Hashemite University
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Medical School Committee

Scientific Team
الفريق العلمي

PHARMACOLOGY

Lecture : 4

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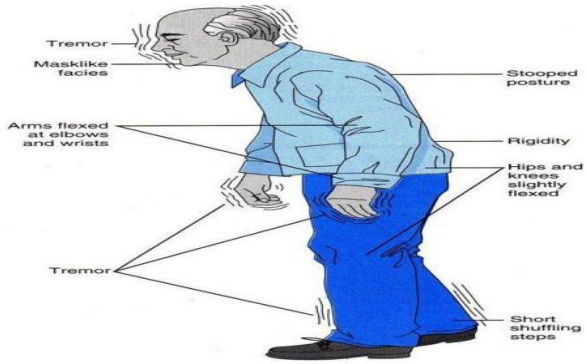
Drugs for Neurodegenerative Diseases

Parkinson's Disease

• Parkinsonism: is a progressive neurological disorder of muscle movement, characterized by tremors, muscular rigidity, bradykinesia and postural and gait abnormalities

هسا في فرق بين لما نحكي Parkinson disease وبين parkinsonism. هسا الparkinsonism هو syndrome بيجي نتيجة الmovement progressive neurological disorder of muscle فهذول بصير عندهم tremors وبكون او بزداد نتيجة الحركة مع الrest بكون موجود بس بزداد مع الحركة

وكمان بصير عندهم muscle rigidity وبسموها lead-pipe rigidity وبصير عندهم bradikinesia وبصير عندهم posture abnormality الي هي stooped posture وgait abnormality الي shuffling gait الي بوخذ فيها short step واجريه بزحفو على الارض



Parkinsonism: Etiology

• Idiopathic (Parkinson's disease): primary or idiopathic destruction of dopaminergic neurons in the basal ganglia.

هو الparkinson disease بحصل نتيجة idiopathic reason بس في other cause بؤدي لل parkinsonismمثل

• Secondary parkinsonism:

❑ Viral encephalitis

❑ CO or manganese poisoning.

❑ Drug-Induced parkinsonism "pseudoparkinsonism" e.g., haloperidol

Parkinson's Disease: Pathophysiology

• Destruction of the dopaminergic neurons in the substantia nigra area in med brain→ ↓ dopaminergic stimulation in the corpus striatum.

• The dopaminergic neurons fire tonically (not in response to certain stimuli).

• Parkinson's results from reduced dopaminergic inhibition of the cholinergic neurons in the neostriatum, resulting in overproduction of acetylcholine→ loss of control on muscle movement

هسا سبب الparkinson انو بصير destruction of the dopaminergic neurons in the substantia nigra
بس السبب الي ادى لهاض الdestruction مش معروف

هسا هاي الarea شو بتعمل ؟ هسا الsubstantia nigra بتبعث neuron لل neostratum(cudate nucleus and putamen nucleus) فال substania negra بتقرز dopamine الي بشتغل على D2 على الneostratum الي بشتغل ك inhibitory على neostratum

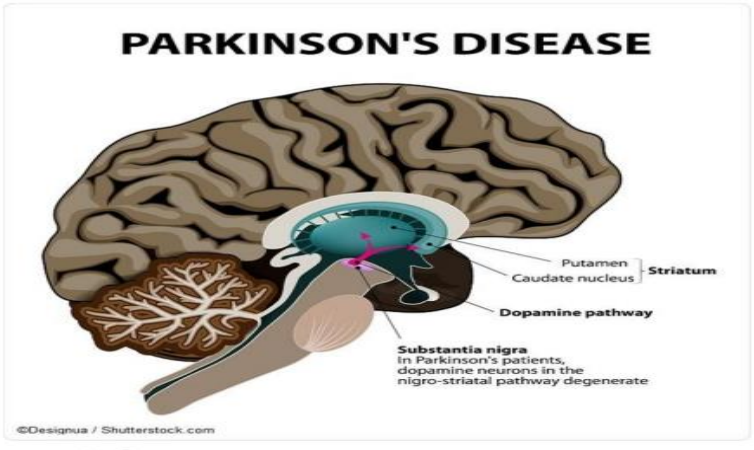
هسا عملية الreleasing of dopamine by substantia nigra بكون tonic release يعني انو continuous in resting change is tonic بس هو rate of release اما بنقلل او بنزيد ال signal فاذا بدنا نغير releasing release

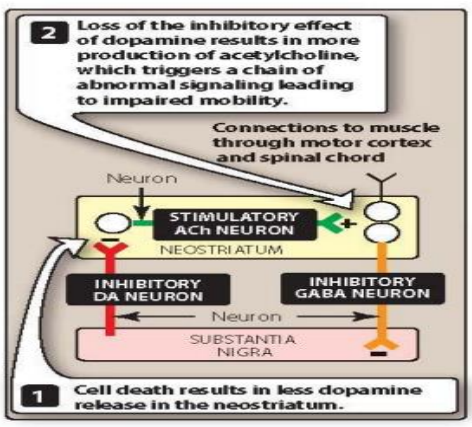
And in neostriatum have interconnecting neuron is cholinergic neuron release Ach and these Ach connection to muscle through motor cortex and spinal cord

فهسا بالوضع الطبيعي دايما ال dopamine طالع وعامل inhibition على الcholinergic neuron حتى يخليه under controlled بس لما بدي اتحرك بتغير الrate of release وبالتالي ال dopamine is inhibit the movement

هسا الcholinergic neuron بعمل activation لinhibitory neuron وبفرز GABA على ال Substenia nigra وبعمل negative feed back

فلو يزيد الdopamine بقل الcholinergic ولو يقل الdopamine بويد ال cholinergic وبالتالي ال substania nigra بعمل regulation of movement فاذا خربت هاي الcycle راح يصير movement abnormality فالي بصير بال parkinson هو destruction of substania nigra فانت خسرت الcontrol inhibitory على الcholinergic neuron فراح يصير rapid firing والsignal باتجاه الcord motor cortex and spinal بزيد والن





نتيجة abnormal of movement

Strategy of therapy

Antiparkenson drug aim is to restore dopamine/Ach balance

1-Enhance dopamine synthesis (dopamine precursors)

2-Dopamine receptor agonism

3-Acetylcholine antagonism

4-Dopamine degradation inhibition

Drugs Used in Parkinson's Disease

• Levodopa and carbidopa

• Selegiline and rasagiline

• Catechol-O-methyltransferase inhibitors

(COMTis).

• Dopamine receptor agonist

• Amantadine

• Antimuscarinic agents

ANTI-PARKINSON DRUGS
Amantadine SYMMETREL
Apomorphine APOKYN
Benztropine COGENTIN
Biperiden AKINETON
Bromocriptine PARLODEL
Carbidopa LODOSYN
Entacapone COMTAN
Levodopa (w/Carbidopa) SINEMET, PARCOPA
Pramipexole MIRAPEX
Procyclidine KEMADRIN
Rasagiline AZILECT
Ropinirole REQUIP
Rotigotine NEUPRO
Selegiline (Deprenyl) ELDEPRYL, ZELAPAR
Tolcapone TASMAR
Trihexyphenidyl ARTANE

Levodopa and carbidopa

**Main state for treatment

Mechanism of action:

• Levodopa: is metabolic precursor of dopamine.

• Levodopa must be administered with carbidopa.

• Carbidopa is a decarboxylase inhibitor, that diminishes the metabolism of levodopa in the periphery → increasing the availability of levodopa at BBB.

**Without carbidopa, most of levodopa is metabolized in the periphery.

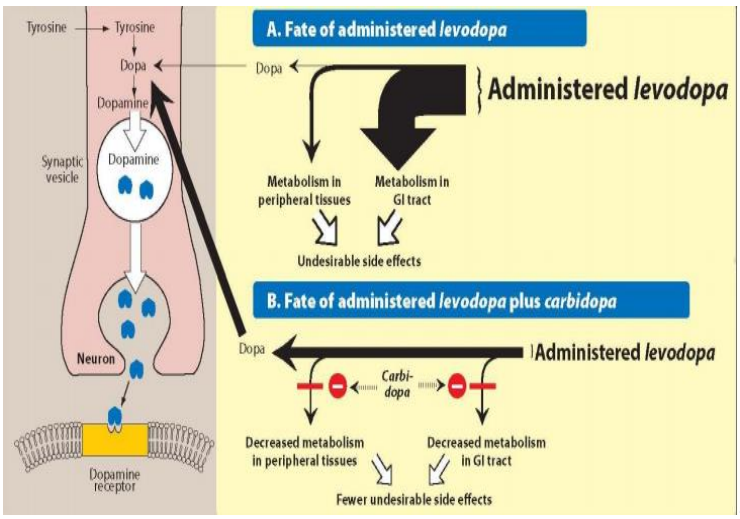
Dopamine is produce from tyrosine which tyrosine is convert to L-dopa by tyrosine hydroxylation the L-dopa convert to dopamine by decarboxylation

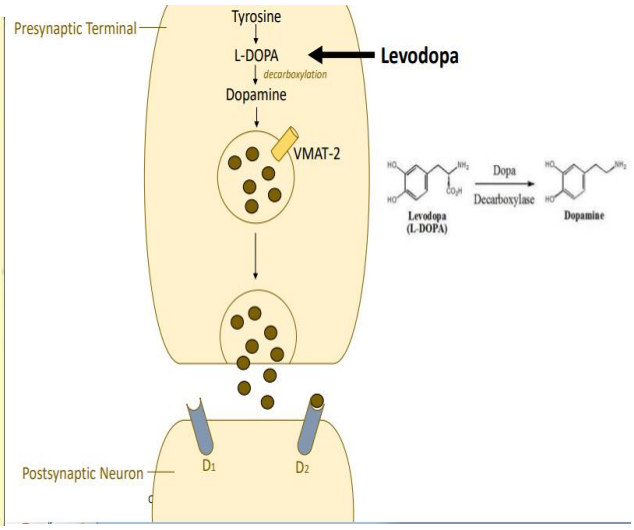
هسا الlevodopa هو نفسه الL-dopa وبالتالي هو metabolic precursor of dopamine

طيب هسا بالparkenson disease ما بكون في 100% destruction of substania nigra بضل نسب منعم شغال فبنعطيهم Levodopa لحتى يطلعو dopamine بس with progression of disease lead to more substenia nigra destruction فالlevodopa ببطل يشتغل

هسا لازم مع الlevodopa نعطي carbidopa الي decarboxylase inhibitor لانو الlevodopa هو oral drug قبصيرلو absorption عن طريق الintestine فالمشكلة انو ال levodopa بصيرلو metabolism in peripheral tissue مش بس بالbrain محل ما بدنا يشتغل عشان يتحول لdopamine كمان بال peripheral tissue especially in GI tract فبصيرلو decarboxylation وبتحول لdopamine برة الcns

هسا الlevodopa هو permeability to BBB بس الdopamine مش permeability because is charge فبالتالي الlevodopa الي تحولت لdopamine بالperipheral tissue ما رح نتستفيد منعا لانو الdopamine ما بعبر الBBB وكمان لما بتحول لdopamine in peripheral tissue هو اصلا catecholamine فالو تاثير على الcirculation فبتالي many adverse effect لذلك لازم نعطي carbidopa الي هوdecarboxylase inhibitor فبقلل عندي الperipheral metabolism فيصير الlevodopa more بوصل للBBB وبالتالي اقلside effect وشغلة كمان انو الcarbidopa ما بعبر الBBB قما باثر على ال dopamine synthesis in CNS





Therapeutic uses

• Levodopa + carbidopa: the gold standard of symptomatic treatment for Parkinson's disease.

*two-thirds of patients respond well to levodopa+carbidopa for the first few years then they experience a decline in response.

**"wearing off " phenomenon (symptoms of Parkinson's start to return or worsen with progression of the disease)

هسا لحتى يشتغل الlevodopa لازم يكون في بقايا من الsubstania nigra مع الوقت بصير further destruction of substania nigrsa فبصير phenomena اسمخت wearing off phenomena هون المريض على الرغم من destruction of substernia بسبب ال experience symptom again بصير الا انو استعمال الlevodopa nigra

Pharmacokinetics

• Levodopa is given orally and rapidly absorbed from the gut.

-administered on an empty stomach (high-protein diet interferes with its transport to the brain). Should be give 30 min before food

• SHORT half-life (1-2 hours).because rapid metabolize levodopa to dopamine by decarboxylation which present in in everywhere in the body

-results in fluctuation in its plasma concentration→ fluctuation in motor function.

(*) "on-off" phenomenon (sudden swings from mobility to bradykinesia that are not related to plasma levels in a simple way)

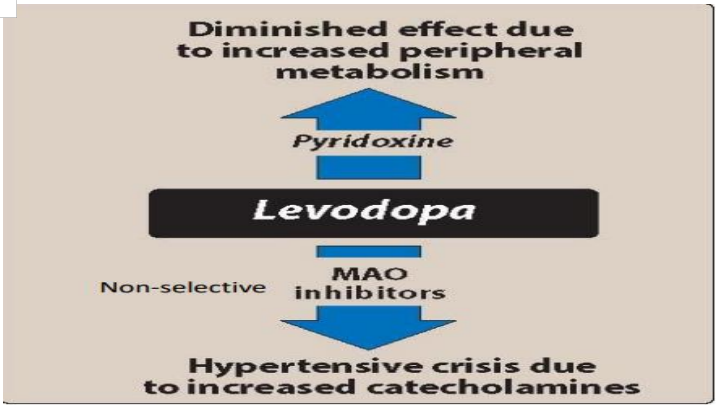
هسا المlevodopa بتنعطى orally وبصيرلو absorption from GI tract للplasma بعدين from 1-2 hours half life بعدين بصرلها metabolism and excretion وبعدين بنعطيه second dose فبرد بطلع فالcurve تبعو طالع نازل بسبب انو short half life وهاض بعمل fluctuation in it is plasma concentration بالتالي combination therapy او appropriate dose وهاي حلها انو نعطي fluctuation in motor function

هسا الon-off phenomena هي الها علاقة بال fluctuation انو بصير sudden change بالsymptom بصيريروح ويرجع الsymptom بطريقة عشوائية ما بتعتمد على تركيز الLevodopa وهاي احد الcomplication للLevodopa

Drug-drug Interaction

اذا اعطينا الlevodopa مع الpyridoxine(B6) بزيد الdecarboxlation reaction للlevodopa وبقلل كمية ال levodopaاللي رايح للbrain

كمان الMAO inhibitor اذا اعطبته مع الlevodopa راح يصير hypertensive crisis لان الMAO موجود بال neuron ,liver and kidney وهو مهم لmetabolic of catecholamine فلما تعطي levodopa بؤدي انو very high level of dopamine and فبصير MAO inhibitor الdopamine عالي وتروح تعطي dopamine has effect on cardiac muscle so lead to hypertensive crisis



Adverse effects:

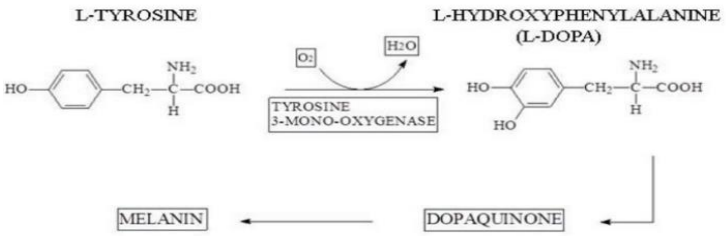
• Peripheral effects:

❑ Simulation of chemoreceptor trigger zone because it is out side BBB and dopamine act on chemoreceptor zone so lead to: Anorexia, nausea and vomiting

❑ Dopaminergic stimulation of the heart and have inotropic and chronotropic effect: tachycardia, extrasystole

❑Adrenergic action on iris: mydriasis

❑Catecholamines oxidation: melanin pigmentation, brownish saliva and urine.in chronic use of levodopa these will oxidation specially in skin so convert to melanin because melanin is tyrosine derivative so lead to melanin deposit and pigmentation



• Central effects:

❑ Visual and auditory hallucinations because dopamine have role in limbic system which is reword pathway

❑ Dyskinesia involuntary face movment

❑ Mood changes

(These CNS effects are the opposite of parkinsonian symptoms and reflect the overactivity of dopamine at receptors in the basal ganglia)

هسا لما يقل عندنا الdopamine بصير عندنا depression بس لو واحد في عندو high dopamine بعمل euphoria
او راح يصير psychotic symptom فلو واحد معاه psychotic واعطيته levodopa بزداد سوء ولو واحد عندو low dopamine deprivation بزدا سوء لانه antipsycotic واعطيته dopamine

Catechol-O-methyltransferase inhibitors (COMTis)

Entacapone and tolcapone

Mechanism of action:

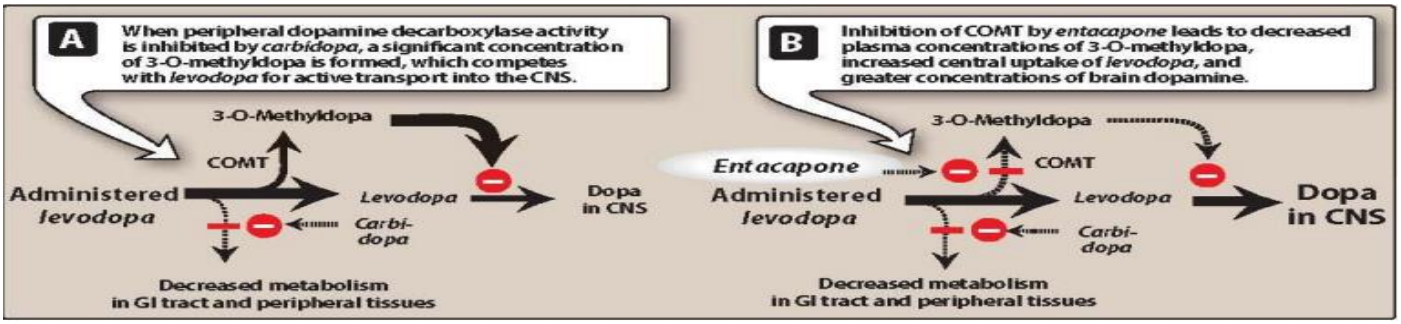
• The methylation of levodopa by COMT to 3-O-methyldopa is a minor pathway for levodopa metabolism.

• When carbidopa is used→ more 3-O-methyldopa is formed by COMT→ 3-O-methyldopa competes with levodopa transport to the brain.

• Entacapone and tolcapone are selective and reversible inhibitors of COMT → decrease plasma concentration of 3-O-methyldopa → enhance levodopa transfer to the brain.

• Both drugs decrease "wearing off" phenomenon.

هسا احنا حكينا انو بالperipheral tissue بصيرلها metabolism عن طريق الdecarboxylation mainly قبل ما
تروح عالbrain بس في هناك كمان طريقة لل metabolism specific in peripheral tissue is COMT
pathway و هاض الenzyme الي هوCOMT بشتغل على الlevodopa وبحوله لل3-O-methyldopa و هاض
الpathway is minor pathway بس لما نعطي بصير carbidopa shift towered these alternative
pathway فالCOMT بحول الlevodopa لـ3-O-methyldopa هسا هاض المركب كمان بدخل للBBB
وبعملcompete with levodopa transport مش بس انو بقلل الlevodopa بالplasma فالحل انو نعطي
COMT inhibitor فهون بنخلي الlevodopa عالي وبروح للbrain وبتحول لـdopamine وبقلل الـ3-O-
methyldopa الي بخرب دخول الlevodopa للBBB



Pharmacokinetics

• Both drugs are orally administered.

• Highly bound to plasma albumin.

• Tolcapone has a longer half-life

Adverse effects:

• Both drugs have similar side effects profile as levodopa+carbidopa

• Tolcapone: this life threating condition in small percent of people fulminating hepatic necrosis (does not occur with entacapone)

MAO Inhibitors: Selegiline and Rasagiline

Mechanism of action:

Interfere with dopamine degradation at level of synapse at brain

COMT present in peripheral but MAO present in neuron and degradation of dopamine

• Selegiline: selective MAO B inhibitor → decreases dopamine degradation → increases dopamine levels in the brain. But if increase dose level the selectivity will loss and inhibit MAO-A

both MAO A and MAO B efficiently metabolize dopamine however type B degrades dopamine more. (MAO A predominantly metabolizes norepinephrine).

• Rasagiline is an irreversible and selective inhibitor of brain MAO B and is 5 times more potent than selegiline

هسا حكسنا انو الtyrosine بتحول لL-Dopa والL-dopa بتتحول لdopamine قلو اعطينا الlevodopa بنزود الdopamine بعدين بصيرلو هى

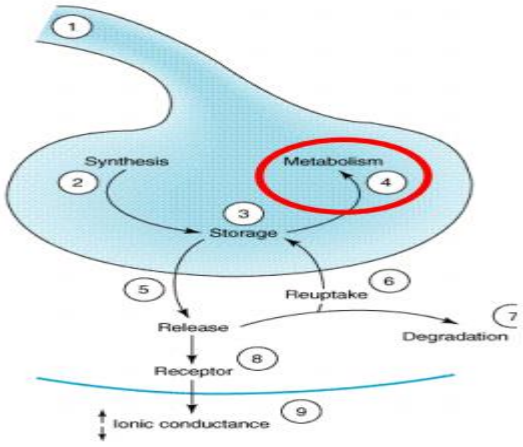
وبعد ما packaging in vesicle in synaptic terminal then release arrival from action potential يصيرلو release بصيرلو reuptake through dopamine transport وجزء منو بصيرلو degradation by MAOوهاض الenzyme الو انواع نوعA هاض بعمل للdegradation norepinephrine اما الMAO-B بعمل MAO –B selective inhibitor عالي بعطي dopamine فاذا بدي اخلي الdegradation to dopamine

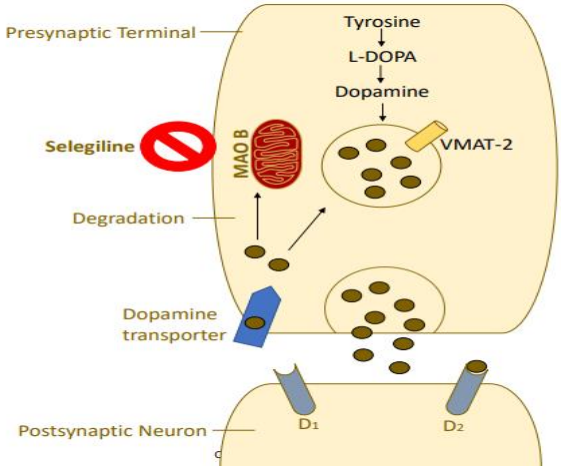
Sites and Mechanisms of CNS Drug Action Metabolism:

•COMT and MAO

•Antiparkinsonian

•Antidepressants





Therapeutic uses:

• Seligiline is often administered with levodopa:

delays breakdown of nigrostriatal dopamine→ prolongs levodopa action → decreases fluctuation in motor function. "on-off phenomenon

Adverse effects:

• Insomnia: due to its metabolism to methamphetamine and amphetamine. So should give druf at morning

Unlike selegiline, rasagiline is not metabolized to amphetamine-like substances → less insomnia.

Dopamine Receptor Agonists

Give this type of drug when the substania nigra almost destruction in advance disease and no dopamine release so give dopamine agonist

Drugs: there is two type ergot or non ergot

• Bromocriptine (ergot derivative)

• Rotigotine, apomorphine, pramipexole and ropinirole (nonergot derivatives).

Mechanism of action

• Direct dopamine receptor 2 (D2)agonism.(inhibitor receptor)

Therapeutic uses:

• Patients exhibiting fluctuation in response to levodopa.

• Parkinson's disease complicated by motor fluctuations and dyskinesia.

• Ineffective in patients who have not responded to levodopa.

يعني هون لو مريض اخذ levodopa بس ما اتحسن عليه غالبا ما رح يتحسن معdopamine agonist بس ممكن نعطيه لواحد كان ماشي على الlevodopa بس بعدين بطل يشتغل بالadvance stage

• Apomorphine is given by injection to treat severe and advanced stages of Parkinson's disease (also given in emergencies to treat sudden freezing i.e. immobility "off" phenomenon)

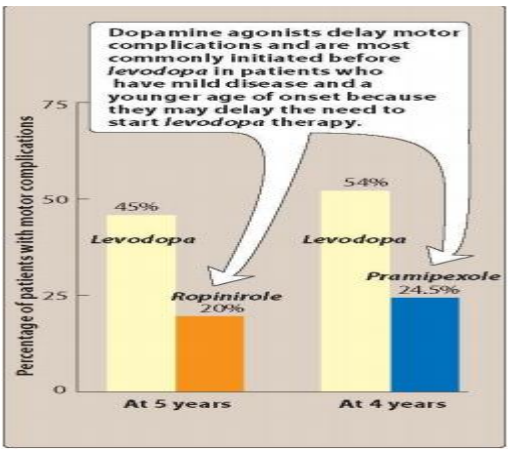
نعطيه بحالات الemergency بالadvance state بصير sudden state immobile بسبب sever decrease of dopamine

Therapeutic advantage of dopamine agonists

If used in early in patient of mild disease at very young age these decrease the need to levodopa ,carbidopa therapy

وكمان لو ال patient اخذlevodopa,carbidopa ممكن على حوالي 5سنين راح يعمل motor complication بنسبه 45% بس لو اعطينا معاه ropinirole and pramipexole لو اعطيناهم early in young patient that have Parkinson disease راح يقلل الrisk for levodopa complication

معلومة الparkinson disease ال,incidancejhu بعد عمر ال60: 1 من كل 100



Pharmacokinetics

ما شرحو الدكتور

Characteristic	*Pramipexole*	*Ropinirole*	*Rotigotine*
Bioavailability	>90%	55%	45%
V_d	7 L/kg	7.5 L/kg	84 L/kg
Half-life	8 hours[1]	6 hours	7 hours[3]
Metabolism	Negligible	Extensive	Extensive
Elimination	Renal	Renal[2]	Renal[2]

Adverse effects

• Similar to levodopa. Sedation, hallucination, confusion, nausea and hypotension

• Bromocriptine: pulmonary and retroperitoneal fibrosis with chronic use epically to ergot

•nonergot derivatives do NOT cause fibrosis.

Amantadine

Mechanism of action:

• Antiviral used to treat influenza.

• Amantadine increases the release of dopamine, blocks cholinergic receptors and inhibit NMDA glutamate receptors.

Therapeutic uses:

• Amantadine is less efficacious than levodopa in the treatment of Parkinson's disease.so not main state for treatment so is third or fourth line

• Effective against rigidity and bradykinesia

Antimuscarinic agents

Drugs

• Benztropine

• Trihexyphenidyl

• Procyclidine

• Bioperiden

Mechanisms of action

• Blockade of cholinergic transmission produces effects similar to augmentation of dopaminergic transmission → correct the imbalance of dopamine/acetylcholine ratio.

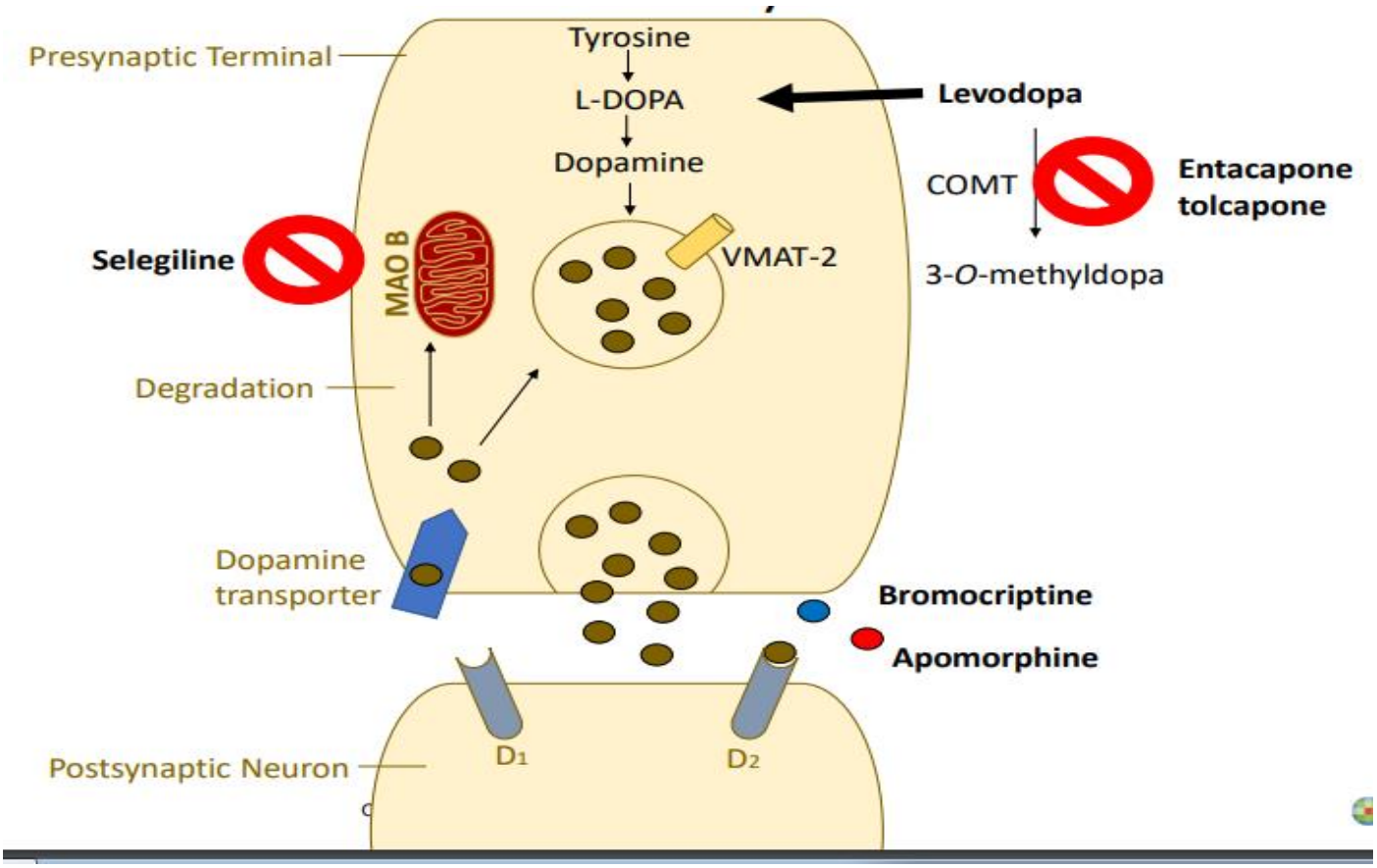
Therapeutic uses

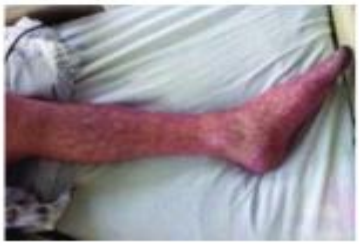
• Much less efficacious than levodopa and always used in adjuvant to other antiparkinsonian therapy. So mainly used as combination therapy with levodopa

• Anticholinergics are mainly used in antipsychotic-induced parkinsonism.

هسا لو كان واحد صار معو psychotic symptom نتيجة الlevodopa over use of ممكن نستخدم antimuscaricnic لانو ما باثر على الdopamine

Summary



Drug	Mechanism of Action	Adverse Effects
I. Bromocriptine, Pramipexole &Ropinirole (Given alone or with L-dopa). **Apomorphine**	Direct D_2 agonists. (Less fluctuation due to rapid absorption - longer $t_{\frac{1}{2}}$). is given **SC in emergency** (sudden freezing i.e. immobility) as it is rapid and more effective than L-dopa.	- Similar to L-dopa; with more psychosis. - Vasospasm & cardiac fibrosis **(bromocriptine)**
II. Amantadine (Given alone or with L-dopa).	- ↑ DA release (mild effect) → enhances L-dopa effect. - Blockading cholinergic receptors - Block glutamate receptor (NMDA) → ↓ glutamate excitotoxicity → ↓ neuronal degeneration • **more effective against rigidity and bradykinesia**	- Insomnia. - Hallucination. - Livido reticularis: purple spotting of skin 
III. Selegiline (Adjunct to L-dopa/carbidopa). **Rasagiline**	Selective inhibitor of MAO-B → delays breakdown of nigrostriatal DA → prolongs L-dopa action → ↓ fluctuation **5 times more potent**	- Insomnia (due to its metabolism to methamphetamine and amphetamine) - Hallucination. - Very low risk of cheese reaction. **No Insomnia**
IV. Entacapone (Adjunct to L-dopa/carbidopa). **Tolcapone**	COMT inhibitor → ↓ L-dopa peripheral metabolism → ↑ its bioavailability & **prolongs its action → ↓ fluctuations.** **Relatively longer duration**	- Similar to L-dopa /carbidopa. **+ Diarrhea.** **Fulminant hepatic necrosis**

Summary Of The Therapeutic Strategy

•Levodopa+carbidopa is the mainstay (first-line) therapy of Parkinson's disease (mostly in combination with a MAO B inhibitor or COMT inhibitor).

•MAO B inhibitors and COMT inhibitors are given in adjunct to levodopa+carbidopa therapy.

-----MAO B inhibitors increase efficacy of levodopa and decrease fluctuation in motor response

-----COMT inhibitors increase efficacy of levodopa and decrease "wearing off" mechanism.

•Dopamine agonists can be given alone in young and mild parkinsonians (to delay levodopa use) OR in combination with levodopa+carbidopa if disease is in progress.

•Antimuscarinics are used in adjunct with levodopa+carbidopa (or in cases of antipsychotics-induced parkinsonism).

How to decrease fluctuation in motor response to levodopa?

حكينا انو الfluctuation اجيت بسبب الshort half life of levodopa

1-Addition of a MAO B,inhibitor or a COMT inhibitor or a dopamine agonist

2-Shortening of the interval between doses of levodopa+carbidopa

3-Using slow-release preparations of levodopa+carbidopa

نهاية التلخيص سامحونا على اي اخطاء