Corso di Laurea in CTF

Farmaci per il trattamento della malattia di Parkinson

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MALATTIA DI PARKINSON

gangli della base striato

tremore, rigidità, bradicinesia, instabilità posturale

↓ DA ↓ DA Ach → farmaci dopaminergici
+ anticolinergici

↓ TH!

STR SN
FC NA VTA

malattia a progressione invalidante

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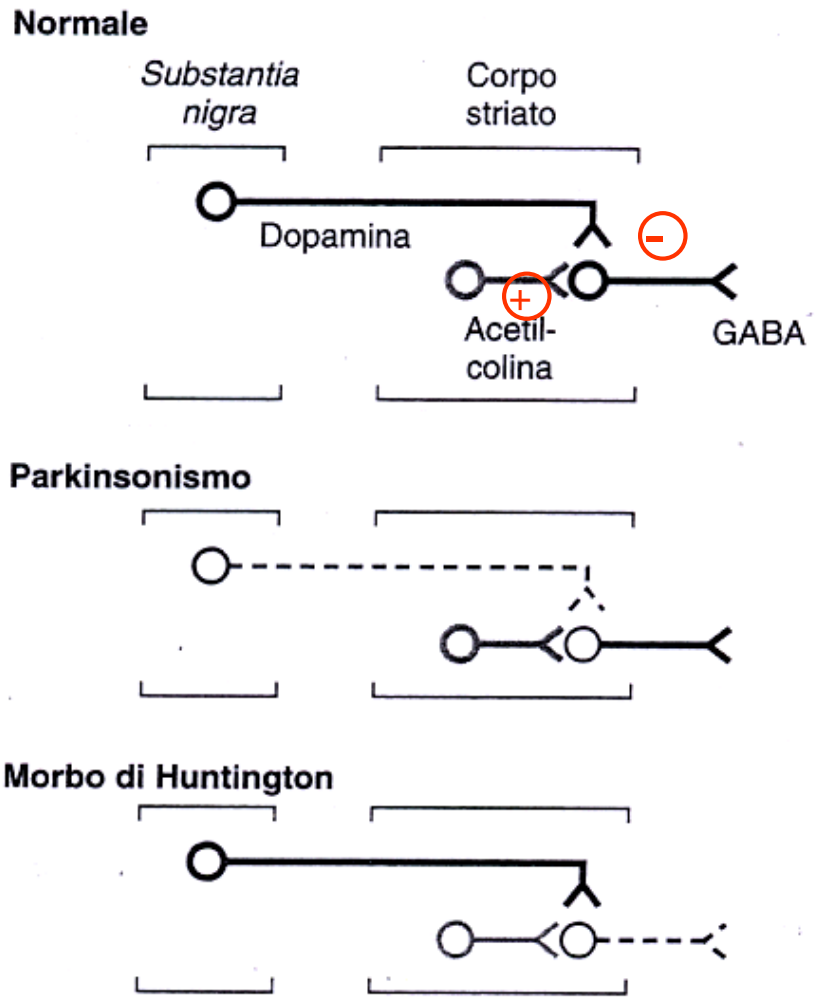
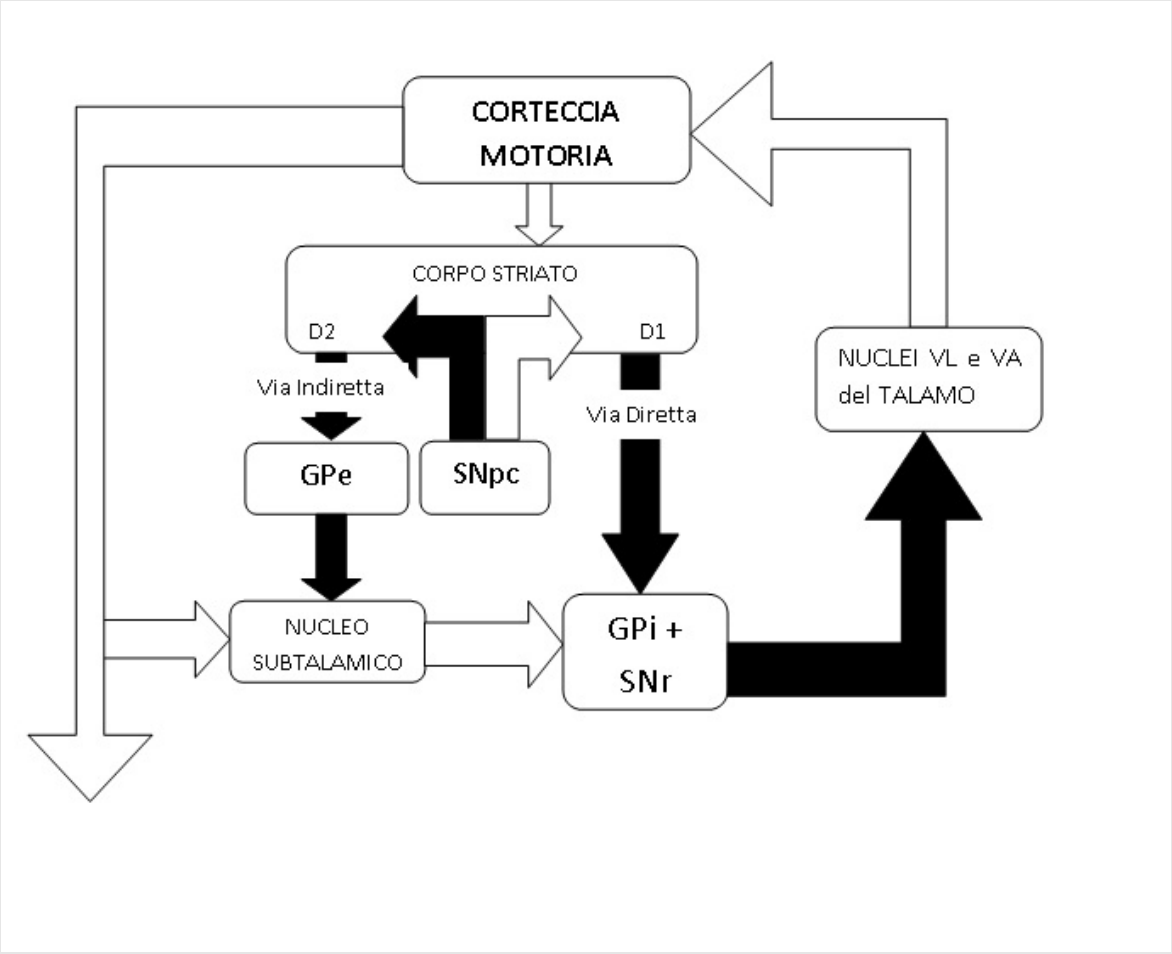
Rappresentazione schematica dei neuroni la cui degenerazione determina il parkinsonismo e la corea di Huntington




CORTECCIA MOTORIA
CORPO STRIATO
D2
D1
Via Indiretta
Via Diretta
GPe
SNpc
NUCLEI VL e VA del TALAMO
NUCLEO SUBTALAMICO
GPi + SNr

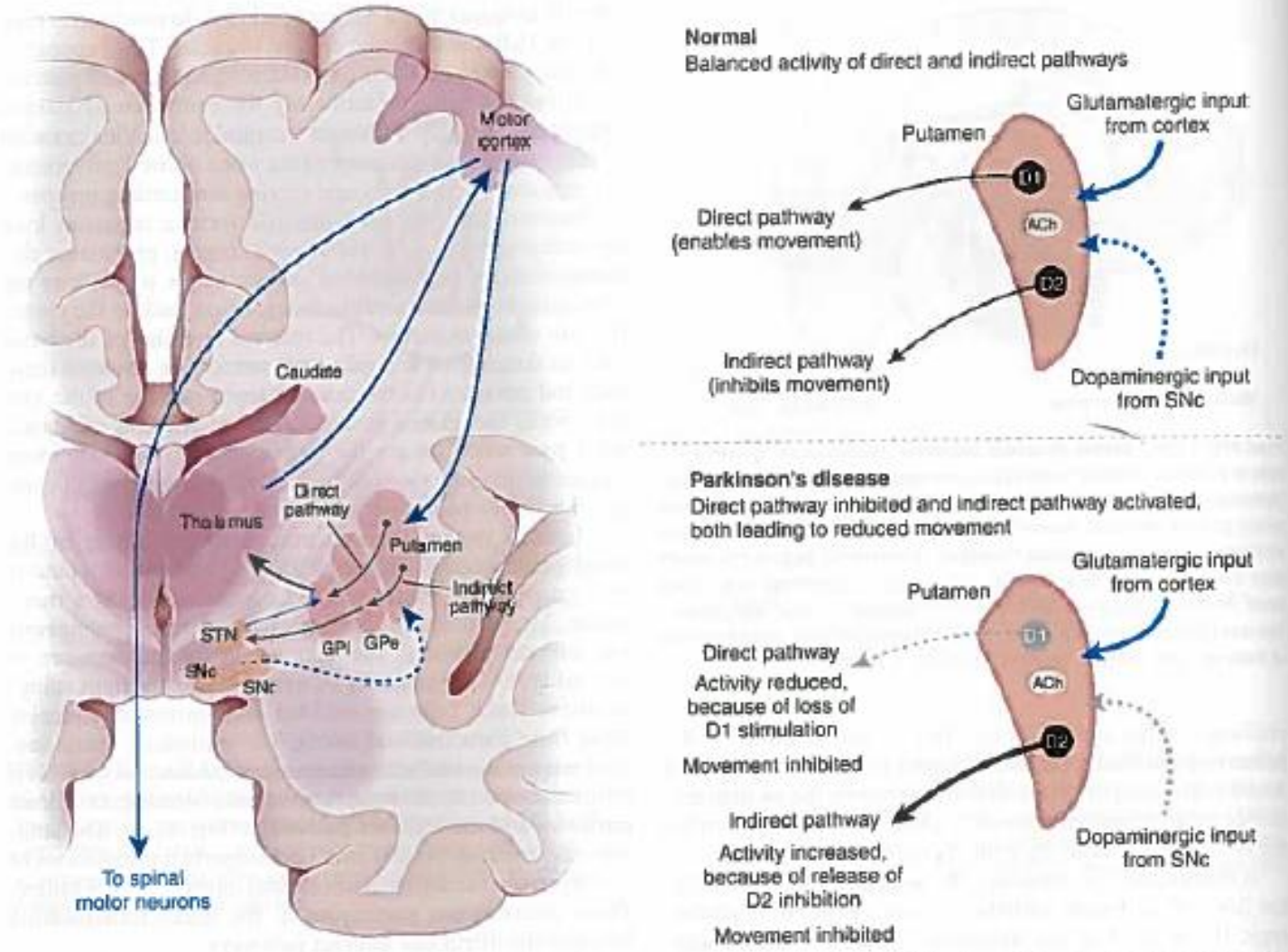


FIGURE 13-7. Effect of Parkinson's disease on dopaminergic pathways that regulate movement. Two principal pathways in the basal ganglia regulate movement: the indirect pathway, which inhibits movement, and the direct pathway, which enables movement. Dopamine inhibits the indirect pathway and stimulates the direct pathway, yielding a net bias that allows purposeful movement. Excitatory pathways are shown in *blue*, and inhibitory pathways are shown in *black*. The direct pathway signals from putamen to GPi to thalamus to cortex, while the indirect pathway signals from putamen to GPe to STN to GPi to thalamus to cortex. GPi, internal segment of the globus pallidus; GPe, external segment of the globus pallidus; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus. **Inset:** Both direct and indirect pathway neurons in the putamen receive inputs from the nigrostriatal dopaminergic system (*dotted blue arrow*) and from cortical glutamatergic systems (*solid blue arrow*), process these inputs in the context of local cholinergic influences (*ACh*), and transmit a GABAergic output (*not shown*). Degeneration of dopaminergic neurons in the substantia nigra results in understimulation of the direct (movement-enabling) pathway and underinhibition of the indirect (movement-inhibiting) pathway. The net result is a paucity of movement. *Dotted gray arrow* indicates decreased activity caused by understimulation, and *thick black arrow* indicates increased activity caused by underinhibition.

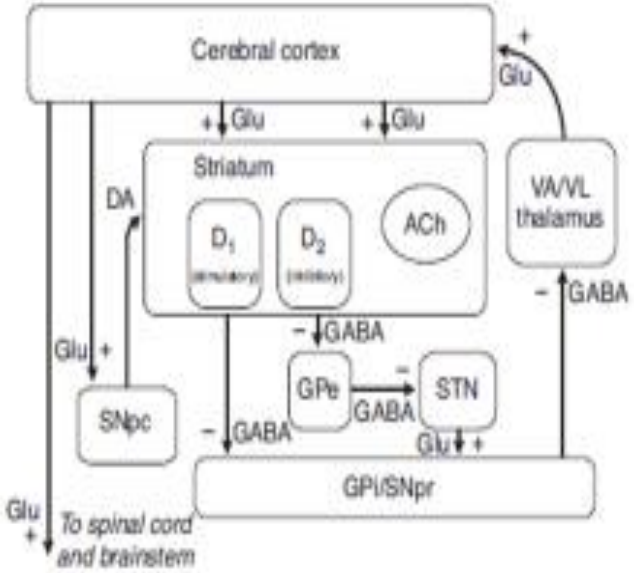


Figure 22–2. *Schematic wiring diagram of the basal ganglia.* The striatum is the principal input structure of the basal ganglia and receives excitatory glutamatergic input from many areas of cerebral cortex. The striatum contains projection neurons expressing predominantly D_1 or D_2 dopamine receptors, as well as interneurons that use ACh as a neurotransmitter. Outflow from the striatum proceeds along two routes. The direct pathway, from the striatum to the substantia nigra pars reticulata (SNpr) and globus pallidus interna (GPi), uses the inhibitory transmitter GABA. The indirect pathway, from the striatum through the globus pallidus externa (GPe) and the subthalamic nucleus (STN) to the SNpr and GPi, consists of two inhibitory GABAergic links and one excitatory glutamatergic projection (Glu). The substantia nigra pars compacta (SNpc) provides dopaminergic innervation to the striatal neurons, giving rise to both the direct and indirect pathways, and regulates the relative activity of these two paths. The SNpr and GPi are the output structures of the basal ganglia and provide feedback to the cerebral cortex through the ventroanterior and ventrolateral nuclei of the thalamus (VA/VL).

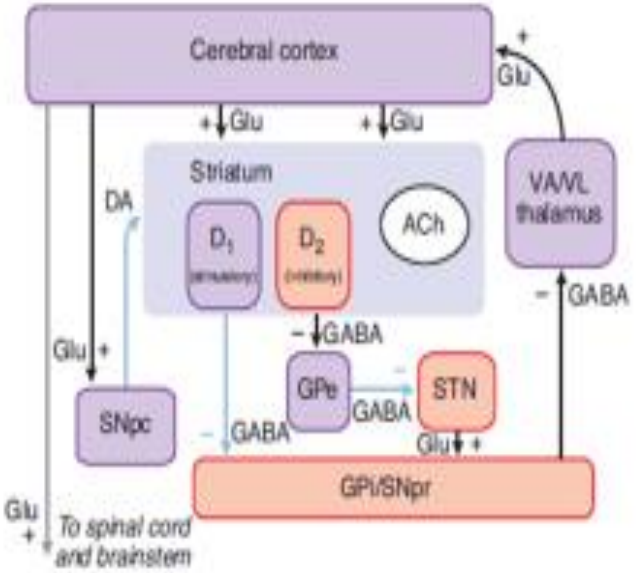


Figure 22–3. *The basal ganglia in Parkinson disease.* The primary defect is destruction of the dopaminergic neurons of the SNpc. The striatal neurons that form the direct pathway from the striatum to the SNpr and GPi express primarily the *excitatory* D_1 DA receptor, whereas the striatal neurons that project to the GPe and form the indirect pathway express the *inhibitory* D_2 dopamine receptor. Thus, loss of the dopaminergic input to the striatum has a differential effect on the two outflow pathways; the direct pathway to the SNpr and GPi is less active (*structures in purple*), whereas the activity in the indirect pathway is increased (*structures in red*). The net effect is that neurons in the SNpr and GPi become more active. This leads to increased inhibition of the VA/VL thalamus and reduced excitatory input to the cortex. Light blue lines indicate primary pathways with reduced activity. (See legend to Figure 22–2 for definitions of anatomical abbreviations.)

neurotransmitters. For example, the neuropeptides substance P and

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rec. DA

D_1 Gs — D_1 (sub. nigra)

D_2 G_i — D_2 (striato)

stimolazione D_2 scopo effetto terapeutico + importante

DA non attraversa la BEE, la LEVODOPA sì (precursore DA passa la BEE → decarbossilata a DA)

assoc. levodopa con inib. periferica DOPA-decarboss. → ↓ 75%

dose levodopa

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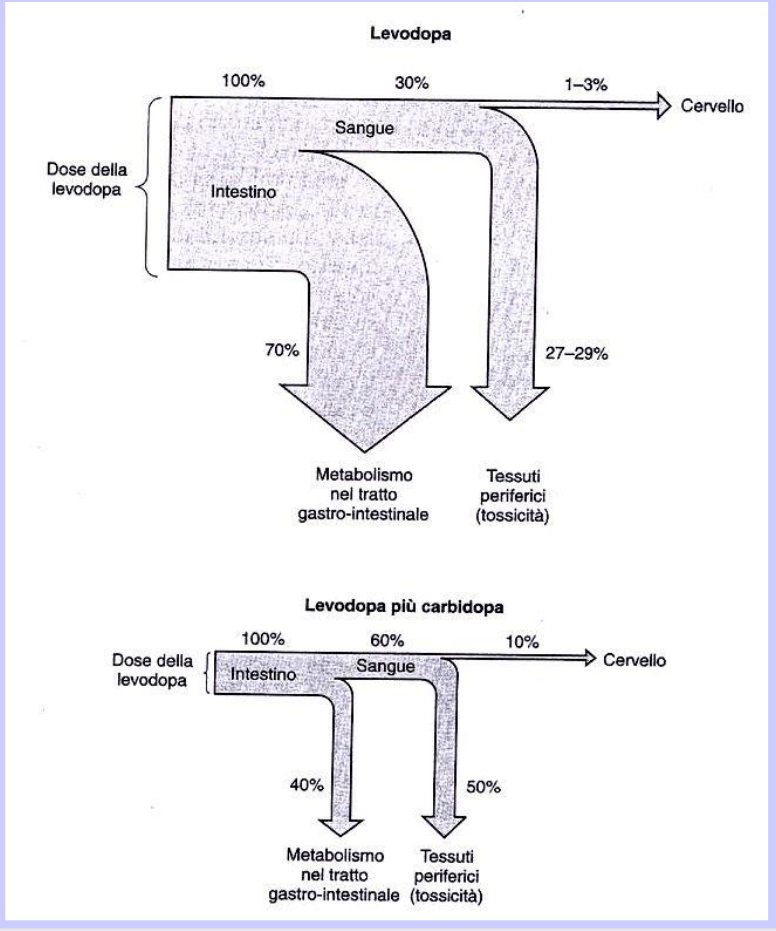
Destino della levodopa somministrata per via orale ed effetto della carbidopa (o benserazide) valutati da studi su animale



fluttazioni risposta cronicamente con freq. ↑

→ fenomeno on-off → drug holiday!

altri eff. ind.: midriasi → glaucoma!

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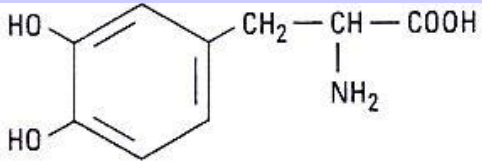
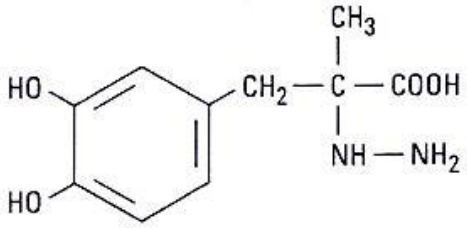
Levodopa: efficacia maggiore nei primi anni di terapia

Alcuni farmaci usati nel trattamento del parkinsonismo



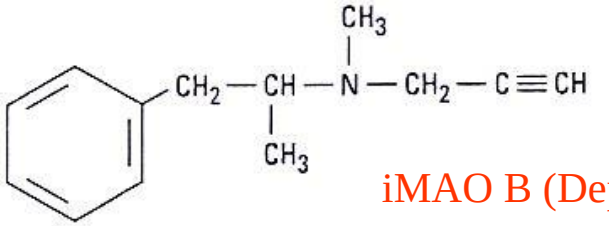
Diidrossifenilanina
(dopa)



Carbidopa o benserazide L + b (MADOPAR)

(generalmente associato a L)

SINEMET 1:10



Selegilina (ass)

iMAO B (Deprenyl) (rallenta catabolismo DA)

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L: migliora quadro clinico Parkinson (bradicinesia)

eff. coll.:

- anoressia, nausea, vomito, 80% pz. x stim. c. emetici
- G.I.: se L ass a C o B → ↓ eff. coll. ↓ 20%
- C.V.: aritmie, tachic. x aumento sintesi amine biogene (stim)
- discinesie: sosp. temporanea → drug holiday
- eff. comp.: depress., ansia, insonnia, confus. → clozapina

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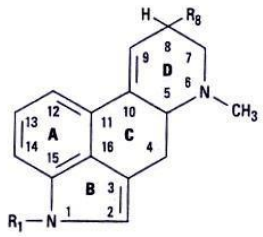
AGONISTI DOPAMINERGICI D_2

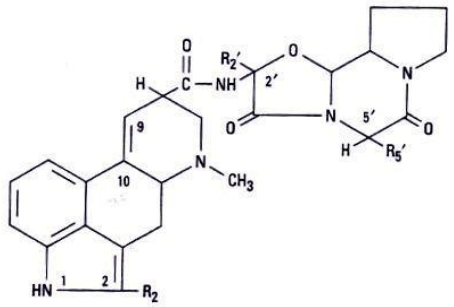
- bromocriptina D_2
- pergolide D_1 e D_2 prolunga il periodo ON in pz. con fluttuazioni

Principali derivati dell'ergolina (alcaloidi della segale cornuta)

Alcaloidi aminici



Alcaloidi peptidici



	R_1	R_8
6-Metilergolina	—H	—H
Acido lisergico	—H	—COOH
Dietilamide dell'acido lisergico (LSD)	—H	—C(=O)—N(CH_2—CH_3)$_2$
Ergonovina (ergometrina)	—H	—C(=O)—NHCH(CH_2OH)CH_3
Metisergide	—CH_3	—C(=O)—NH—CH(CH_2OH)—CH_2—CH_3

	R_2	R_2'	R_5'
Ergotamina[1]	—H	—CH_3	—CH_2—(benzene)
α-Ergocriptina	—H	—$CH(CH_3)_2$	—CH_2—$CH(CH_3)_2$
Bromocriptina	—Br	—$CH(CH_3)_2$	—CH_2—$CH(CH_3)_2$

PERGOLIDE

[1]La diidroergotamina manca del doppio legame tra i carboni 9 e 10.

ass o no a levodopa

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eff. sfav.:

- ✓ g.i. anoressia nausea vomito
- ✓ c.v. ipotensione posturale
- ✓ discinesie
- ✓ disturbi mentali
- ✓ cefalea artralgie rossore dolore edema ai piedi

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INIBITORI COMT (inibizione DOPA-decarbossilasi → ↑ COMT

→ alti livelli 3OMetilDOPA terapia insoddisf.)

TOLCAPONE

→ prolungano att. levodopa

ENTACAPONE (epatotossico)

AMANTADINA (antivirale) stimola sintesi, rilascio e uptake DA

FARMACI ANTIMUSCARINICI

Alcuni farmaci con proprietà anticolinergiche usati nel trattamento del parkinsonismo

Farmaco	Dose giornaliera (mg)
Benzatropina mesilato	1-6
Biperidene	2-12
Orfenadrina	150-400
Prociclidina	7,5-30
Triesifenidile	6-20

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effetti collaterali:

sonnolenza, disattenzione, confusione, xerostomia, visione offuscata, midriasi, ritenzione urinaria, stipsi, tachicardia.

sconsigliati in ipetrofia prostatica, glaucoma

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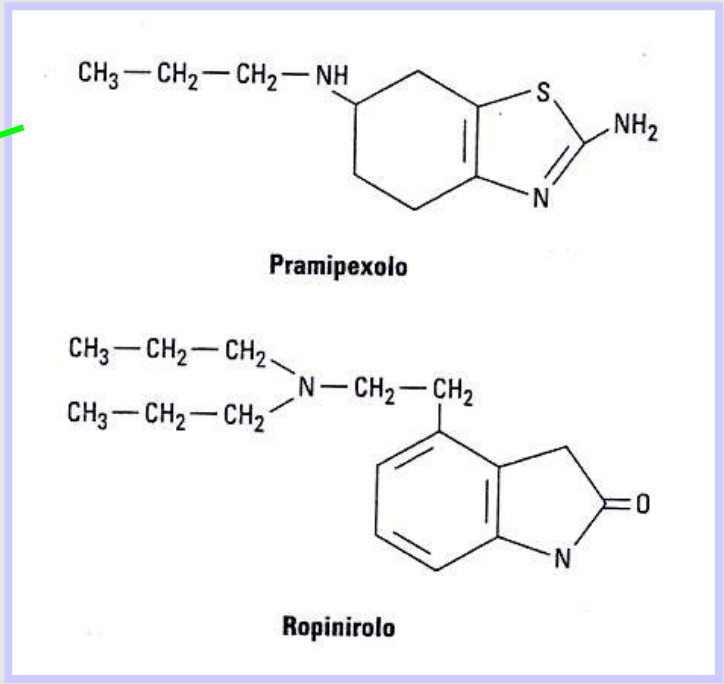
AGONISTI DOPAMINERGICI NON ERGOLINICI

effetto neuroprotettore

Antiossidante, rid. Rad liberi =2 +

neurotrofico neuroni DA mesencefalici



monoterapia

D_2

D_2

monoterapia

effetti collaterali:

- ipotensione
- astenia
- sonnolenza

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iMAO B → selegilina Deprenyl

- potenzia effetto levodopa ↓ on-off
- ritarda la progressione della malattia
  (suo metabolismo è coinvolto in fenomeni antiapoptotici)

rasagilina (+ pot.)

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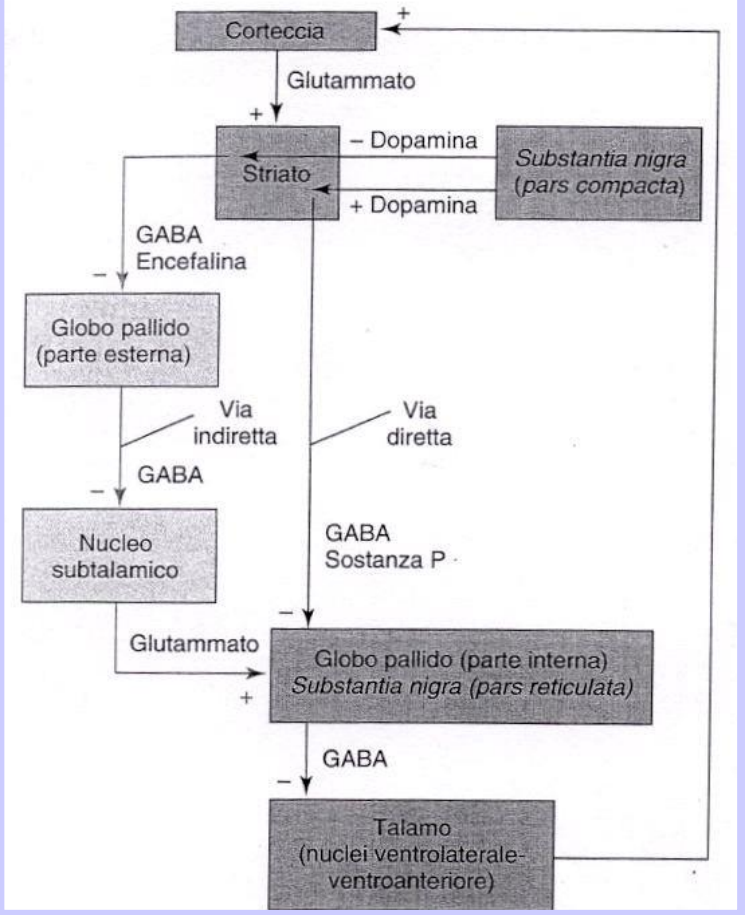
Vit. E scavanger dei radicali liberi O

ruolo glutammato → futuro antag. glut

Circuito funzionale tra corteccia, gangli della base e talamo



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- Sindrome parkinson-simile (fenotiazine)
- Tremore a riposo (Parkinson)
- Discinesia tardiva (effetti collaterali antipsicotici)