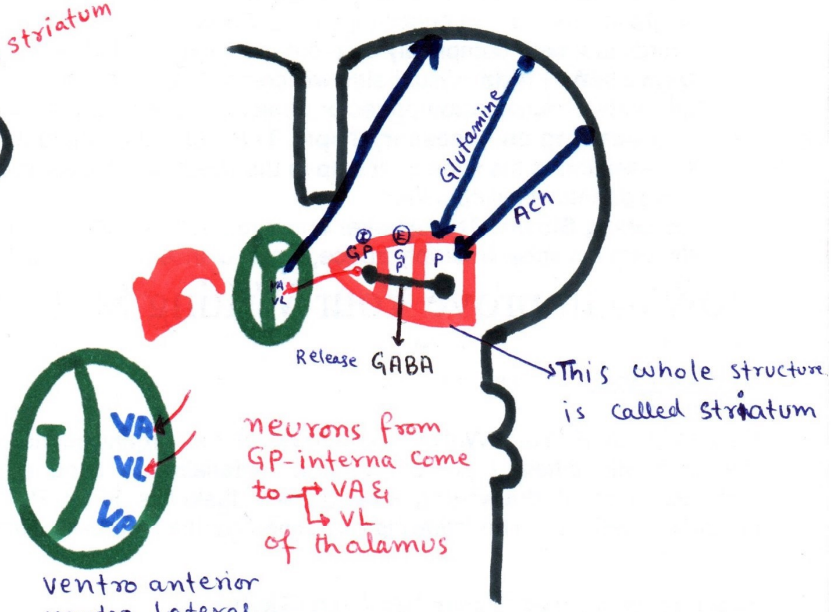
Corticostriatal fibers are stimulatory fibers, some are releasing Acetylcholine ⟶ which are called cholinergic fibers, & some are releasing Glutamine ⟶ which are called glutaminergic fibers.



Direct Pathway

There is a special inhibatory neurons in striatum pass to "Globus pallidus interna" & release GABA



ACTION OF GABA

GABA "A" Receptor

special chainel for Cl^- opens

more Cl^- move in

cell become electronegative

GABA "B" receptor

have Gi receptor

Open K^+-channel

K^+ comes out

cell become electronegative.

Direct Pathway Summary:

Corticostriatal (glutamine / Ach) → Putamen —GABA→ Globus pallidus interna → VA, VL Thalamus → CORTEX

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Indirect pathway

Corticostriatal pathways → Putamen

↓

Globus Pallidus Externa

↓

Subthalamus

↓ g/n fibers

Globus Pallidus interna

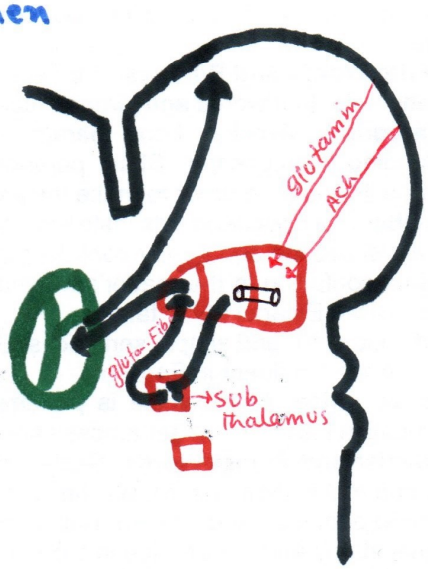
↓

VA VL

thalamus

↓

Cortex



NIGRostriatal Pathway

Substantia nigra

- Concerned with Direct Pathway
- Concerned with Indirect Pathway

* Substintia nigra helps in initiation of movement

action on Direct Pathway:

Substentia nigra → Dopamin → D_1 ® on Direct pathway

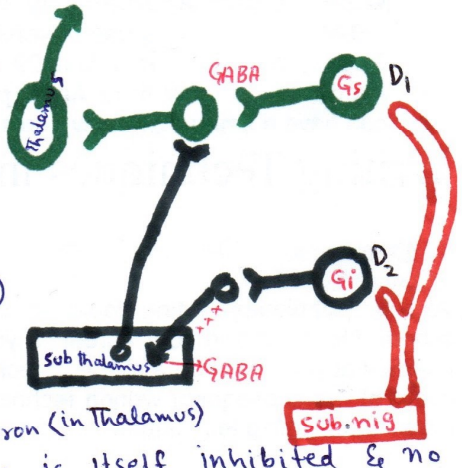
So this pathway will be stimulated (G_s)

↓

It release more GABA one nex neuron the next neuron are inhibited

↓

This inhibited neuron does not inhibit next neuron (in Thalamus) (b/c this is itself inhibited & no action potential occur in this) and doesnit release GABA, so the neuron of thalamus fire to Motor Cortex → which stimulate corticospinal → Muscle contraction occurs



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action on indirect pathway

Substintia nigra ⟶ Dopamin on D_2 of indirect Pathway ⟶ G_i ⟶ this neuron get inhibited

↓

this neuron does not release GABA on next neuron

↓

So nex neuron automatically fire on next neuron

↓

This neuron release GABA on next neuron (sub thalamus)

↓

So this next Excitatory neuron is inhibited

↓

So it doesn't stimulate next neuron (Globus pallidus interna)

↓

So next neuron does not secrete GABA (on Thalamic neuron)

↓

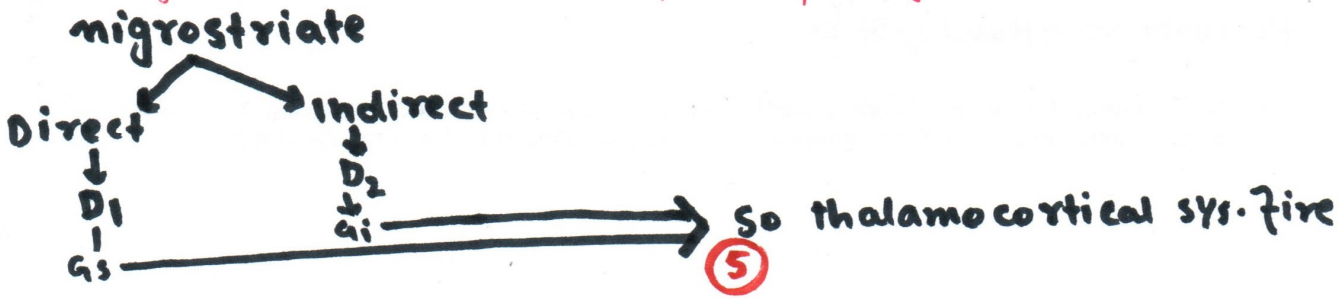
So thalamic neuron does not inhibited, & they will fire on Cortex.

for movement to initiate we need to block GABA release on thalamic neuron.

How this pathway is inhibited?

This pathway is inhibited by nigrostriatal pathway both by Direct & indirect pathways

Nigrostriatal pathway is dopaminergic pathway, this pathway is originated from Pars Compacta of Nigrostriat



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Thalamus have many nuclei, large number of tracts from globus pallidus to thalamus are present.

Pallidothalamic pathway:

This pathway is determining firing of thalamocortical pathway.

In parkinson's disease by the age (↑50y) neurons originating from pars Compacta, of Sub nigra undergo degeneration.

Human brain have more than 10 Billions of neurons.

on average every one neuron communicating with 10,000 other neurons.

when nigrostriatal pathway degenerate, there is decrease in Dopamin release.

In a normal person there is balance B/w Neurotransmitter release.

In parkinson's disease Dopamine decrease and Acetylcholine are uncompensatedly increase, so there is primary defect in the Dopamin Pathway, such person suffer with two problems:

1. with decreased dopamine related activity.
2. with increased Acetylcholine related activity.

- Direct pathway disturbed

e.g:

↓Dopamine ⟶ ↓Gs ⟶ 1st neuron does not release GABA ⟶ 2nd neuron is stimulated ⟶ this 2nd neuron release GABA on Excitatory neuron (thalamic neuron) & Inhibit them, so such person is unable to initiate a movement.

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- Indirect pathway also disturbed

e.g

↓Dopamine → ↓Gi → neuron is not inhibited → this release GABA on next neuron → this neuron does not release GABA on next neuron (subthalamic) → so it does not release GABA on next neuron (Globus pallidus interna) → This neuron release GABA on next neuron (thalamic neuron) & inhibit this neuron → so person is unable to initiate movement.

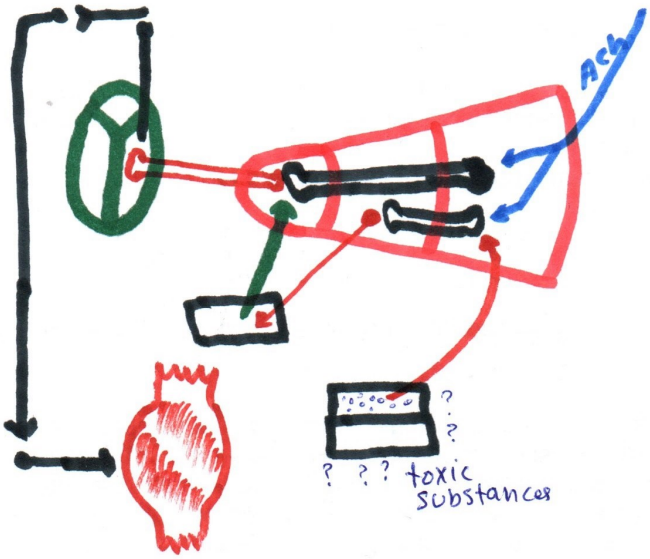
In Parkinson's disease Person have:

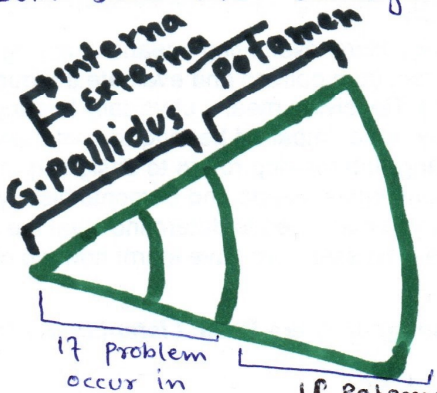
1. Mask like face
2. Serpentine eyes (snake like)
3. Micrographia .... etc
4. Athetosis → slow semipurposeful movements

- **Hemiballismus:** If subthalamus of one side is damaged

Problem occur in Tone, specially at pelvic & shoulder girdle (like Ababic dance)

- **Ballistic:** If subthalamus of both sides are damaged





If problem occur in Globus pallidus Athetosis will occur ↓ e.g (classical indian dance)

If potamen are damaged patien develope "Chorea" ↓ e.g (Mickeal Jackson dance)

If degeneration of nitrostriatal neuron occurs by Toxic substances we give such drug which doesn't cause further degeneration.

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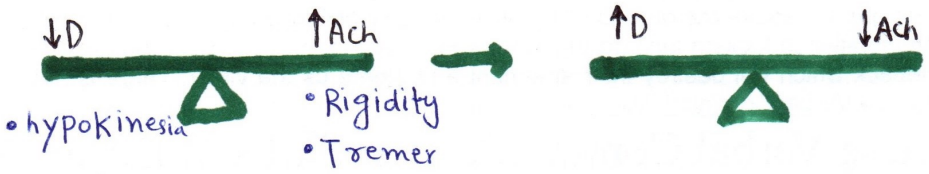
Currently drugs which are used, Restore the level of neurotransmitter.

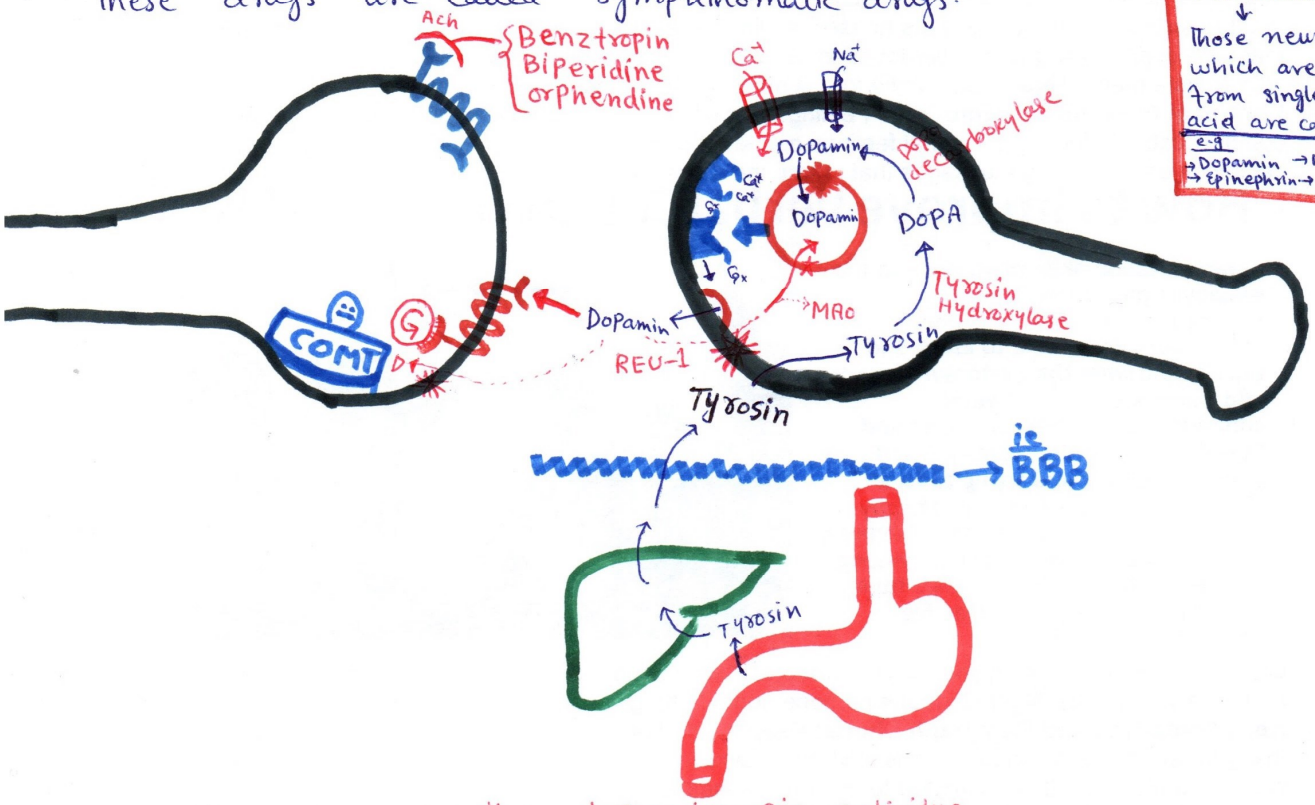


If Dopaminergic Drugs are given 1st hypokinesia are corrected & by the time when balance b/w Dopamine & Acetylcholine is achieved, all symptoms are corrected.

If we give anticholinergic drugs, Acetylcholine decreases, so rigidity & Tremer Corrected.

These drugs are called sympathomatic drugs.

Monoamines
↓
Those neurotransmitters which are made from single Amino-acid are called MA.
e.g
→ Dopamin → N·EPi
→ Epinephrin → serotonin



How we Increase the dopaminergic activity?

- Increase the synthesis of dopamin
  In cerebral arteries Endothelial cells are placed very closely, they doesn't allow every thing to pass.
  Reuptake-1 mechanism is present on all monoaminergic nerve endings
  e.g: EPi, N·EPi, Dopamin, serotonin.

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① Levodopa:

Given orally ⟶ pass through circulation ⟶ Cross BBB ⟶ enter into remaning Nerve ending (other than degenerated)

Levodopa ⟶ (D. Decarboxylase) **Dopamine**

Levodopa increase the synthesis of Dopamine by acting of Dopa-decarboxylase, & convert Levodopa to Dopamine
This large amount of Dopamine make good for whatever Dopamine lost.

Dopamine is not given directly b/c it is highly polar compound therefor can't cross the GIT Mucosa & BBB.

② Amantadine: (an antiviral drug)

(i) ↑ synthesis of Dopamin
(ii) ↑ Release " "
(iii) ↓ Reuptak " "

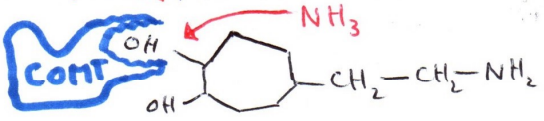
③ Dopamine Receptor agonist: (these drugs stimulate the Dopamine receptor)

(i) Bromocriptin
(ii) Pregolide
] Ergot derivitive Alkalides
(iii) Pramipexol
(iv) Ropinirole

Destruction of dopamine is prevented by given COMT-inhibitor or MAO-inhibitor or inhibitor of both
So on this way whatever dopamine is formed as stored & does not be destroyed.

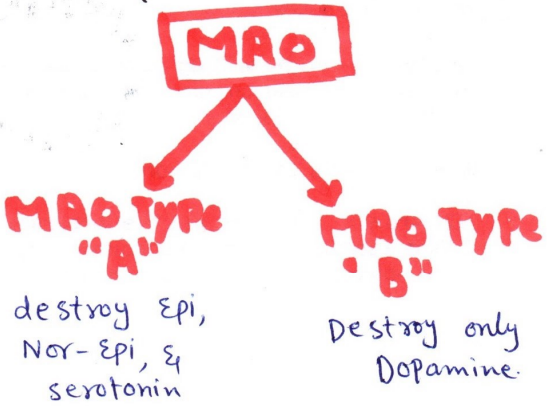
④ Selegline: ⇒ MAO-Type "B" Inhibitor.

⑤ Tolcapan: ⇒ COMT-Inhibitor.



⑥ Benztropin, Bipridine & Orphenidine ⇒ Cholinergic Receptor blocker

⑨



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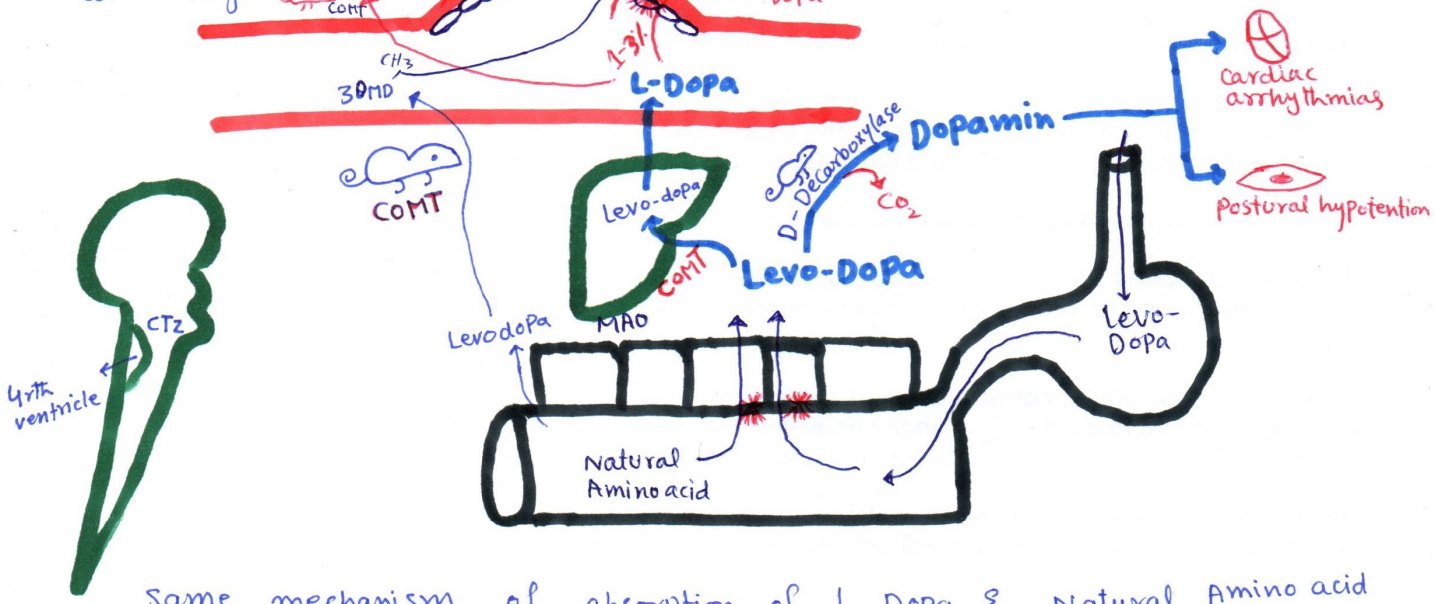
Levo-Dopa:

It is given orally about 40min or 1hr before meal because its absorption depends on Gastric Hcl, and its absorption occur by same pathway as like natural Amino acids.

natural Amino acid e.g: Leucine, Isolucine.

If we take heavy meal e.g meat, than excess Aminoacid is absorbed by this pathway, while levo-dopa does not absorb, so if these patients like proteins, they should take perferably at night.



Same mechanism of absorption of L-Dopa & Natural Amino acid also occur at BBB.

whatever levo-dopa is taken only 1–3% reached to CNS, while other is converted by D-Decarboxylase into dopamine & release Co_2.

this dopamine act on Heart and vascular system.

* They stimulate Cardiac arrhythmias e.g: sinus Tachyarrhythmias
* By acting on vessele it produce postural hypotention, this perephral Dopamine produce many side effects.

Area in 4th ventricle "postrema area" where chemotrigger zone (cTz) lies, this Dopamine also stimulate this area & Produce nausea & vomiting.

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we want more Levo-Dopa to reach to CNS, & less is converted into Dopamin in perephry.

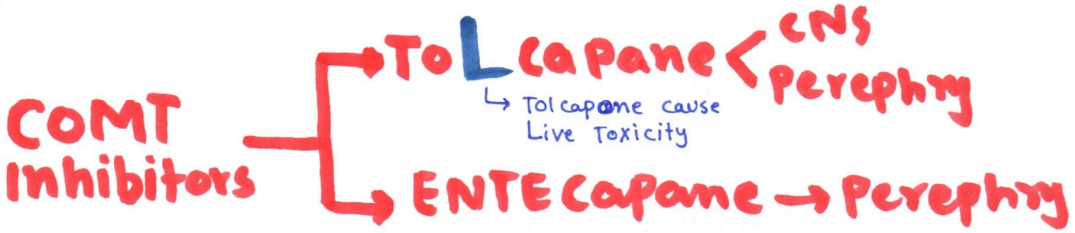
For this purpose we need to destroy this perephral dopamine-decarboxylase enzyme, by giving **Carbidopa** along with Levo-dopa.

So, perephral Dopamine↓ ⟶ ↓ Perephral side effects.

More Levo-dopa reach to CNS, ↑ Dopamine release by nerve endings, so on this way Parkinson's symptoms relive in atleast 1/3 of patients.

This carbidopa increase Levo-dopa to CNS by about 10% i.e from 1–3% to 10%; but still 90% drug is destroyed in perephery.

whatever dopa is escaped from dopa decarboxylase is captured by **COMT** enzyme & this enzyme cause methylation of Dopa, This methylated product produce no side effects but this come in competition with Levo-dopa in absorption from BBB



As Tolcapane cause problems, so we give to such patients Entecapane B/c it act only on perephry.

while Tolcapane produre Liver Toxicity and acts both on → CNS, Perephry.

* If we prescribe Tolcapane we muct Take a written Concent from patient & check the LFT each time.
* This COMT inhibitor ↑es Levo-dopa into CNS, But this ↑es Levo-dopa to CNS will be converted in nerve ending to Dopamin, this high level of dopamine will produce **Dyskinesia.** ie: Central side effects. (in Basal ganglia)

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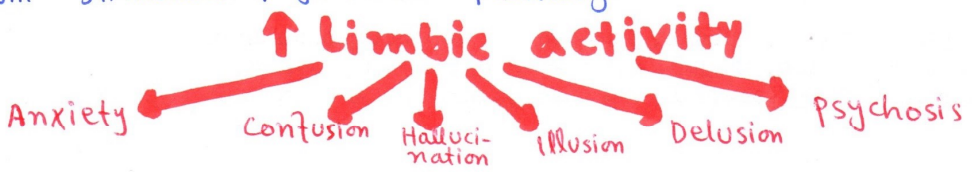
As this high level Dopamine reach to mesolimbic system it will stimulate psychiatric pathway.



Levo-Dopa + Carbidopa = Sinement

Levo-Dopa + Carbidopa + Entacapane = STALEVO

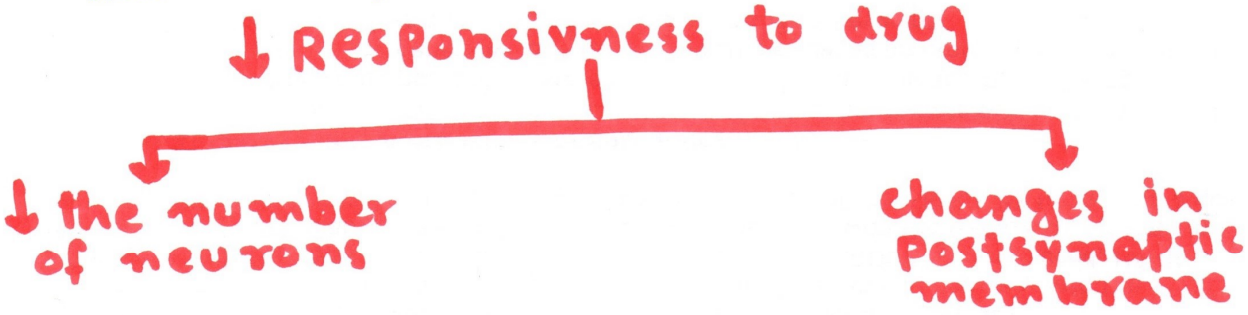
when Levo-dopa is used for treatment in initial few years symptoms disappear, but after that effects decreases and more side effects appear.

Why different people have different degree of responsivness to L-dopa?

when parkinsons become well developed about 70 — 80% of Nigrostriatal pathway is destroyed.

Levo-dopa does not correct destroyed neurons, it only increase work of normal neuron, so when treatment with Levo-dopa starts patient initially feel better because enough Dopamine is synthesized and released by remaning Normal Neurons, But if treatment is Continue as more neurons progressively decrease by age, so number of neurons available for action decreases, so Capability of remaning neurons to keep Nigrostriatal activity is decreased, so effecienty of drug is decrease → ie: why drug loses its action in 3—5 years.

Some people belive Dopamin in CNS is broken down to Metabolites, which further destroy the remaining neurons, so it is better to initially start with drug which increase dopamine receptor.



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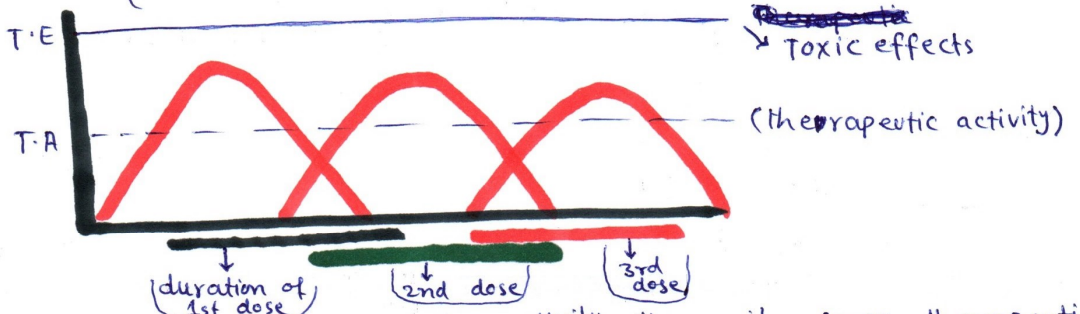
Side effects of Levodopa

- **Perephral**
  - Heart → Tachyarrhythmia
  - Vesseles → Postural hypotention
  - GIT → Anorexia, nausea, vomiting, Peptic ulcer (Parital cell stimulation by Dopamin®)
  - EYE → pupilodialation
- **CENTRAL**
  - **Dyskinesia** (Nigro striatal)
  - **Limbic system** → Anxiety, Insomnia, aggitation, Confusion, Illusion, Dillusion, hallucination
  - **Responce fluctuation** → End of dose, ON OFF Phenomena

END of Dose: e.g: Some patients on Levo-dopa initially have good responce but after that they produce side effects.
ie: End dose of Akinesia.

ON-OFF phenomena:

Let us suppose someone take levo-dopa with 6-hour interval. Than initially after 1st dose as dopamine form, it work well than progressively as number of neuronos decreases, so they decrease capibility to synthesize and store enough dopamine, so Dopamine activity decrease before next dose



If drug level is more than therapeutic activity than it cause therapeutic action.

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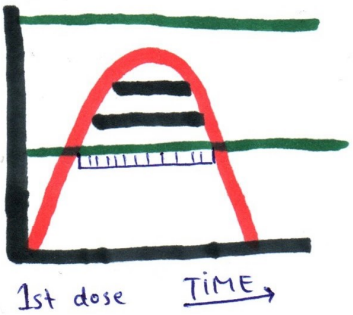
* If drug level is more than therapeutic activity, than it cause therapeutic action.
* If drug level is less than therapeutic activity No benifitial effects occurs.
* If drug level is b/w therapeutic & Toxic effects, it produce good actions.
* If drug level is above Toxic effect, it produce Toxicity.

But As by time Number of neurons decreased, so the Capability to form Dopamin also decreased by End of the dose.



In This patient initially Therapeutic action occurs at all neurons.

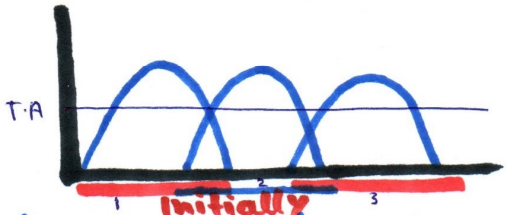
with the time duration of action decreas.

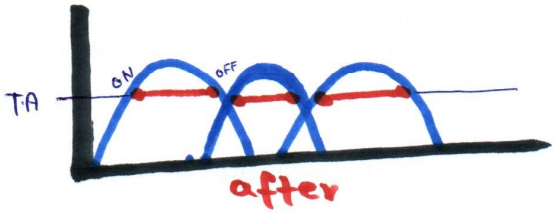
e.g initially even small amount of drug produce large effects.

By the time number of neurons decreases, so inspite of increasing drug further action reduced.

* Initially effect of 2nd dose occurs before 1st dose lost, effect of 3rd dose occur before 2nd lost, but by the time as number of neurons decreases.

After therapeutic time increase, so action of drug now start at high level and ends earlier.





Patient now undergoes ON-OFF Phenomena.

① Number of neurons become less
② destruction of post synaptic membrane

one way to manage such patients is to give:

① Neuroprotective drug
② Increase total dose of drug
③ Give drug with little time duration

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① By increasing dorse, Action ↑es, but level of dose above Toxic effect, cause dyskinesia.

② Give them Direct dopamin receptor blocker.

③ Give antidestructive drugs.

So all other drugs rather than Levo-dopa is given to solve the problem of ON-OFF phenomena, to decrease the ON-OFF phenomena, we further decrease L-dopa.

* Levo-dopa may appears in body secretions e.g⇒ saliva, sweat, Anal secretions, urine & turn all of them brownish colour.

Sometime we give drug holidays to these patients.

ie we does not give them drug for few days, but this is a risky mechanism

Nowadays in most of cases we donit use drug holidays

Because when we give drug holiday to a patient with levodopa we think that all associated problems will be corrected But such patient die b/c if Patient have svear parkinsonismis he have hypokinesia, he cannit swallow & have no saliva & may develop bronchopneumonia such patient may die of Bronchopneumonia or such patient die due to hypokinesia produce stasis in vein & develop thromboembolism so such patient may die b/c of these problems, or this Patient Come with svear hypokinesia and deepression, so if we give holidy to these patient, the patient will Expire.

* Make sure someone is always with patient to care him.

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Contraindication of Levo-dopa

① In patient with psychosis
② Narrow angle glucoma
③ Svear Cardiac diseases, (Especially Tachyarrhythmias)
④ Peptic Ulcer
⑤ Malignant Melanoma.

Dopamine Receptor agonist:

(1) They have some advantages over Levo-Dopa.
ie: they directly stimulate receptor and does not need conversion from precursors.

(2) does not need functional dopaminergic terminals.

Now these drugs are superior to Levo-dopa.

Dopamine receptor Agonists
- Ergot derivities
  - Pregolite $D_1 + D_2$
  - Bromocreptine D_2
- Non-Ergot derivitive
  - Pramipexol $D_3 > D_2$
  - Ropinerol $D_3 > D_2$

* These drugs are given to patient who have "END of DOSE AKenesia"
* These drugs are successful in patient who have ON-OFF-phenomena
* These drugs are even effective in patient who are resistant to Levo-dopa.
* These drugs are also used along with Levo-dopa.
* These drugs have longer half life.
* Now a days these drugs are used as a 1st line.

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* Pramipexol is proven to be Neuroprotective.
  - They belive this drug and its metabolite have some Antioxidant activity, So due to this Antioxidant activity when these drug act on nigrostriatal pathway, it decrease further loss of neuron to some extent.

side effects

Some of side effects Related to Ergot, & Some are not related to Ergot, Most of side effects are due to increased Dopamine.

Dopamine specific side effects

GIT	B.Ganglia	Limbic system	CVS
Anorexia Vomitting Nausea	Dyskinesia	Psychiatric effects	Tachyarrhythmia hypotention

special side effects related to Ergot:

① Pulmonary infiltration
② Digital (Fingers) vasospasticity and Gangrane.
③ Erythromylagia (in this disease feet turn red, tender, swollen and painful.
* If we stop the drug, Erythromylagia disappear within few days.

Non-Ergot drugs produce No Ergot specific side effects, so these drugs are more used.
But these drugs produce all side effects which are due to increased dopamine activity.

Non-ergot specific side effects:

Sometime they produce attack of Irresistable sleep. (which is hazard for patients using heavy machinery).

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MAO-B Inhibitor:

Selegiline: ↓es dopamine destruction → more dopamine Stores → ↑es dopamine supply to nigrostriatal pathway → decrease parkinson's related symptoms.

* It is also a neuroprotective, so decrease further loss of neurons.

⇒* selegiline should not be given to patient which are already on SSRI (selective Serotonine Reuptake Inhibitor)

⇒* selegiline should not be combined with Non-selective MAO Inhibitor.

Rasagiline: is more potent than selegiline.

Side effects of selegiline:

* same as due to Increased Dopamine.

COMT-INHIBITOR:

Tolcapone, Entacapone

Levo-Dopa —COMT→ **3.O.M.D** → It has compitition with Levo-dopa in entring by BBB to CNS.

Levo-dopa to CNS

By giving these drugs we have the following advantages.

① They don't allow Levo-dopa —to✗→ 3.O.MD, so more Levo-dopa reach to CNS.

② By decrease 3.O.MD, they decrease competitor of Levo-Dopa in BBB.

③ decrease destruction of Dopamine → ↑es work of dopamine.

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side effects of COMT-inhibitors

all those side effects, which occur due to ↑es Levo-dopa, so ↑es levo-dopa Toxicity.

special side effects

ToLCapone cause ⟶ Liver Toxicity.

Apomorphine:

This is a powerful stimulator of dopamine receptor.
It is injected subcutaneously and start action within 10min ⟶ 2hr.

If a patient with parkinson's become immobilize & frozen in OFF stage, than Apomorphine injection have powerful action.

It produce very svear nausea.

Amantadine:

* This drug is an antiviral drug used for H.influenza.

It increase synthesis, increase the release & decrease the reuptake of Dopamine.

Recently it was also discovered that this drug stimulate glutaminergic receptor.
ie stimulate thalamocortical pathway and slightly increase the activity in parkinson's patients.

* It works only for few weeks.

side effects:

same as ↑ed Dopamine.

specific side effects:

Levido Reticularis ⟶ skin lesion, specially red lines on skin.
If drug is discontinue, symptoms also disappears.

* These drugs may produce edema, which is treated by diuretics.

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ANTi Cholinergic Drugs:

- Benztropin
- Biperidine
- Orphandine
- Procyclindins
- Tri-hexy-phenidyl

These drugs goes to CNS act on nigrostriatal pathway and decrease Acetylcholine activity.

side effects

① As cholinergic receptor are present throughout cerebral cortex, whene these receptors are blocked patient develope:
- Confusion
- Forgetfulness

ie it Cause undue suppression of CNS.

② act on CVS → Cardiac arrhythmia

③ act on GIT Cause:
- Constipation

④ when act on urinary bladder cause
- Urinary retention.

⑤ cycloplegia

⑥ Dry Mouth.

surgical Procedures:

(1) **Thalotomy**
(2) **Pallidotomy**
(3) **Thalamic stimulation**
(4) **Transplantation of dopaminergic cells:** cells taken from fetus (dead) & put them in parkinson's patient, it work for few months.

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In californea large number of patients came with Parkinson's, They are found be addicts which contain MPTP (a toxic substance) & this is converted by MAO-"B" to MPP+.

MPTP $\xrightarrow{\text{MAO-"B"}}$ MPP+

MPTP enter into pars compacta and converted by MAO-B into MPP+

There are some inherited problems also

* These toxic substances destroy substentia nigra.

If we give substance, which protect substentia nigra neurons, this will be a big achievment.

what happen to substentia nigra neurons when they destroyed?

They undergo process of destruction & lose of dopamine, one of product of Dopamine is Melanine, which produce black colour in substantia nigra, so substantia nigra loses black colour, They develope some intermediate fillament; these are called "Lewy bodies"

After this research Now Dr.s give drugs which are:

(1) Neuroprotective

(2) Antiglutaminergic

(3) antioxidant

(4) Glial tissue derived substances

Glutamine ⟶ open Ca^{+} channels ⟶ neurons overloaded with Ca^{+} ⟶ this high Concentration of Ca^{+} kills the neurons.

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Managment of Movement disorders other than Parkinson's disease:

Tremor: Rhythmic Ossilatory movement around the joint.

* Physiological Postural Tremor: (β_2 R)

They are present normally, & Enhanced by:

- Thyrotoxicosis
- Anxiety
- Fatigue
- Intravenous catechol injection
- Bronchodialator drugs (β_2 stimulators)
- TCAs (Tricyclic Antideepressant) they does not allow nerve ending to Reuptake the Neurotransmitter
- Cocain also block the Reuptake Mechanism
- Lithium drugs

These physiological tremor are initiated by (β_2 Receptor)

R_x ⇒ Propranolol (β_1, β_2 blocker)

* Essential tremor (initiated by β_1 AR)

R_x ⇒ Metoprolol (β_1 blocker)

contraindication of Propranolol ⇒

Essential tremor are reduced to some degree by

- Alcohol Transiently → but Mechanis unknown.
- Anti Epileptic drugs also tes essential tremor.
  - e.g * Primidone
  - * Topiramate

Drugs which stimulate GABA Neurons are:

* Alprazolam

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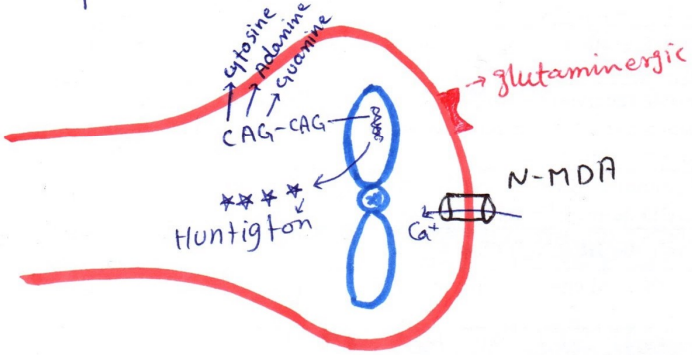
HUNTIGTONS DISEASE

it is an autosomal dominant disorder, have its defective gene on chromosome 4, which are Trinucleotide repeats.

Parkinson disease
- ↓ Dopaminergic activ
- ↑ Ach activity



This protein is present in Gabergic & glutaminergic neuron. glutaminergic Receptor are also called N-MDA (Huntington protein stimulate this receptor)
(N-Methyl-D-Aspartate)

when such neurons are stimulated by glutamine cell are overloaded with Ca^+. high Concentration of Ca^+ are toxic for neurons, & increase enzymes (protease, Nuclease, phosphatase, phospholipase) level, which cause Apoptosis (Exicytotoxicity)

to treat such patients we need to either ↓es Dopamin or ↑es Acetylcholine & glutamine

upto now there is no any drug which ↑Ach & glutamine, so treatment of these patient is to ↓es dopaminergic activity.

These patients develop:
- chorea
- Dementia

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Touretts syndrome

* Chronic Multiple Motor & vocal tics of early onset (childhood, or Adolesent)
* It is due to increased dopaminergic activity

℞ → Haloperidol, pimozide
→ Thalamic stimulation

Restless legs syndrome:

Creeping, svear discomfort in legs & patient is compelled to move about his legs.

In this syndrome:

- sleep of patient is disturbed, they may have somnolence at day time.

Causes May be:

- Idiopathic
- Pregnancy
- Diabetic Neuropathy
- Iron deficieney Anemia

℞

Non Ergot Dopamine receptor agonist
e.g → Ropinirol
· Diazepam

wilson's disease

This is an autosomal recessive disorder in which there is defect in Copper Metabolism.

* Cu may be unduly accomulates in liver & produce **cirrohsis.**
* Cu may accomulate in Basal ganglia, which produce **Abnormal movements** → Tremer, Rigidity, etc Dysarthria
* Cu may unduly accomulate in eyes called "Crisor fashion ring"

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Rx of wilson

1) Penicillinamine:

They through out Cu of the body, but they have many side effects:

e.g:
- Nausea
- Vomiting
- Glomerolonephritis
- SLE
- etc

2) Potassium Disulphide:

Bind in GIT with dietry Cu, so Cu is not absorbed & loss of cupper in feces.

3) Zinc Acetate:

Taken orally bind with Cu in GIT & loss of Cu occur in feces.

DRUGS USED IN AIZHEIMERS DISEASE

This disease clinically present as dementia

De Mentia → alot of mental functions are lost.

Dementia include:
* loss of intellectual functions (even Patient forget that e How to close the buttons)
* loss of recent Memory

It is a progressive disease:

senile plaque (of β amylosed protein)

Neurofibrillary Tingles

loss of cholinergic neurons in cerebral cortex specially in "Nucleus Basalis of massnart"

It is usually a degenerative disease of CNS, in which cerebral cortex undergo degeneration and Atrophy.
* Initially patient come with svear mental functions.
* occur Mostly in old age.

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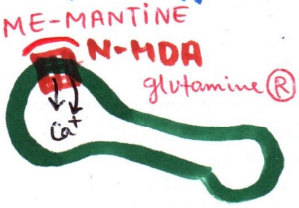
why neuro degeneration occurs?

Cause of neurodegeneration is Exitotoxicity

DRUGS

Excitotoxicity



Ca^+ Toxicity cause degeneration of neurons.
ie Apoptosis

Rx: ME-MANTINE

Side effects
- Confusion
- Agitation
- Restlessness

Central Acetyl choline esterase inhibitor

1. Galantamine (competitive inhibitor of enzyme)
2. DONEPANZIL
3. Revastigmine
4. TACRINE

Non-competative of centrally Acetyl choline esterase.

* Competative inhibitor:
When these drugs ↑es, the inhibitor will displaced.

* Non competative inhibitor:
Inspite of increasing drug inhibitor does not displaced.

Tacrine is used less b/c It is hepatotoxic

Side effects these drugs also inhibit perephral Acetyl choline esterase to some extent.

side effects:

Due to ↑es Ach in perephry:

In GIT
- Anorexia
- Vomiting
- Nausea
- GI Gramps

Ach is important neurotransmitter than drug.
↑Ach ⟶ activity on Muscle ⟶ Muscle cramps

- Alzheimer's patients along with dementia have:
  - Agnuasea
  - Apraxia
  - Athesia

] due to cortical dysfunction

Pharmacologic Treatment just delay the lost of further neurons.

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End of lecture
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