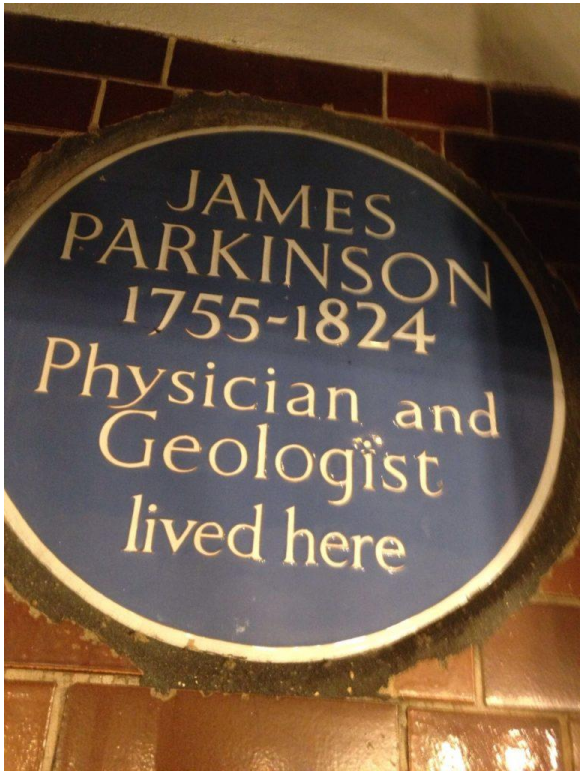
Parkinson Disease



AN

ESSAY

ON THE

SHAKING PALSY.

BY

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MEMBER OF THE ROYAL COLLEGE OF SURGEONS.

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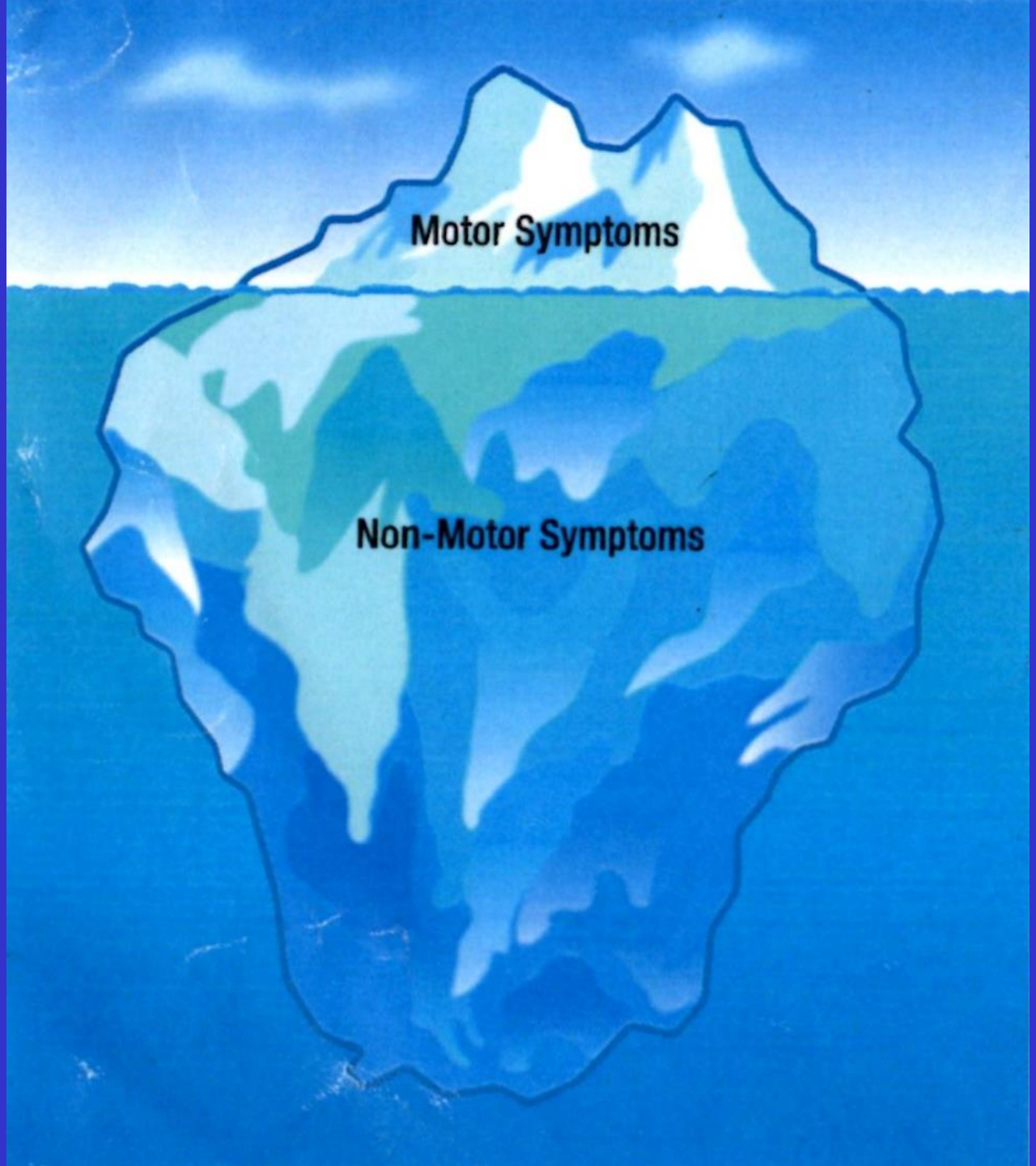
1817.

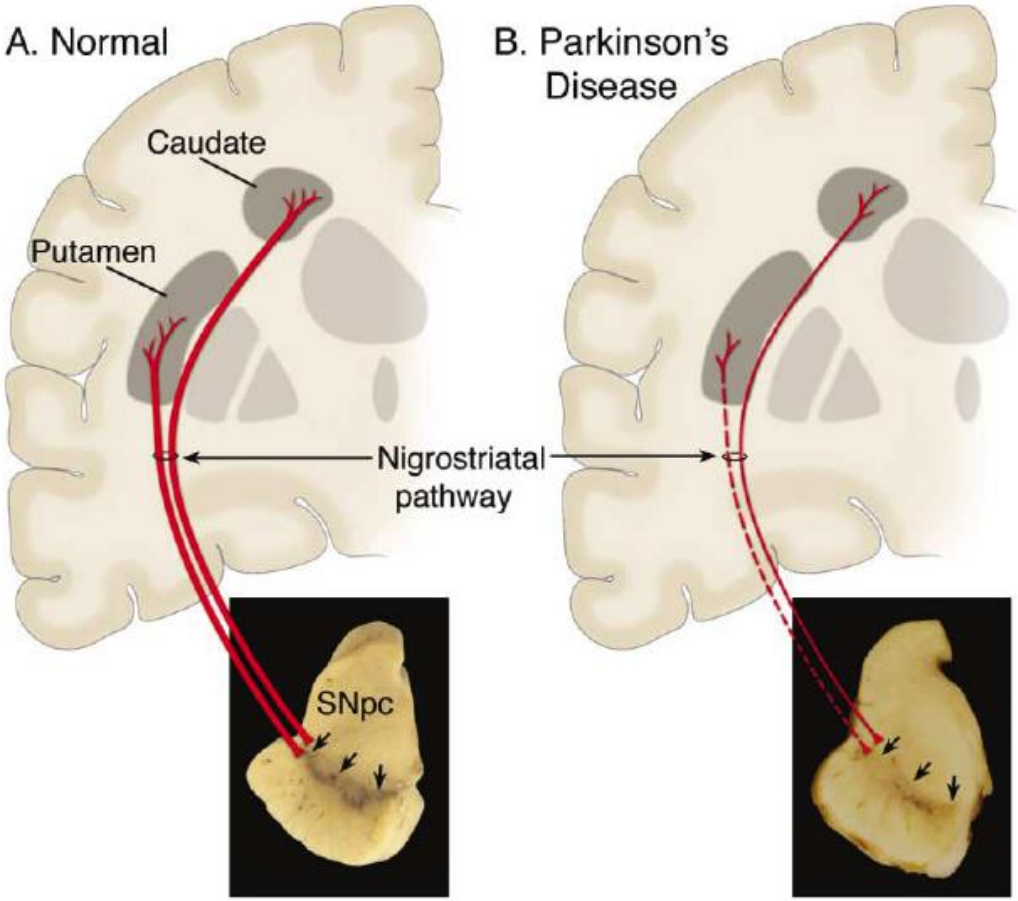

Tremore
Postura
Inclinata
Mimica
facciale
a 'maschera'
Rigidità
Tremori

Cardinal symptoms of PD:
bradykinesia, hypo- / akinesia, muscle stiffness, resting tremor (asymmetric onset), postural instability, speech and writing disorders, forward bent posture, small gait and freezing (sudden stops in gait)

Non-motor symptoms:
hypotension, constipation, bladder dysfunction and thermoregulation along with sleep disorders, fatigue and weight loss

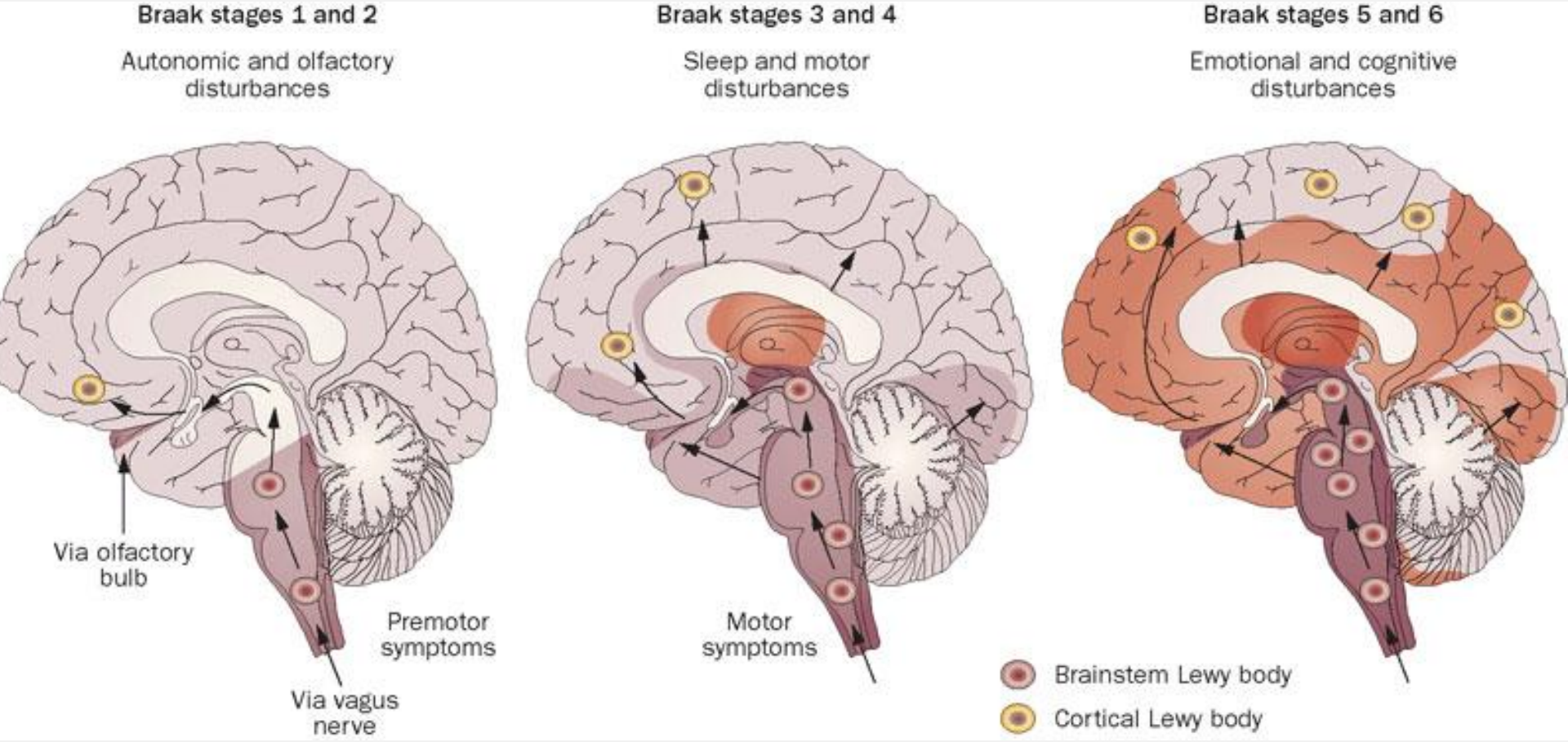
Depression, anxiety, cognitive deficits


Motor Symptoms
Non-Motor Symptoms


A. Normal
B. Parkinson's Disease
Caudate
Putamen
Nigrostriatal pathway
SNpc

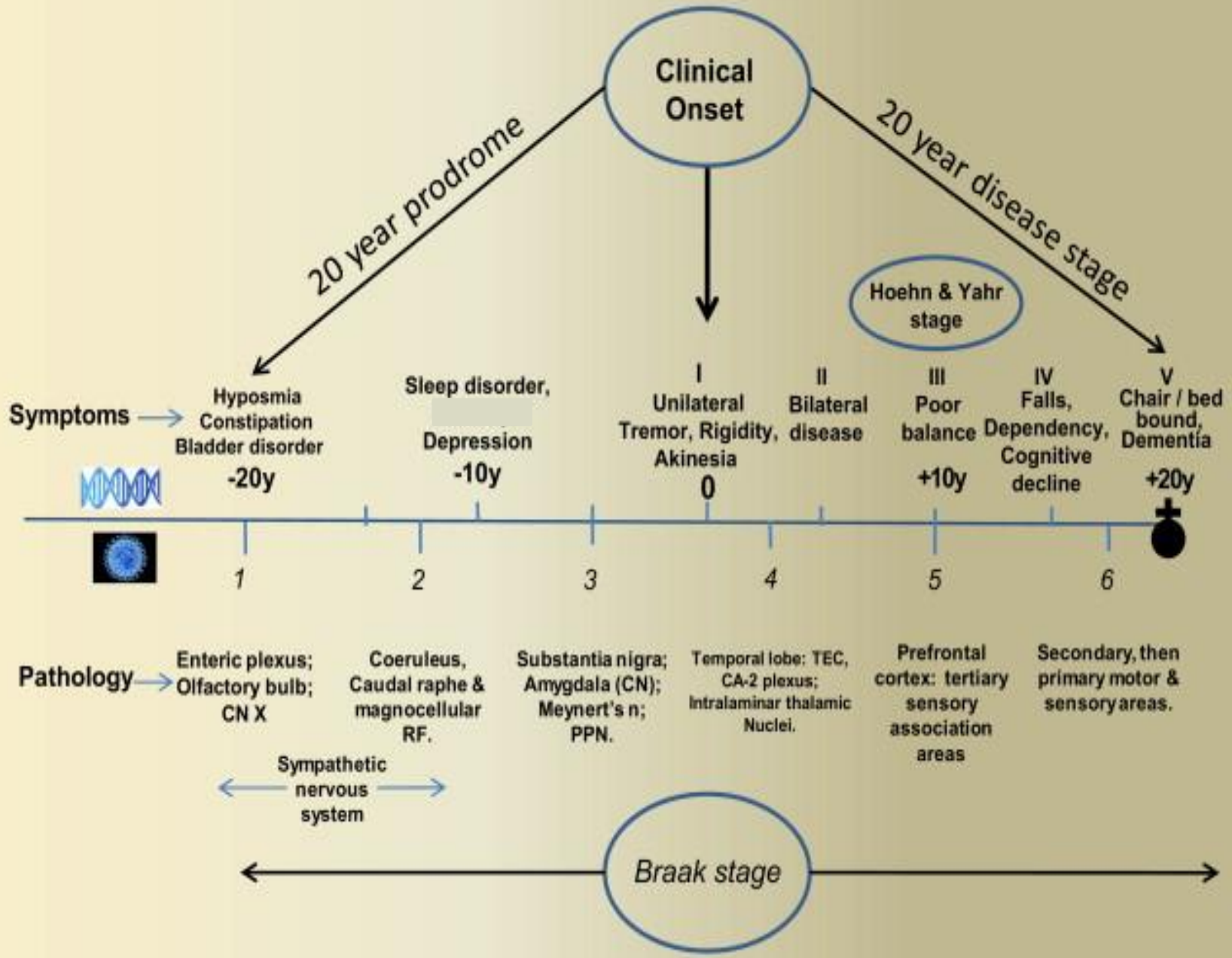

C.
Lewy Body
Synuclein
Ubiquitin

Parkinson’s disease progression

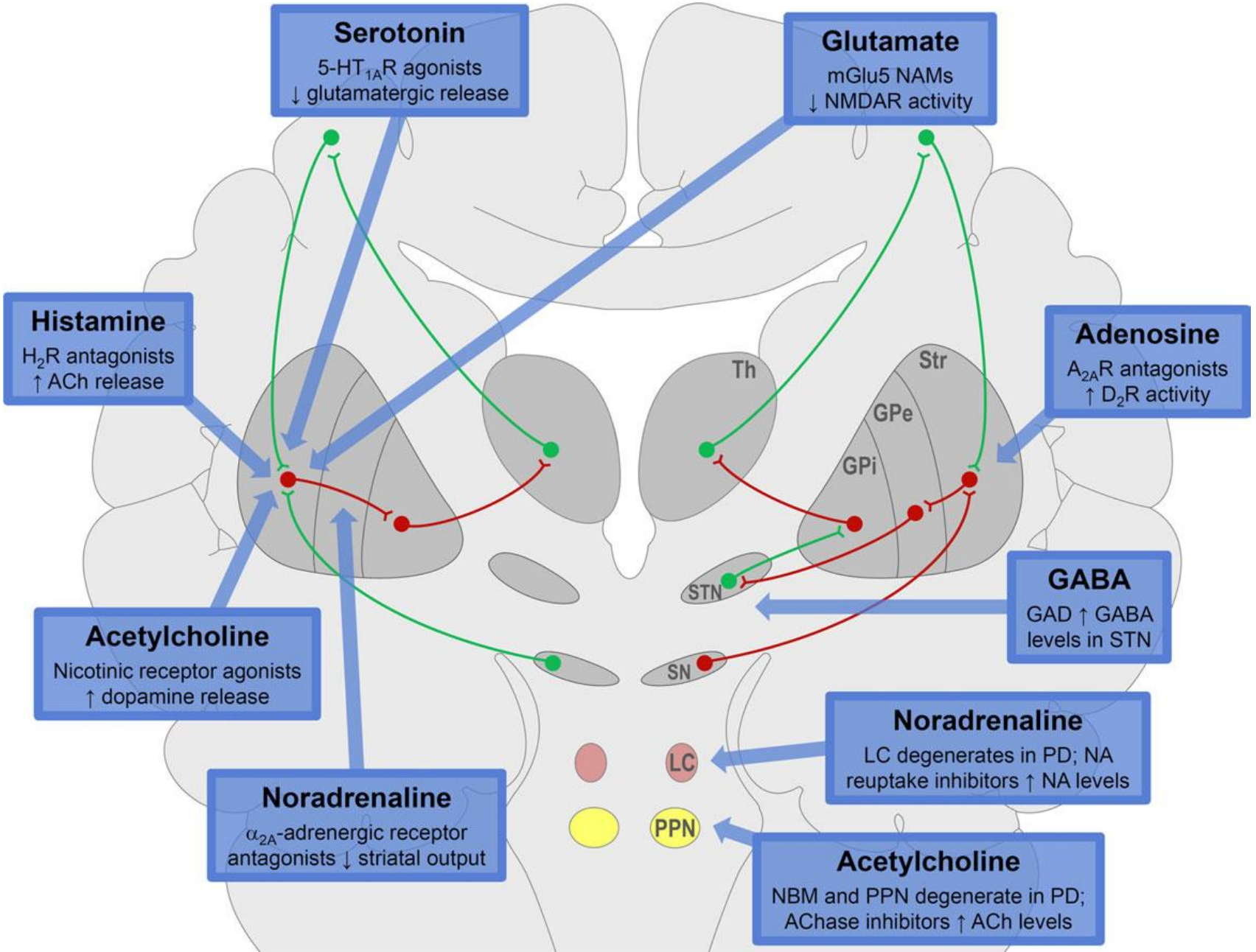


Alfa synuclein ad Lewy bodies

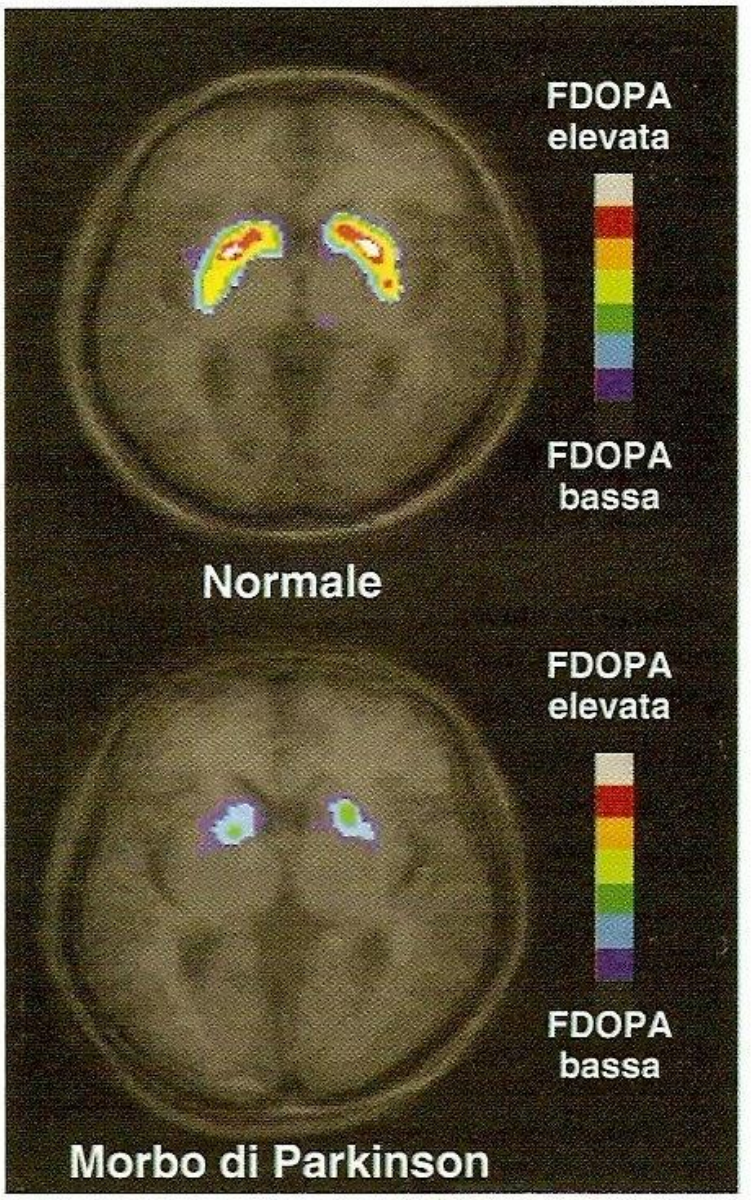
Parkinson's Disease Timeline

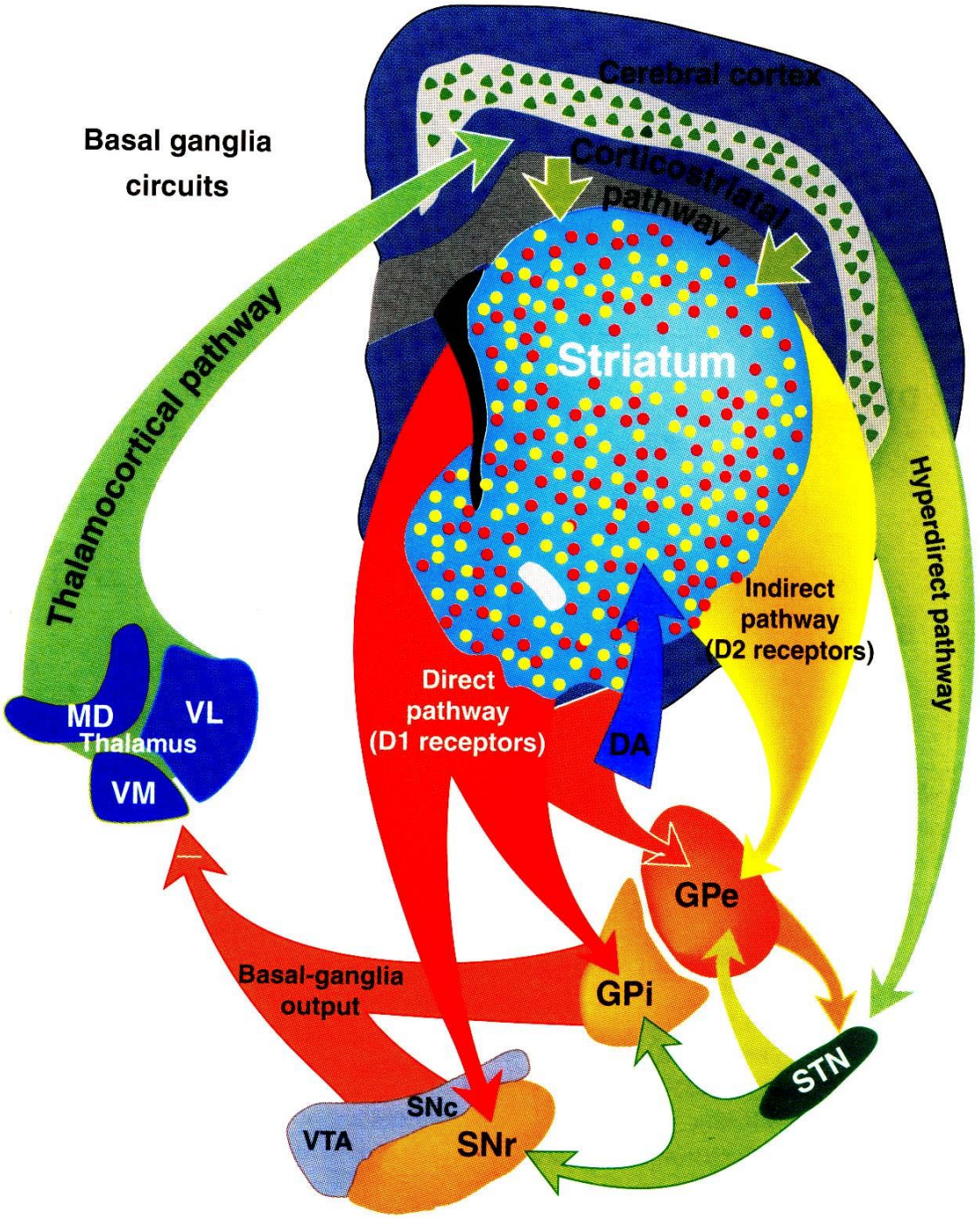


Involved Neurotransmitters a part from dopamine



Difference in fluoro-dopa levels between healthy subjects and parkinsonian




Basal ganglia
circuits
Cerebral cortex
Corticostriatal
pathway
Striatum
Thalamocortical pathway
Hyperdirect pathway
Indirect
pathway
(D2 receptors)
Direct
pathway
(D1 receptors)
DA
MD
VL
Thalamus
VM
GPe
Basal-ganglia
output
GPi
STN
SNc
VTA
SNr

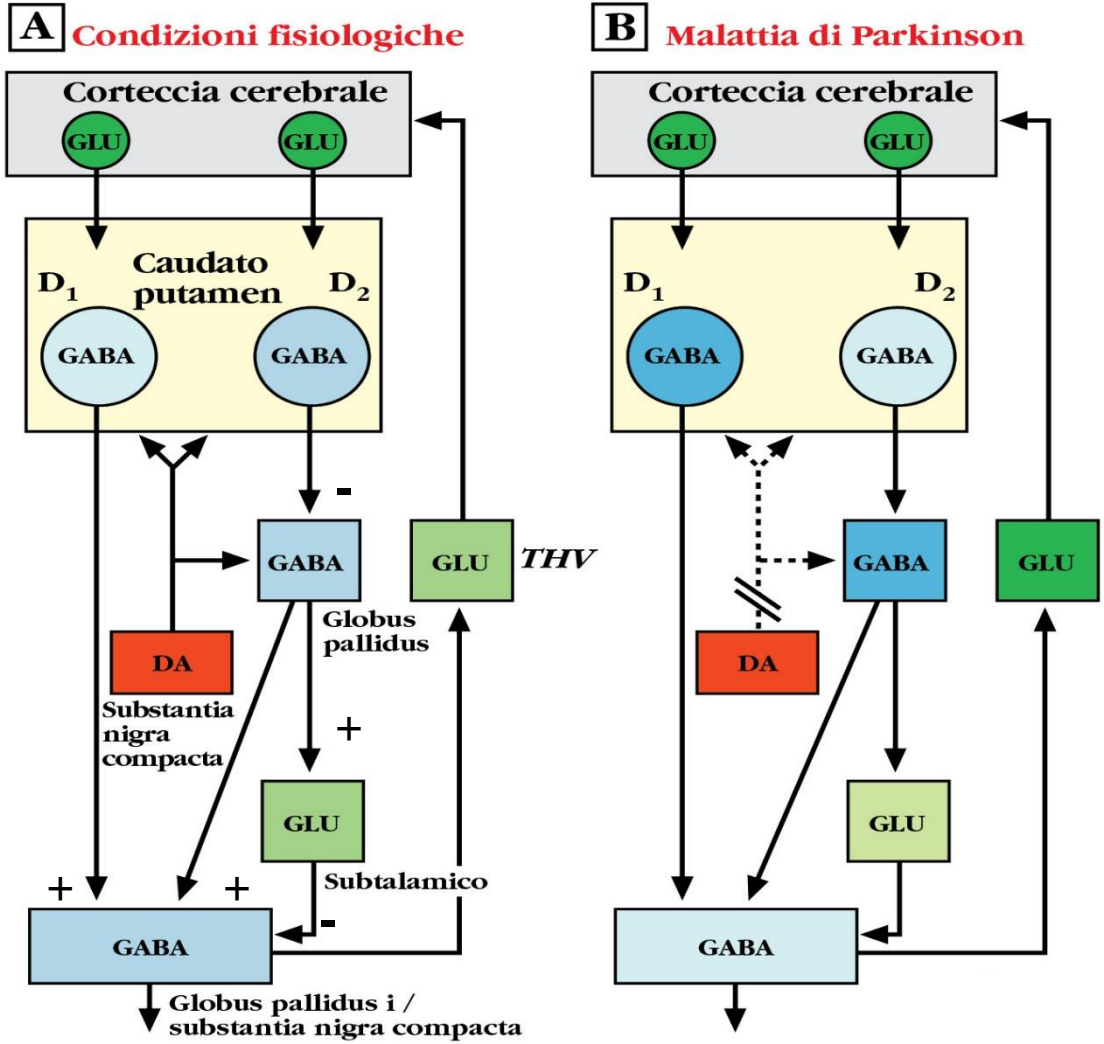
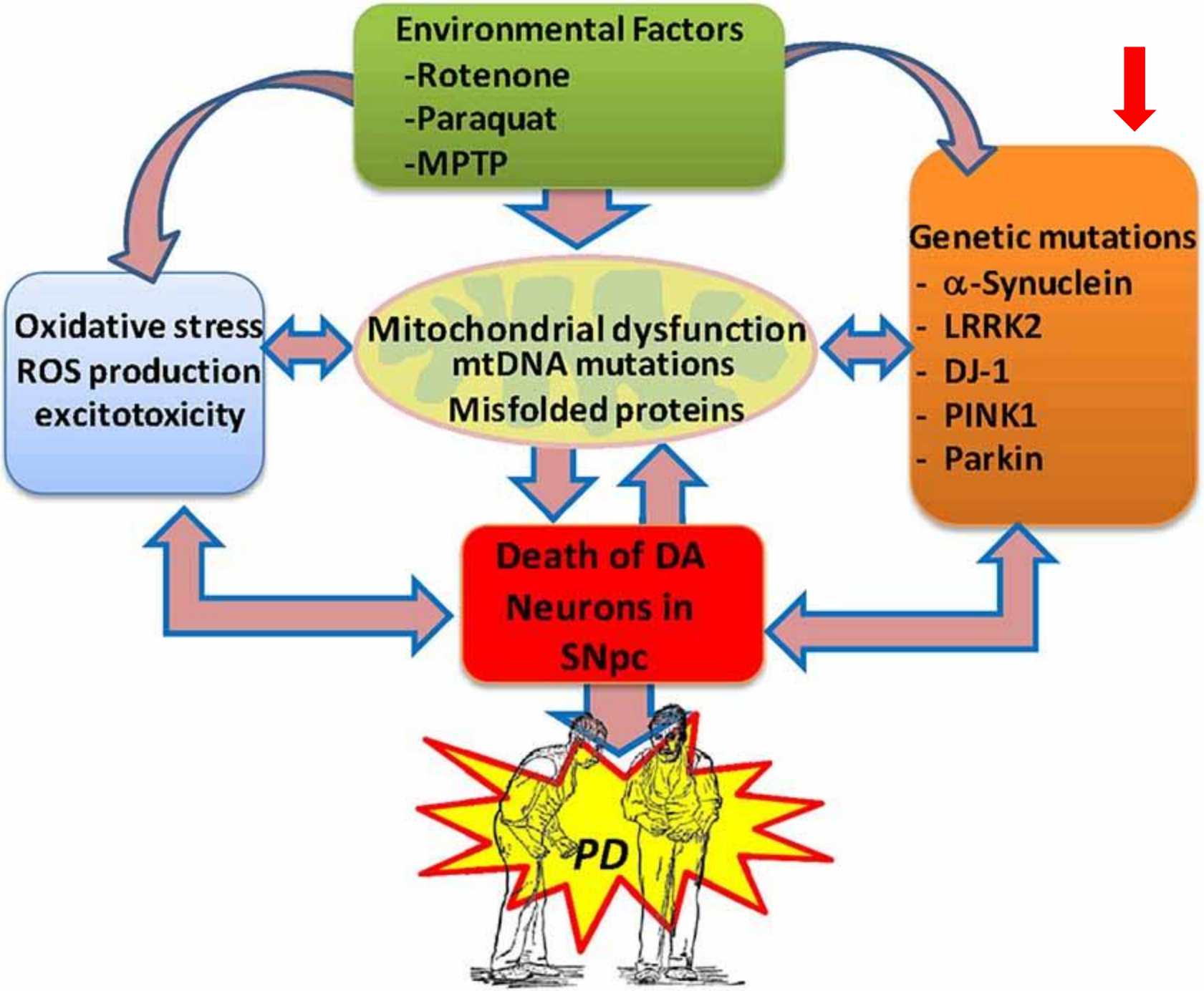


Figura 27.3. Rappresentazione classica dei nuclei della base in condizioni fisiologiche (A), e in presenza di disordini del movimento quali la malattia di Parkinson (B) e la malattia di Huntington (C). Per le abbreviazioni vedere il testo. La linea tratteggiata indica le popolazioni neuronali che vanno incontro a degenerazione nelle due patologie. Obeso et al., Pathophysiology of the basal ganglia in Parkinson's disease. Trends Neurosci, 23, S8, 2000.

Mechanisms


Environmental Factors
-Rotenone
-Paraquat
-MPTP
Genetic mutations
- α-Synuclein
- LRRK2
- DJ-1
- PINK1
- Parkin
Oxidative stress
ROS production
excitotoxicity
Mitochondrial dysfunction
mtDNA mutations
Misfolded proteins
Death of DA
Neurons in
SNpc
PD

Genetic mechanisms involved in Parkinson's disease

α-synuclein *in the locus 4q21-23, (onset around 45 years and with rapid symptoms)*

DJ-1, *in the 1p36 locus, causes modifications of α-synuclein*

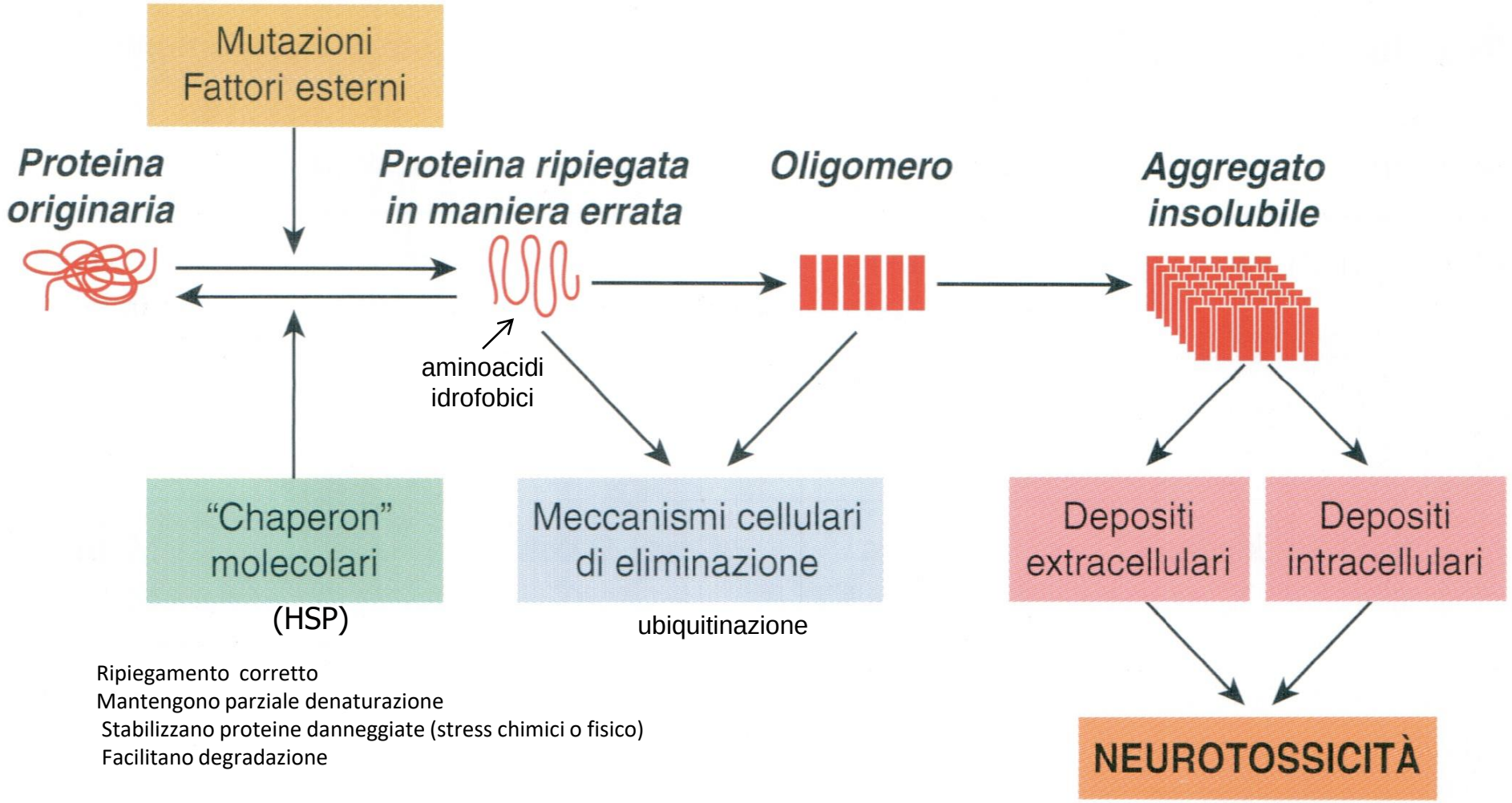
parkin, *in the locus 6q25.2-27, (juvenile forms, with onset around the age of 32, characterized by the absence of Lewy bodies in the brain) is a ubiquitin ligase*

leucine-rich repeat kinase 2 (LRRK2), *(interacts with the terminal c of parkin), the mutated LRRK2 causes apoptosis. Present in cytoplasm and mitochondria*

hydrolase of C-terminal ubiquitin L-1 (UHC-L1), *in the 4p-14 locus (proteins destined to be degraded by the ubiquitin system are previously labeled with poly-ubiquitin chains and subsequently degraded by the proteasome)*

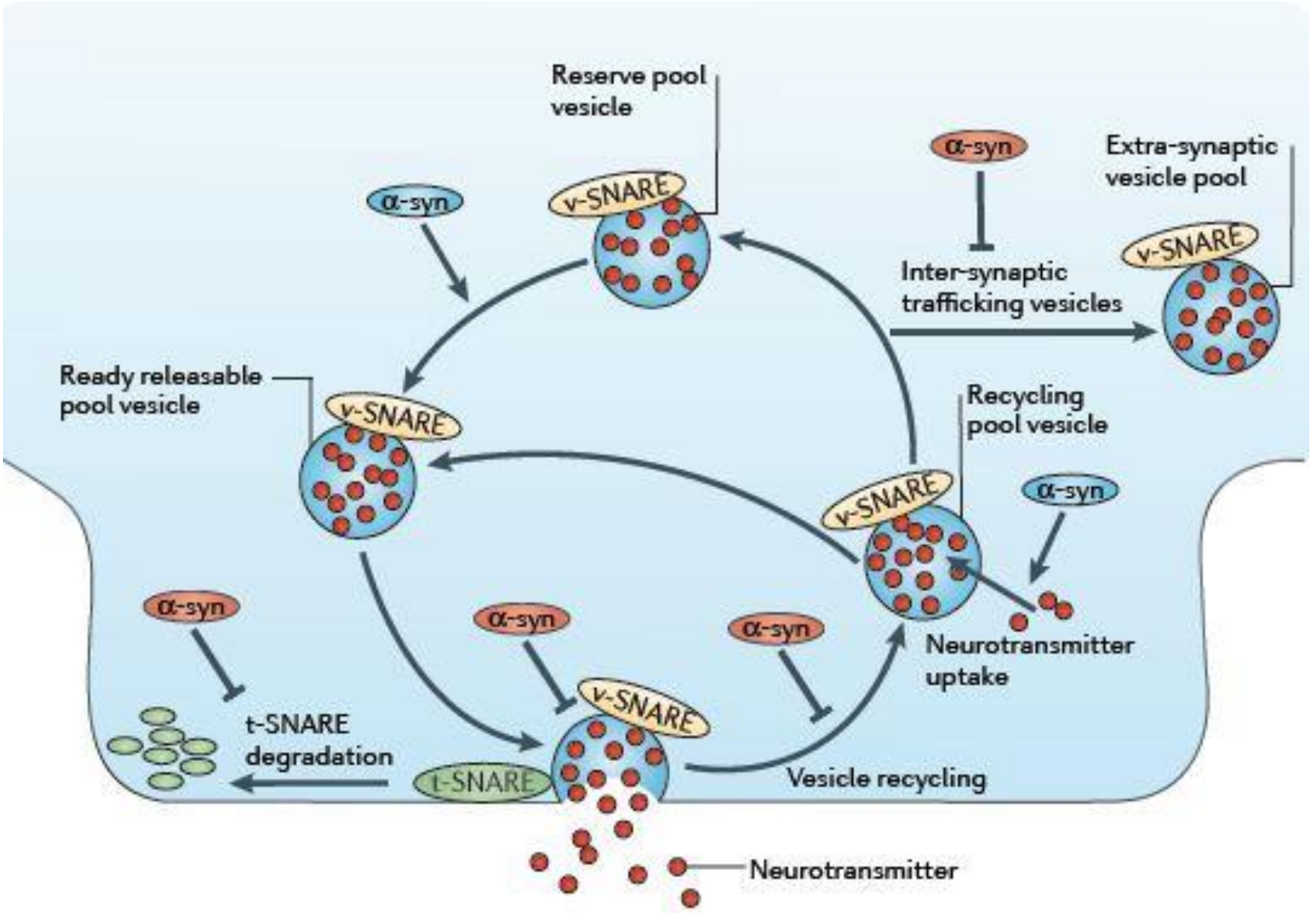
PINK 1 *(PTEN-induced kinase 1) located in the mitochondria*

“Misfolding” proteine



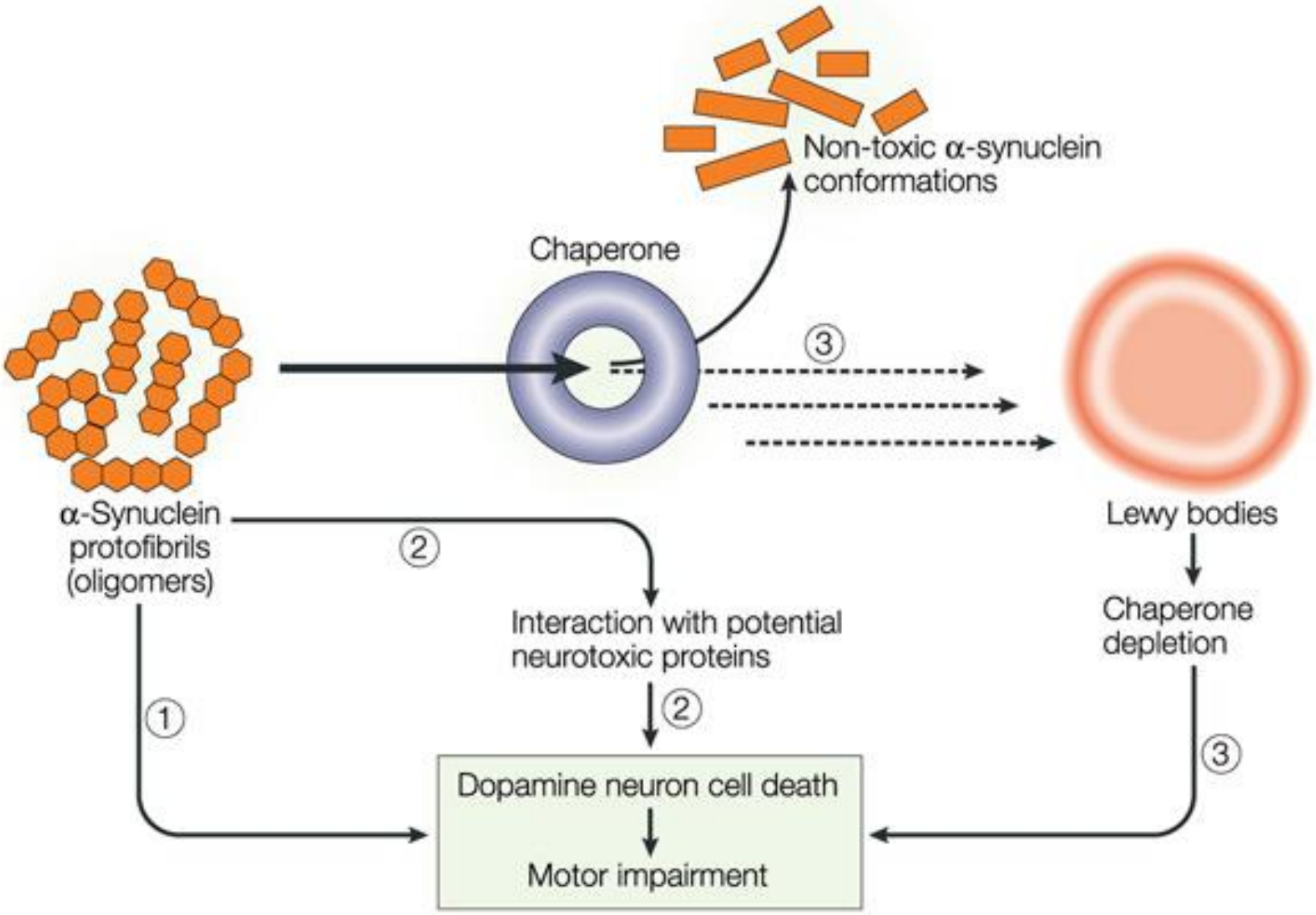
Ripiegamento corretto
Mantengono parziale denaturazione
Stabilizzano proteine danneggiate (stress chimici o fisico)
Facilitano degradazione

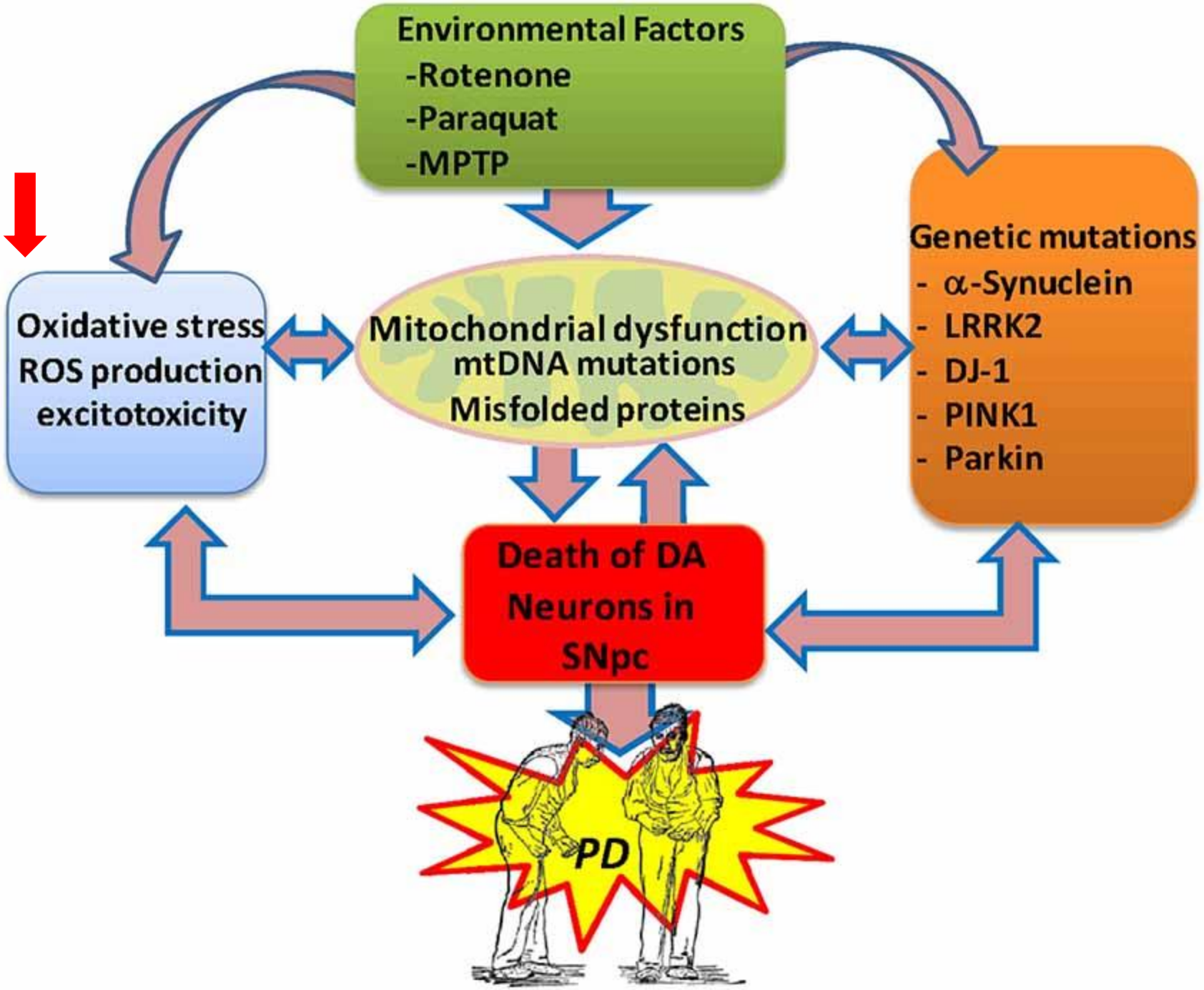
Alpha Synuclein



N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE)-complex

Alfa-synuclein

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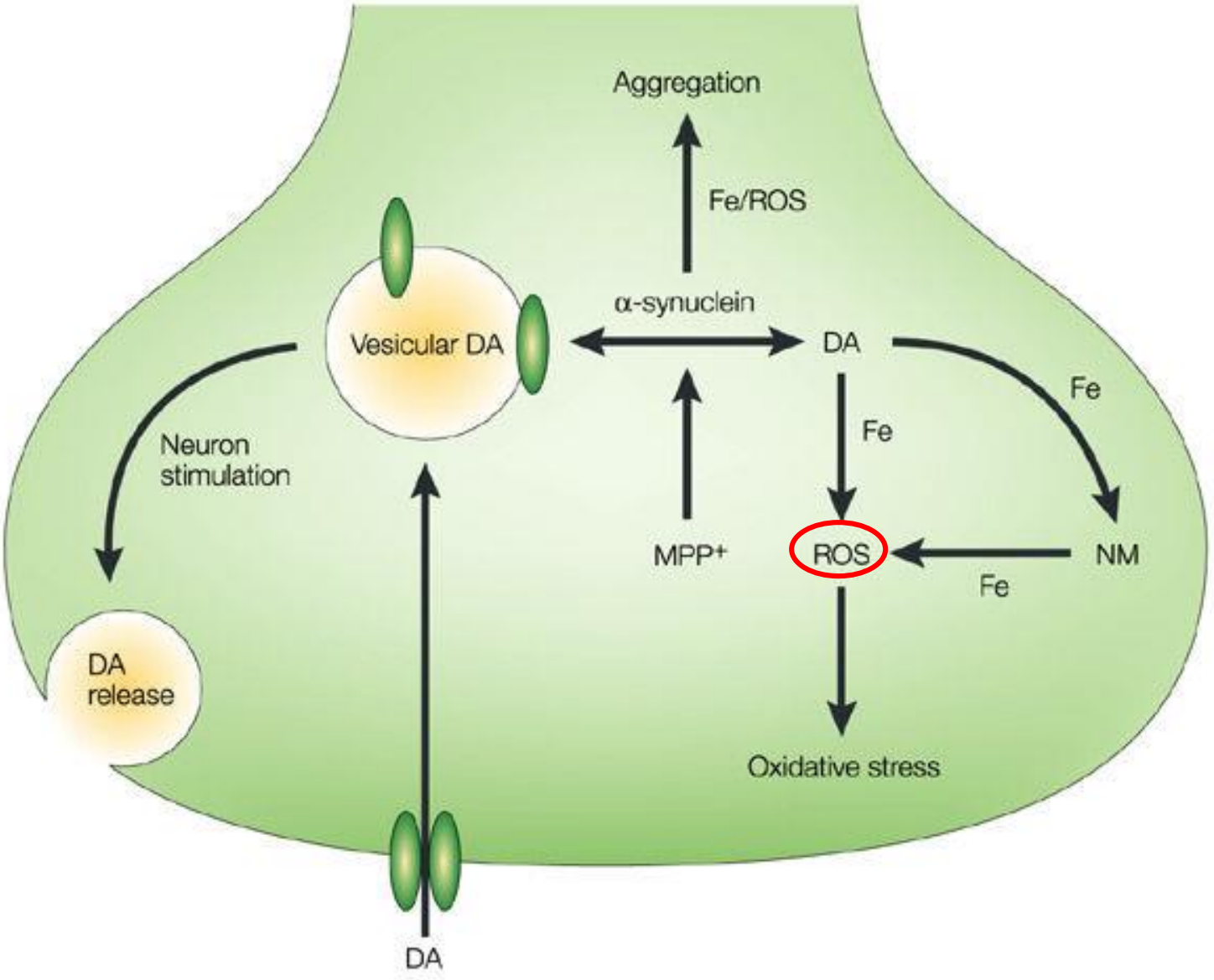
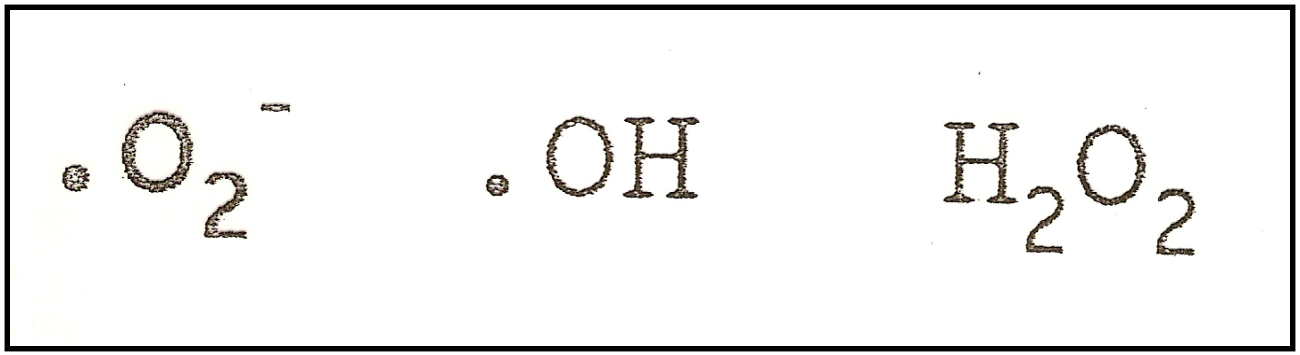
Oxidative stress



Oxidative Stress

ROS



ATTACCANO GRUPPI SH (PROTEICI)
IMPEDISCONO GENERAZIONE ATP DA MITOCONDRI
GENERANO AGENTI OSSIDANTI H_2O_2
INATTIVANO ENZIMI
ATTACCANO DNA (SINTESI ERRATA)
ATTACCANO FOSFOLIPIDI

Le difese contro il danno ossidativo

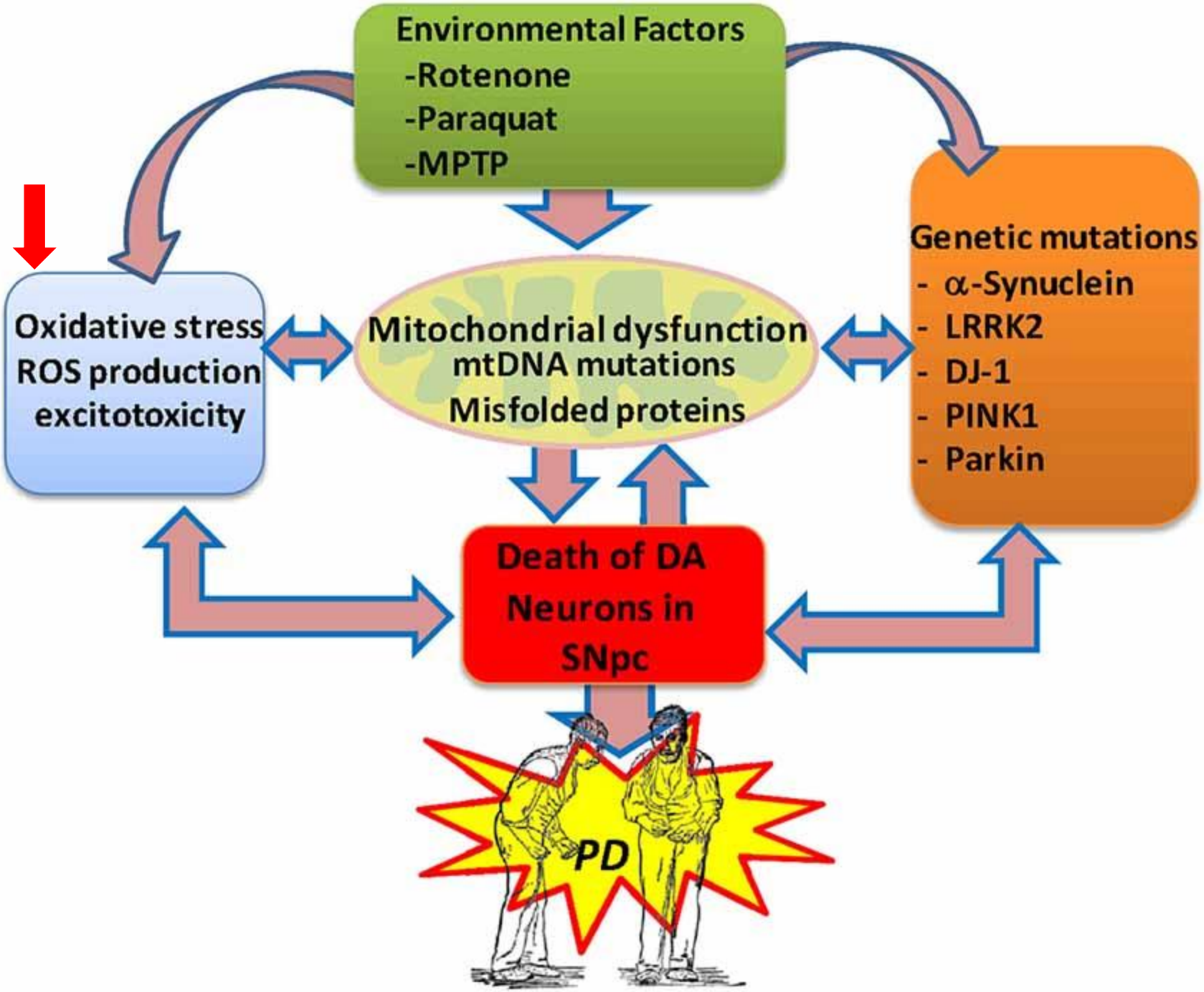
Una serie di difese previene o ripara il danno molecolare causato dai radicali liberi, ma la loro azione è nell'insieme imperfetta. Sembra che alcune di queste difese con il passare del tempo diventino meno efficaci.

ANTIOSSIDANTI
(neutralizzano o comunque limitano l'attività dei radicali liberi)

CLASSE	MOLECOLA	ATTIVITÀ
ENZIMI	Superossido-dismutasi	Trasformano il radicale superossido in perossido di idrogeno
	Glutatione, perossidasi e catalasi	Convertono il perossido di idrogeno in acqua e ossigeno molecolare
	Vitamina E e beta carotene	Reagiscono con i radicali liberi, impedendo loro di attaccare le strutture cellulari; sono liposolubili e quindi riescono a proteggere le membrane
ALTRE SOSTANZE	Acido urico e vitamina C	Reagiscono con i radicali liberi del citoplasma
	Chelanti dei metalli	Impediscono al ferro, al rame e ad altri metalli di transizione di catalizzare le reazioni ossidative

Enzymes

- **SUPEROXIDE DISMUTASE** $O_2^- + O_2^- + 2H^+ \longrightarrow H_2O_2 + O_2$
- **CATALASE** $2H_2O_2 \longrightarrow 2H_2O + O_2$
- **PEROXIDASE** $H_2O_2 + R(OH)_2 \longrightarrow RO_2 + 2H_2O$
- **GLUTATIONE PEROXIDASE** $2GSH + H_2O_2 \longrightarrow GS\text{-}SG + 2H_2O$
  $ROOH + 2GSH \longrightarrow ROH + GS\text{-}SG + H_2O$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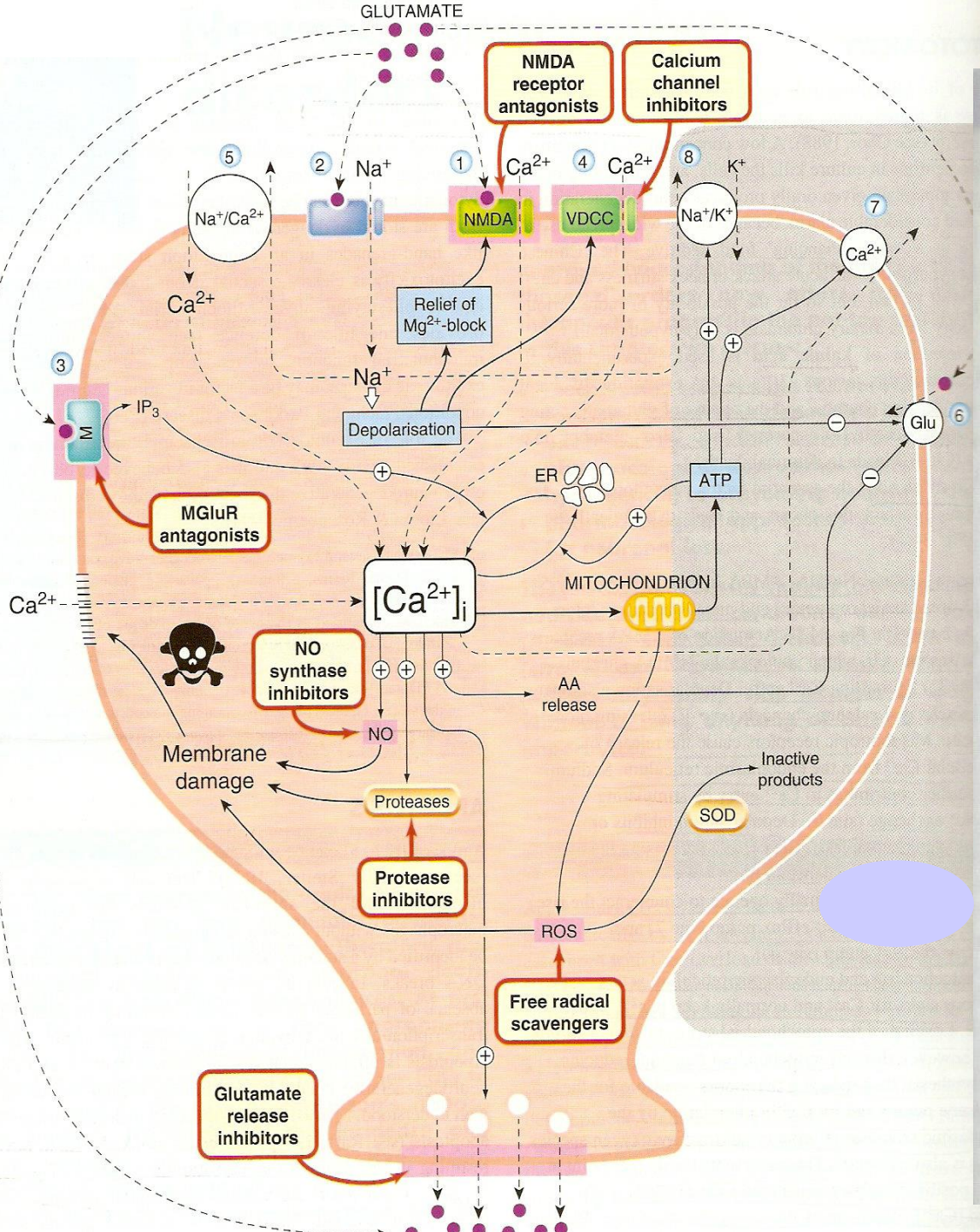
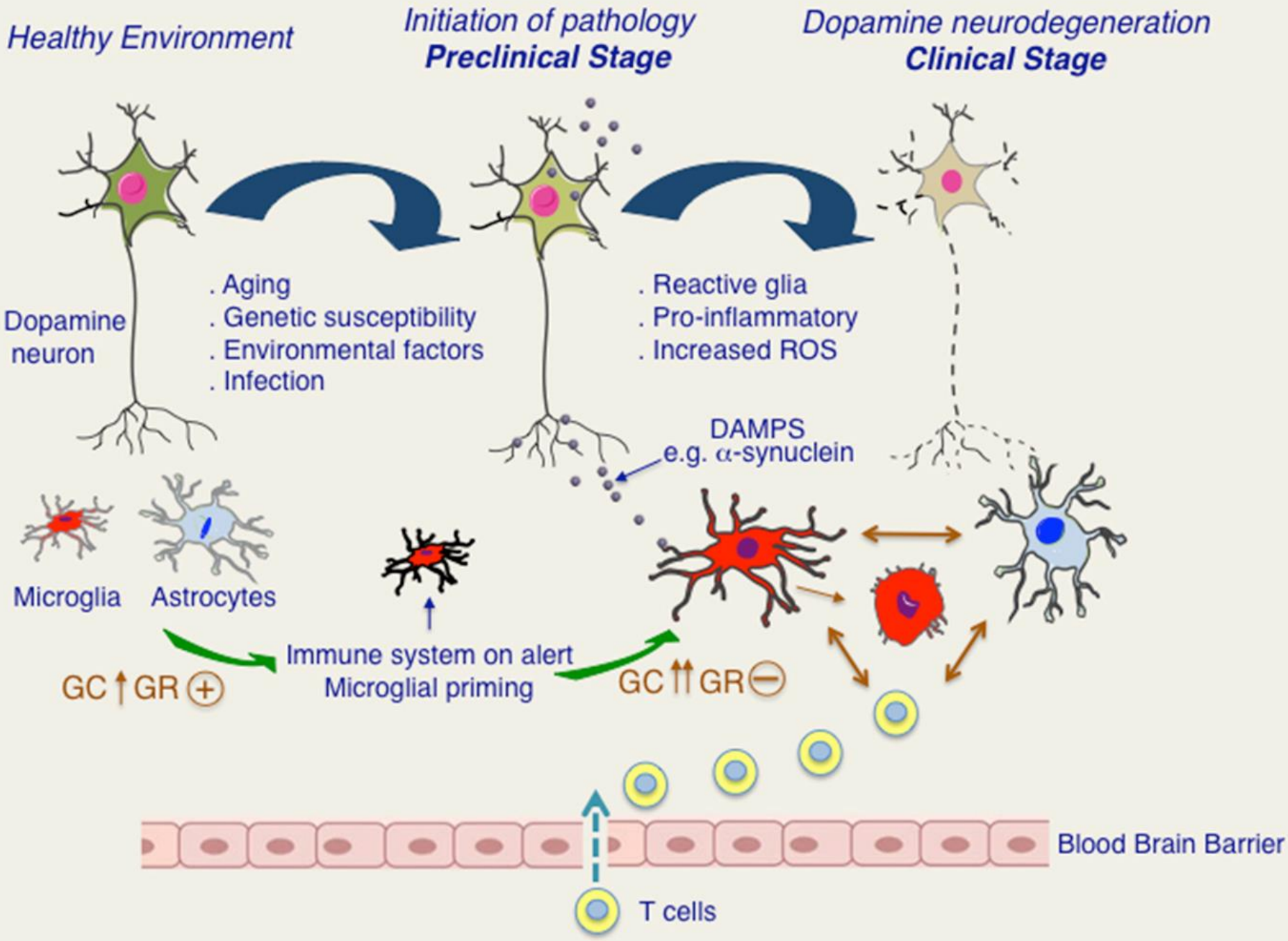


Excitotoxicity and oxidative stress

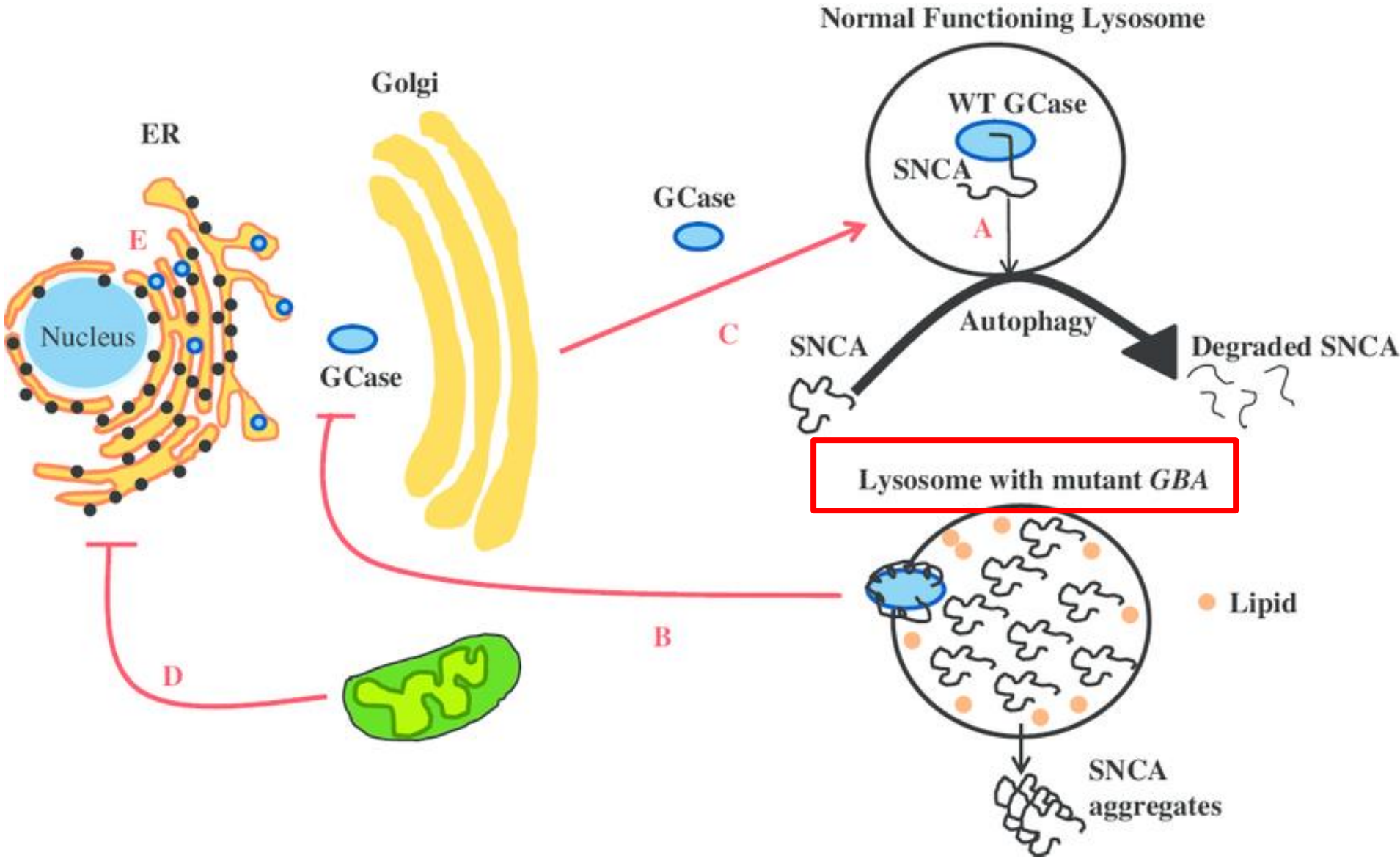
- Excitatory amino acids (EAA, e.g. glutamate) can cause neuronal death.
- Excitotoxicity is associated mainly with activation of NMDA-receptors, but other types of EAA receptors also contribute.
- Excitotoxicity results from a sustained rise in intracellular Ca^{2+} concentration (Ca^{2+} overload).
- Excitotoxicity can occur under pathological conditions (e.g. cerebral ischaemia, epilepsy) in which excessive glutamate release occurs. It can also occur when chemicals such as kainic acid are administered.
- Raised intracellular Ca^{2+} causes cell death by various mechanisms, including activation of proteases, formation of free radicals, and lipid peroxidation. Formation of nitric oxide and arachidonic acid are also involved.
- Various mechanisms act normally to protect neurons against excitotoxicity, the main ones being Ca^{2+} transport systems, mitochondrial function and the production of free radical scavengers.
- Oxidative stress refers to conditions (e.g. hypoxia) in which the protective mechanisms are compromised, reactive oxygen species (ROS) accumulate and neurons become more susceptible to excitotoxic damage.
- Excitotoxicity caused by environmental chemicals may contribute to some neurodegenerative disorders.
- Measures designed to reduce excitotoxicity include the use of glutamate antagonists, calcium channel blocking drugs (calcium antagonists) and free radical scavengers; none is yet proven for clinical use.

Neuroinflammation

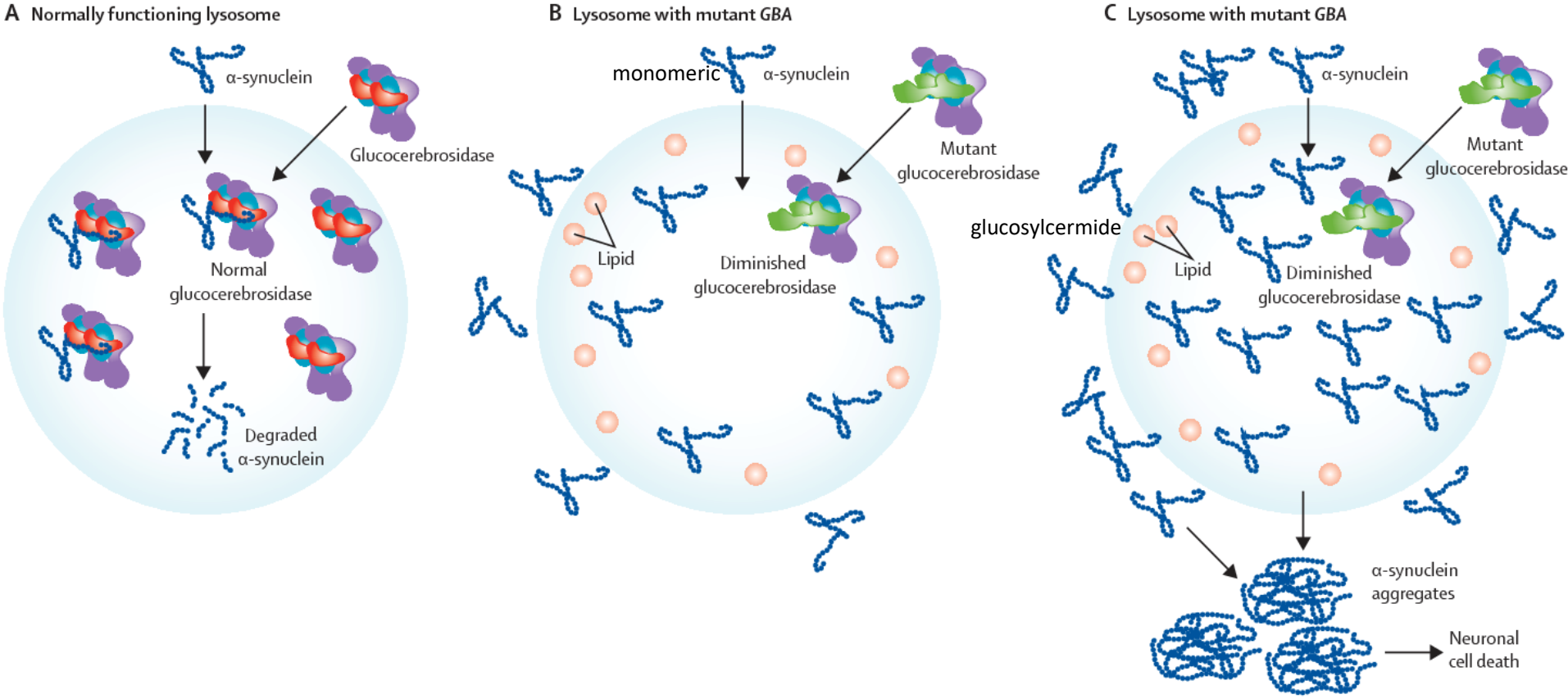

Healthy Environment
Initiation of pathology
Preclinical Stage
Dopamine neurodegeneration
Clinical Stage
Dopamine neuron
. Aging
. Genetic susceptibility
. Environmental factors
. Infection
. Reactive glia
. Pro-inflammatory
. Increased ROS
DAMPS
e.g. α-synuclein
Microglia
Astrocytes
Immune system on alert
Microglial priming
GC ↑ GR ⊕
GC ↑↑ GR ⊖
Blood Brain Barrier
T cells

Glucocerebrosidase deficiency

- Mutations in the glucosylceramidase beta (GBA) gene are associated with neurodegenerative diseases marked by protein aggregation
- GBA encodes the lysosomal enzyme **glucocerebrosidase**, which breaks down glucosylceramide
- The link between GBA mutations and protein aggregation is that lysosomal accumulation of glucosylceramide causes impaired autophagy
- Changes in the turnover and abundance of proteins is associated with **extracellular vesicles** (EVs), which are vehicles for the spread of protein aggregates in neurodegenerative disease
- Gba1b mutants had six times as many EVs as controls
- EV abundance contributed to the accumulation of protein aggregates
- Glucocerebrosidase deficiency causes pathogenic changes in EV metabolism and may promote the spread of protein aggregates through extracellular vesicles


Normal Functioning Lysosome
WT GCase
SNCA
A
Golgi
ER
GCase
E
Nucleus
C
SNCA
Autophagy
Degraded SNCA
GCase
Lysosome with mutant GBA
Lipid
B
D
SNCA
aggregates

Mutation in glucocerebrosidase (GBA) gene and ASN aggregation



(A) normally functioning lysosome, wild-type glucocerebrosidase might interact with α-synuclein, facilitating the lysosomal component of α-synuclein degradation. **(B)** In most cases, when glucocerebrosidase is mutated, α-synuclein remains in the monomeric form and other processes are active in its degradation. **(C)** In some patients, glucocerebrosidase is mutated and the cell is unable to degrade α-synuclein. Lysosomal function is compromised and increased oligomeric forms of α-synuclein lead to neuronal cell death and the development of parkinsonism.