Neurodegenerative disorders

May 16, 2017

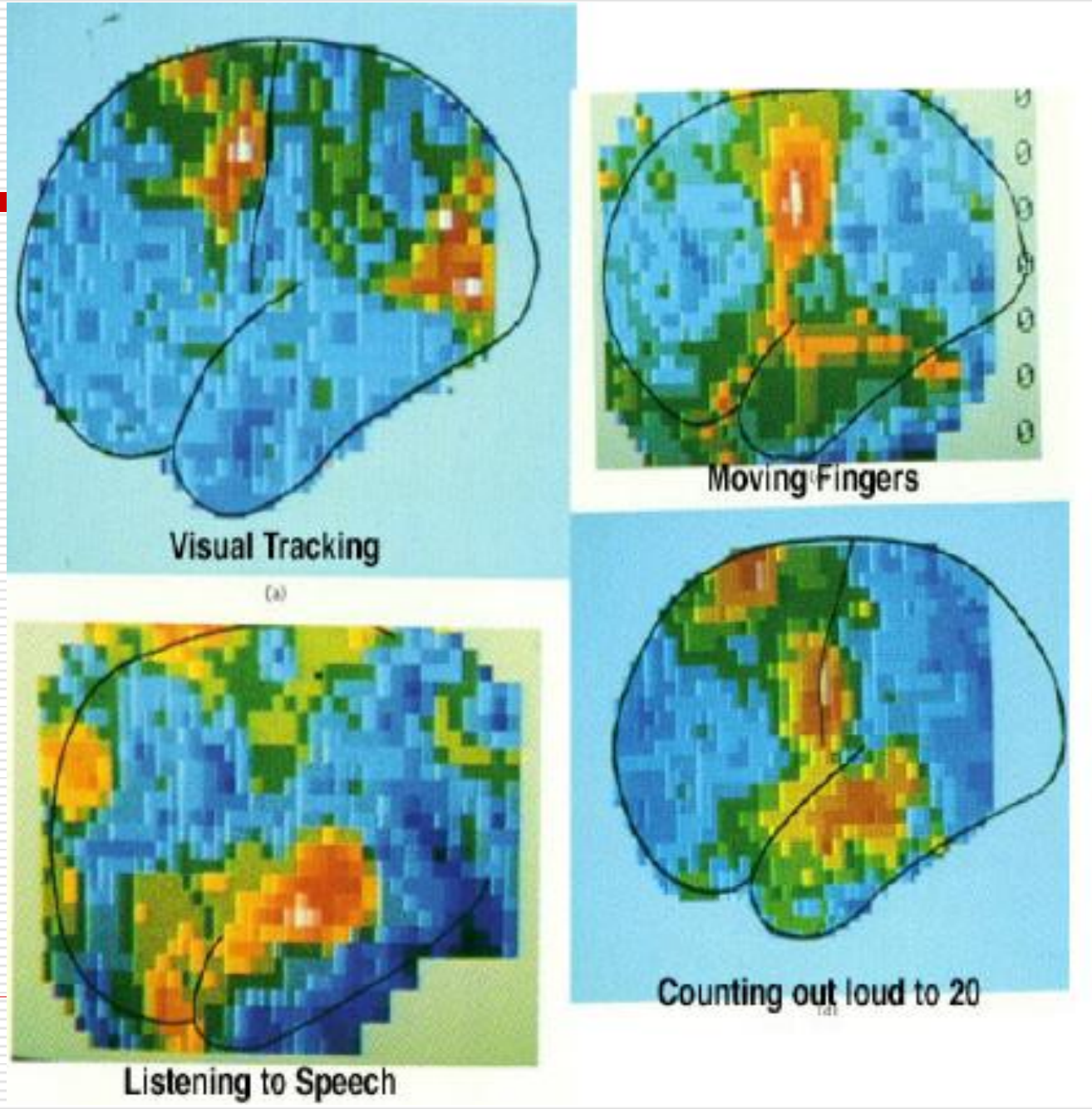
Patogenesis?

- Inflammation
- Axon loss
- Metabolism

Electric and magnetic detection of changes

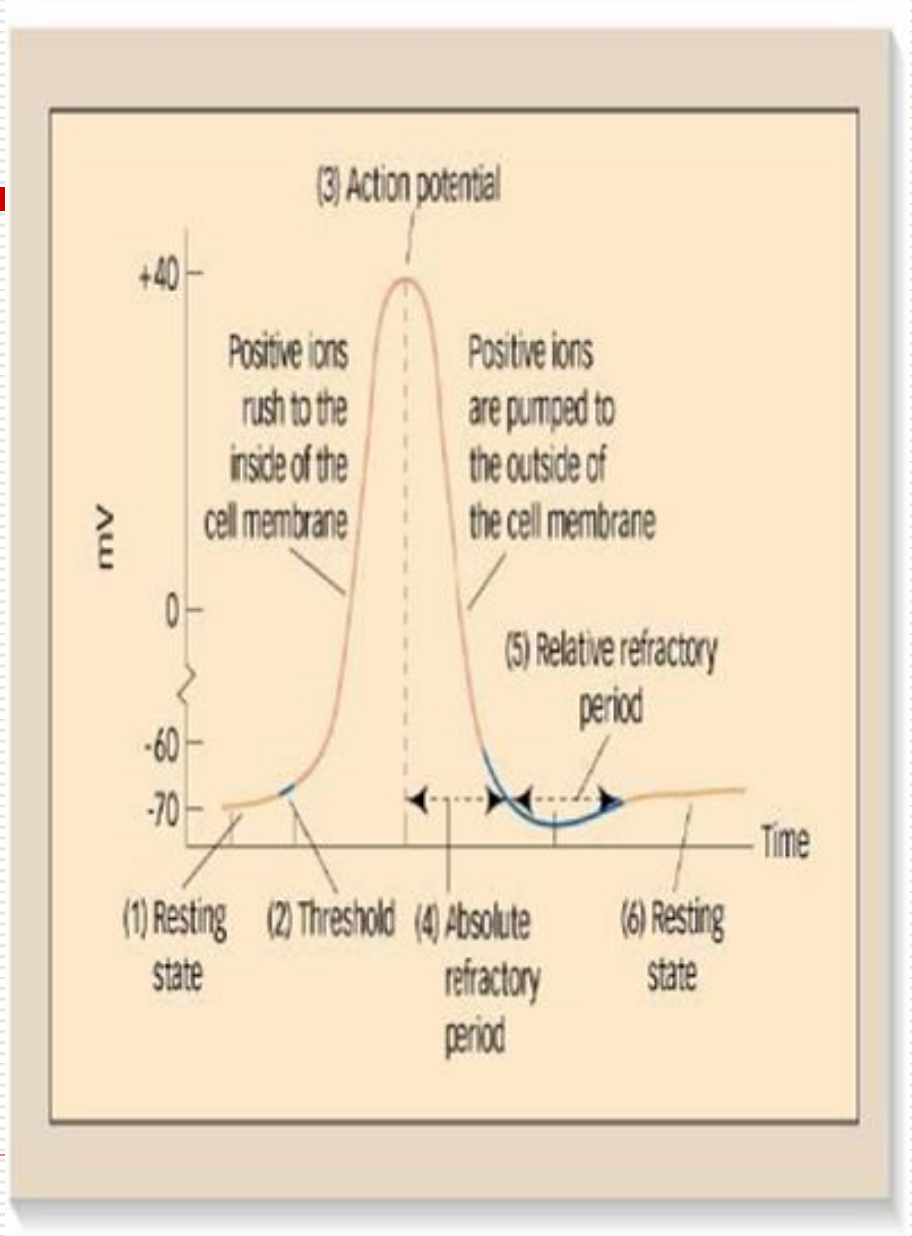
- EEG
- Transcranial magnetic stimulation (TMS)
- Positron emission tomography (PET)
- Magnetic resonance imaging (MRI)

PET


Visual Tracking
Moving Fingers
Listening to Speech
Counting out loud to 20

Interneuronal communication:

- Action potential („nothing or everything“)
- Electric impuls along axon
- Cationic influx as a result of pressure, voltage, light or other neuron stimulation
- Excitation and inhibitory synapses
- Threshold existance
- Characteristics of action potential can be changed



Hematoencephalic barrier

- Is a barrier between blood and cerebrospinal fluid
- Dynamic process of molecular entry towards to CSF.
- Concentration of CSF proteins dependes on their origin (blood or brain).
- Concentration of originally blood proteins is increasing countinuously during their way from brain ventricles to the spinal cord channel due to passive difusion.
- Movement energy of CSF is done by the differences between arterial and venous system.
- When the barrier is not fuctionning well, blood protein concentration is modulated by CSF flow; decreased CSF flow increases entry of blood proteins

Insulin, glucose and brain

- Originally metabolism of glucose in brain considered as insulin-insensitive
- Glial metabolism is insulin dependent (insulin/IR).
- Brain can considered a tissue sensitive to glucose and insulin.
- Common distribution of insulin, IR, GLUT1 and GLUT4 in certain brain areas, especially in hippocampus and plexus chorioideus.

CSF

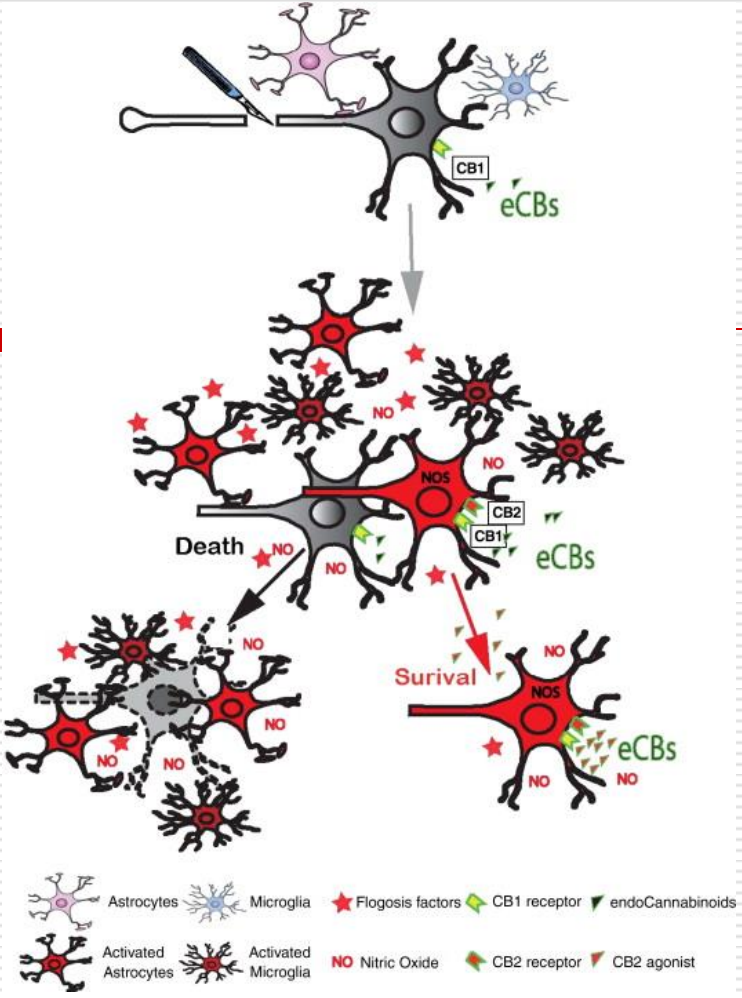
- is generated by filtration of blood in the choroid plexus and by diffusion from the extracellular matrix of the brain into the ventricles.
- The CSF surrounds the brain and the spinal cord and there is a constant diffusion of brain proteins into the CSF; approximately 20% of the protein contents of the CSF are estimated to be derived from the brain.
- CSF is produced at a rate of 500 ml/day and turns over approximately 4 times per day by drainage into the blood; thus, many ongoing processes in the CNS are reflected in the protein composition of the CSF.

Insulin, glucose and brain

- Postprandial insulin levels maximally stimulate the glucose metabolism in brain cortex, either directly (similarly as in peripheral tissues), or indirectly by pathway of insulin stimulated neuronal activation.
- Main transporter: GLUT1 in glial cells, partly sensitive to insulin.
- Insulin possibly stimulates accumulation of glucose in glial cells and its metabolisation on lactic acid for neurons which had been stimulated by insulin.

Insulin, glucose and brain

- Insulin is also able to inhibit noradrenalin (NA) uptake which activates glial NA β-adrenoreceptors. This is leading to release of glucose from glycogen storage in glial cells.
- Any problems in cooperation of insulin and glucose metabolism in neurons potentially decrease ATP synthesis which is leading to apoptosis.



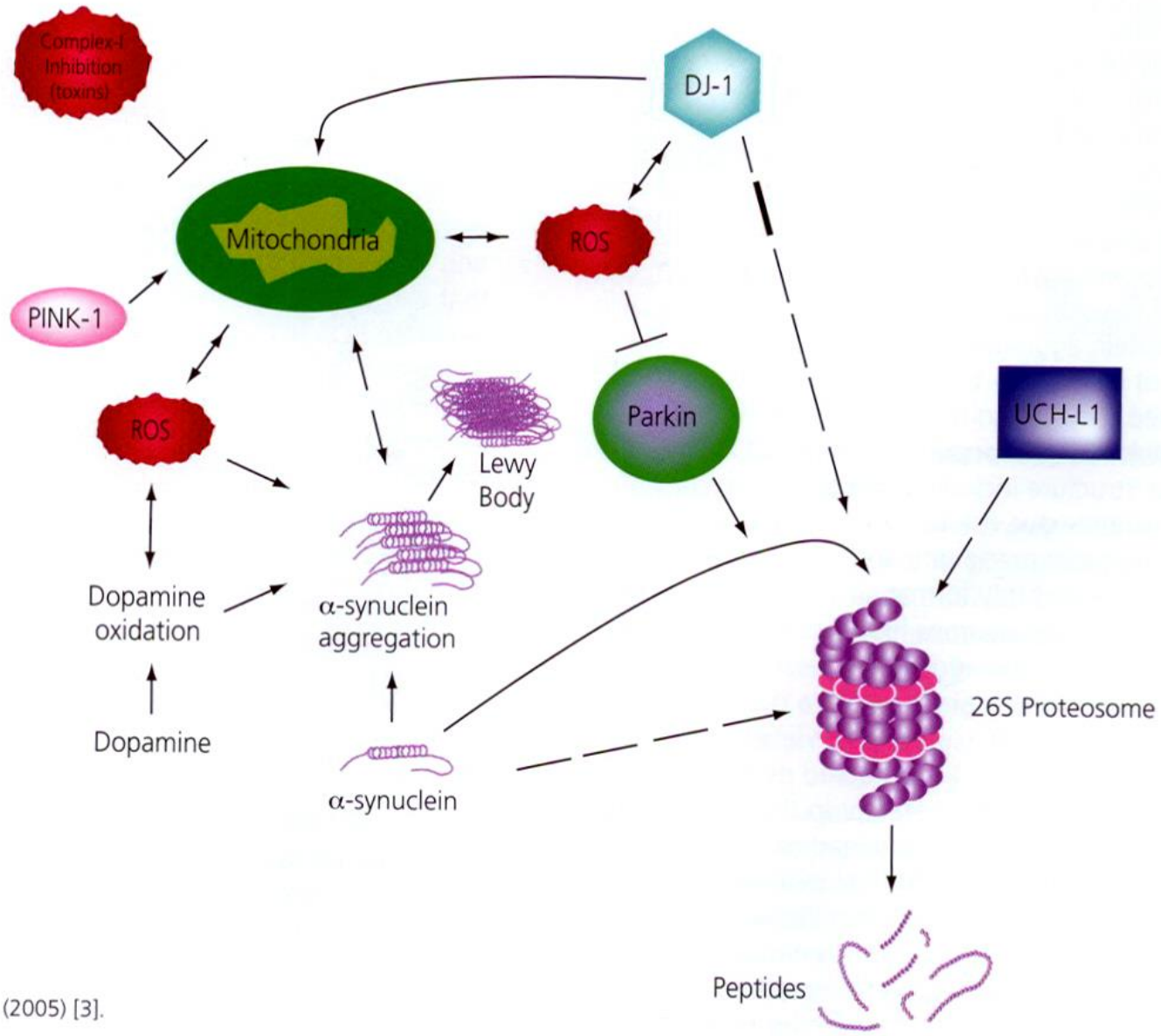
Schematic of the hypothesized remote cell death mechanisms. After axotomy neuronal and glial changes take place. Axonal lesion can trigger nitric oxide synthase synthesis and changes in the expression of cannabinoid receptors with the appearance of the cannabinoid receptor type 2 in neurons. Neurons that do not present these changes rapidly degenerate. Neuronal changes are associated with both microglial and astrocytic activations. Selective activation of CB2 receptor is associated with neuronal survival and inhibition of the reactive gliosis.

Table 1. Genes Associated with Parkinson's Disease

Locus	Map Position	Gene	Inheritance	Pathology
PARK 1	4q21-q23	α-synuclein	Dominant, high penetrance	LB positive
PARK 2	6q25-q27	parkin	Recessive	LB negative
PARK 3	2p13	Unknown	Dominant, Incomplete penetrance	LB positive
PARK 4	4p15	Unknown	Dominant, high penetrance	LB positive
PARK 5	4p14	UCH-L1	Dominant	Unknown
PARK 6	1p36-p35	Unknown	Recessive	Unknown
PARK 7	1p36	DJ-1	Recessive	Unknown
PARK 8	12p11-q13	Unknown	Dominant, Incomplete penetrance	LB negative
PARK 9	1p36	Unknown	Recessive	Unknown
PARK 10	1p32	Unknown	Non-Mendelian	Unknown
PARK 11	2q36-q37	Unknown	Non-Mendelian	Unknown
? ? ? ? ? ?	2q22-q23	NR4A2	Dominant	Unknown

Adapted from Bonfante, et al., *J. Med. Chem.* (2004).

Figure 5. Parkinson's Disease Pathways



Adapted from Moore, et al., (2005) [3].

α-Synuclein (SNCA)

- This presynaptic protein (140 AAs) is a main compound of intracellular aggregates (Lewy´s bodies - PD).
- Three missence mutation identified in the gene SNCA which is coding synuclein in patients with familiar parkinsonism with a deficit of cognitive functions.
- Dynamics of synuclein in vivo depends on many metabolic functions , especially related to proteasome and lysosomal activities.
- Decrease of synuclein concentration in patients with neurodegenerative diseases; exactly was not explained.

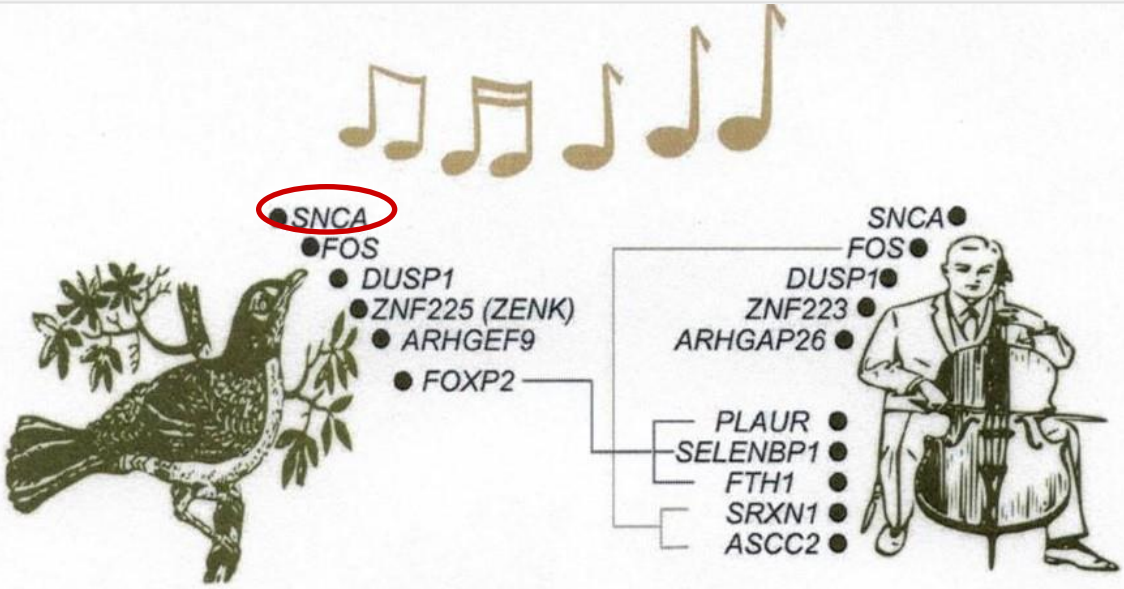


Figure 3 | Evolutionary conservation of music perception/production. The genes up-regulated after music performance such as *SNCA*, *FOS*, and *DUSP1* have been demonstrated to be regulated in the song control system of songbirds[26,28,47–49] whereas *ZNF223* and *ARHGAP26* have been known to be functionally similar to *ZNF225 (ZENK)* and *ARHGEF9* that are regulated during song perception and production in songbirds[50,72,73]. The up-regulated genes *SRXN1* and *ASCC2* are the known target genes of *FOS*. The up-regulated genes *PLAUR*, *SELENBP1* and *FTH1* are the known direct target genes of *FOXP2*. *FOXP2* gene has been known to be a very important candidate gene for song and speech development. Reduced activity of *FOXP2* has been known to interfere with dopaminergic modulation of vocal variability, thus impairing song and speech development[74]. The vector graphics of songbird and cello player have been obtained from Openclipart (https://openclipart.org/) and modified.

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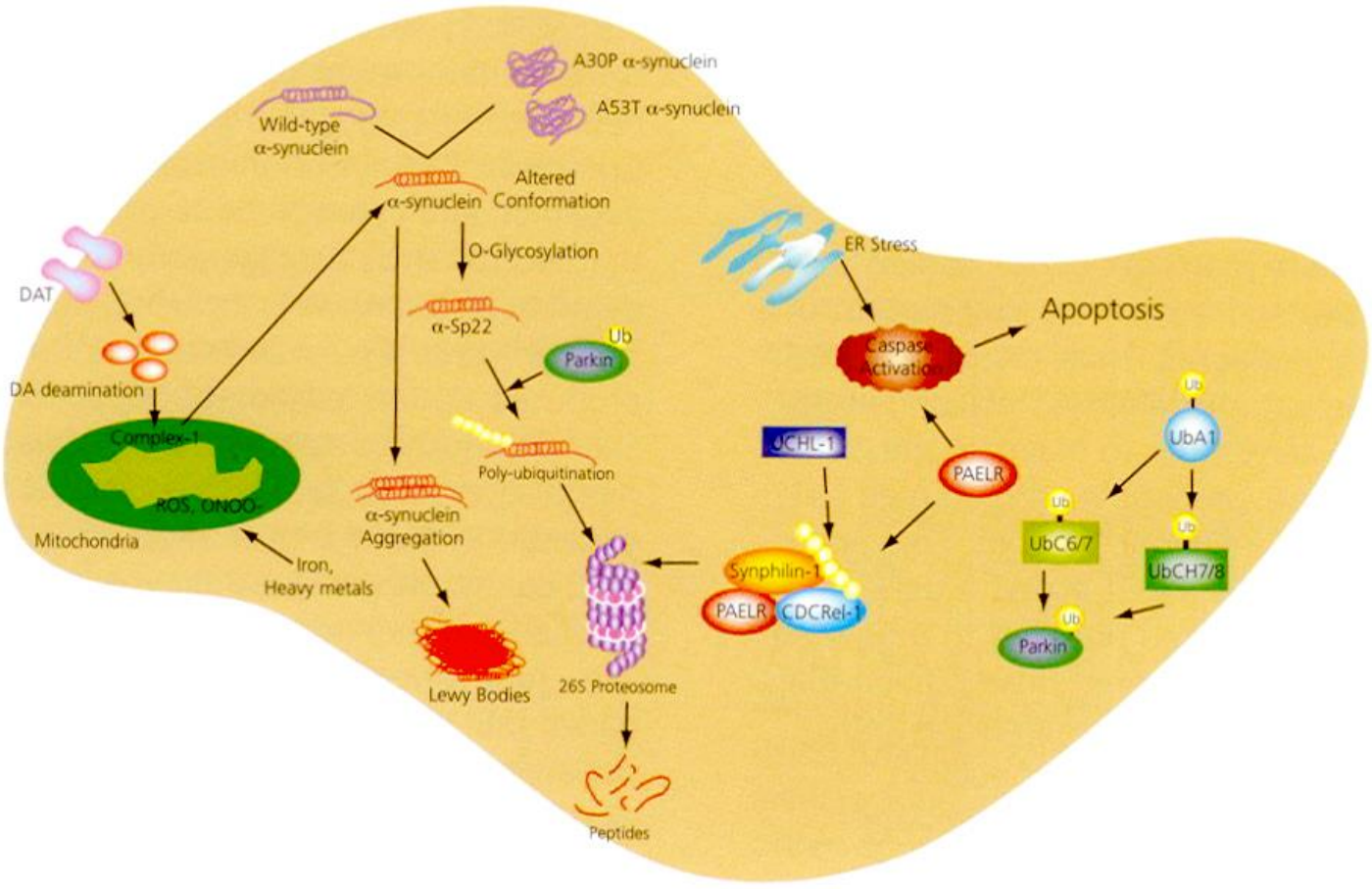
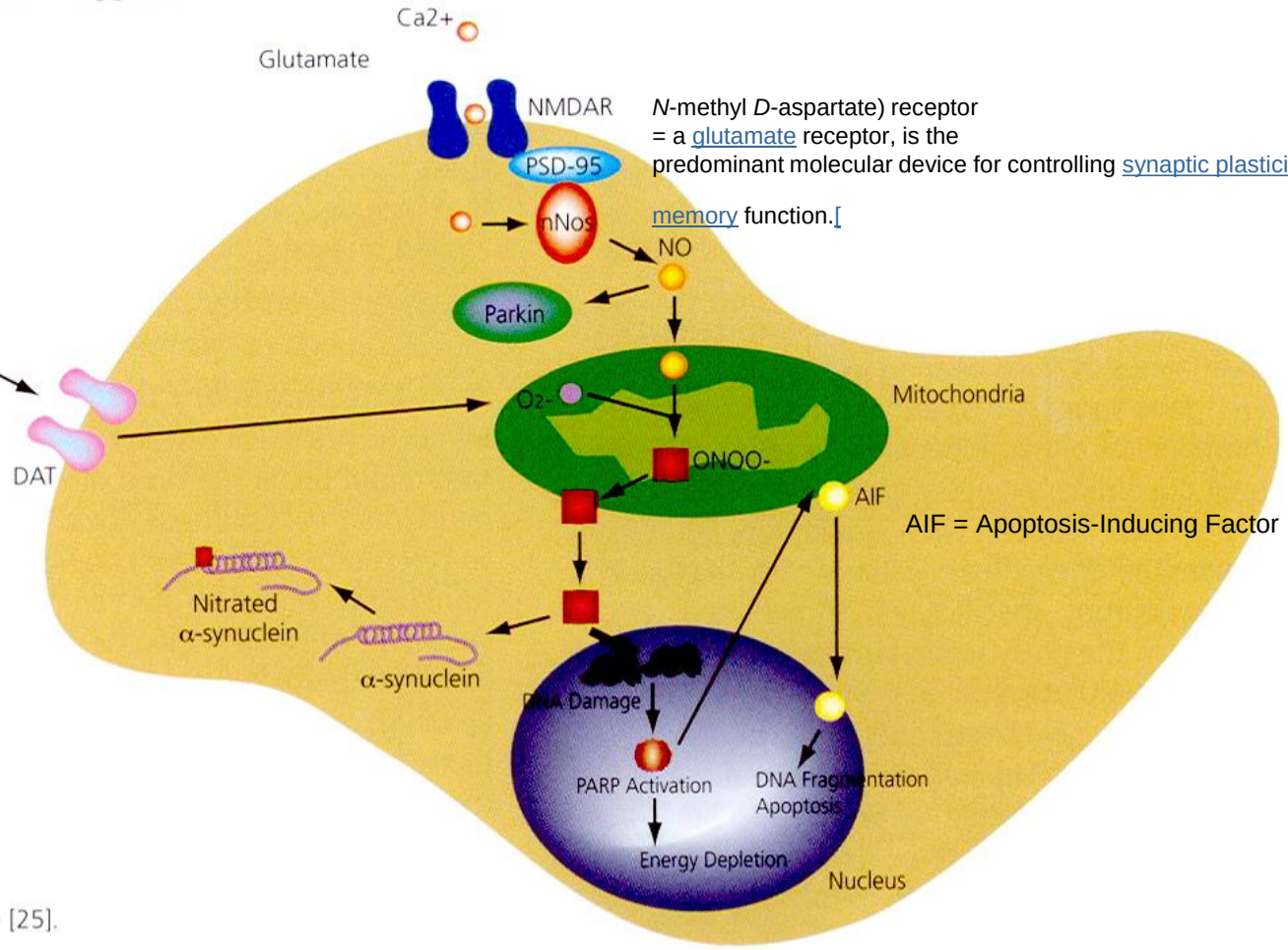
Figure 6. Oxidative Stress Pathways



Adapted from Wersinger and Sidhud (2002) [18].

Figure 7. Effect of Neurotoxin Triggers



Adapted from Zang, et al. (2005) [25].

N-methyl *D*-aspartate) receptor
= a glutamate receptor, is the predominant molecular device for controlling synaptic plasticity and memory function.[

MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) is a neurotoxin that causes permanent symptoms of Parkinson's disease by destroying dopaminergic neurons in the substantia nigra of the brain

AIF = Apoptosis-Inducing Factor

PARP=Poly (ADP-ribose) polymerase

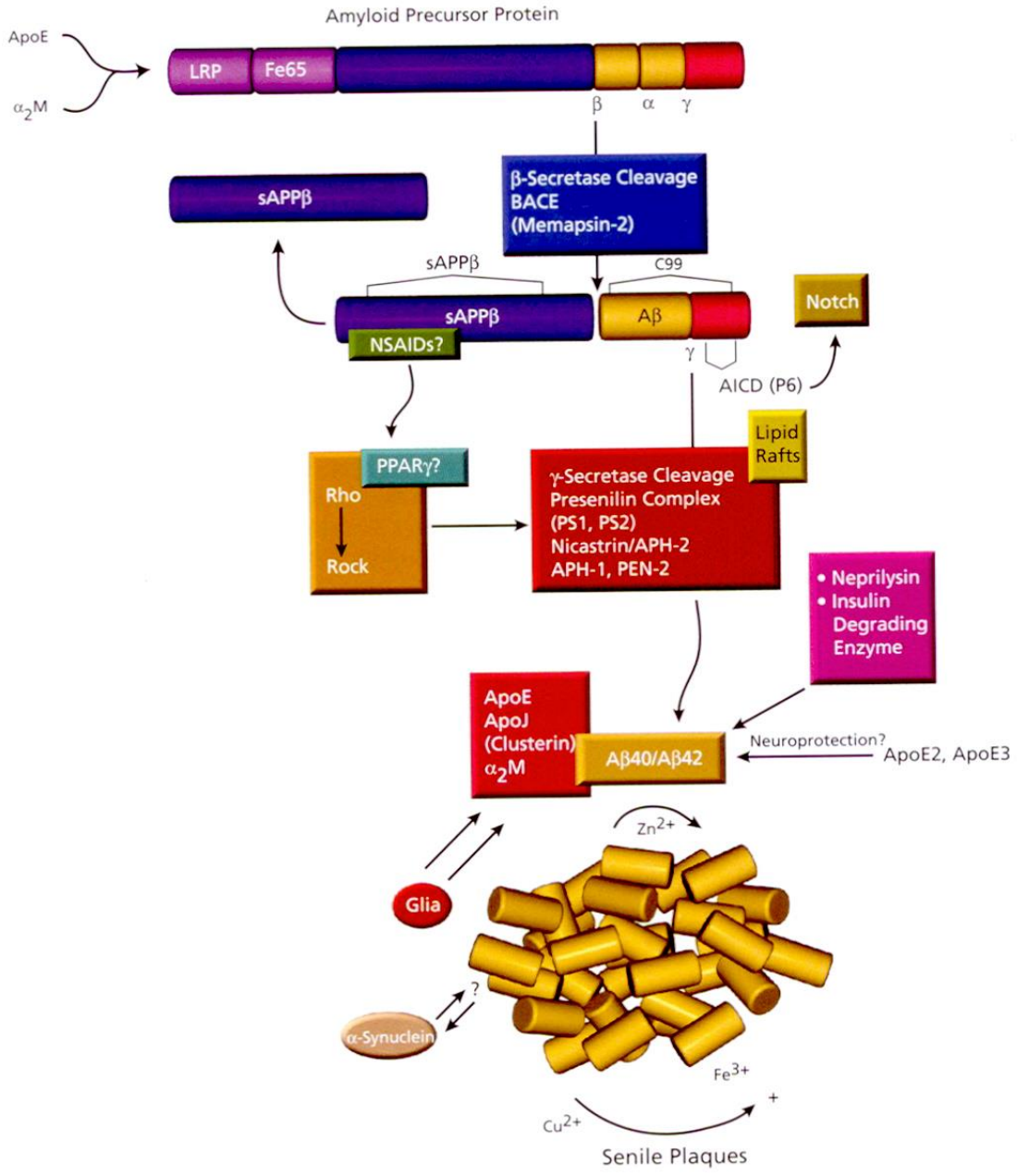
Alzheimer's disease (AD)

- Alzheimer's disease (AD) is a progressive brain amyloidosis that injures brain regions involved in memory consolidation and other higher brain functions.
- Neuropathologically, the disease is characterized by accumulation of a 42 amino acid peptide called amyloid β (Aβ42) in extracellular senile plaques, intraneuronal inclusions of hyperphosphorylated tau protein in neurofibrillary tangles, and neuronal and axonal degeneration and loss.

Alzheimer´s disease

- Cerebrovascular and neuronal dysfunction leading to progressive loss of cognitive functions
- Tau protein and extracelular amyloid plaques whose main compound is amyloid β (Aβ).
- Aβ (38–43 AK) is a side proteolytic product of amyloid precurzor protein (APP).
- Oligomeric Aβ types (the smalest are dimers) are the most synaptotoxic.
- The early onset of AD (<1%) is caused by mutations in APP, presenilin 1 (PSEN1) or presenilin 2 (PSEN2) which are leading to increased formation of APP.

Figure 2. β-Secretase Pathway



Amyloid-β -Peptides

- Amyloid- β (A β) peptides with different lenght are formed during enzymatic cleavage of 120 kDa transmembrane amyloid precursor protein (APP) by 3 different secretases: β-secretase (BACE-1), γ-secretase and metalloproteinase α-secretase.
- The formed peptides have a different tendency to aggregate according to their lenght and a degree of posttranslational oxidation.
- Amyloid plaques in the brain of patients with Alzheimer´s diseases (AD) are formed especially by carboxyterminally prolonged forms of A peptidase, as is A 1-42.

TACE=TNFα converting enzyme
Neuroinflammation?

Figure 1. α-Secretase Pathway

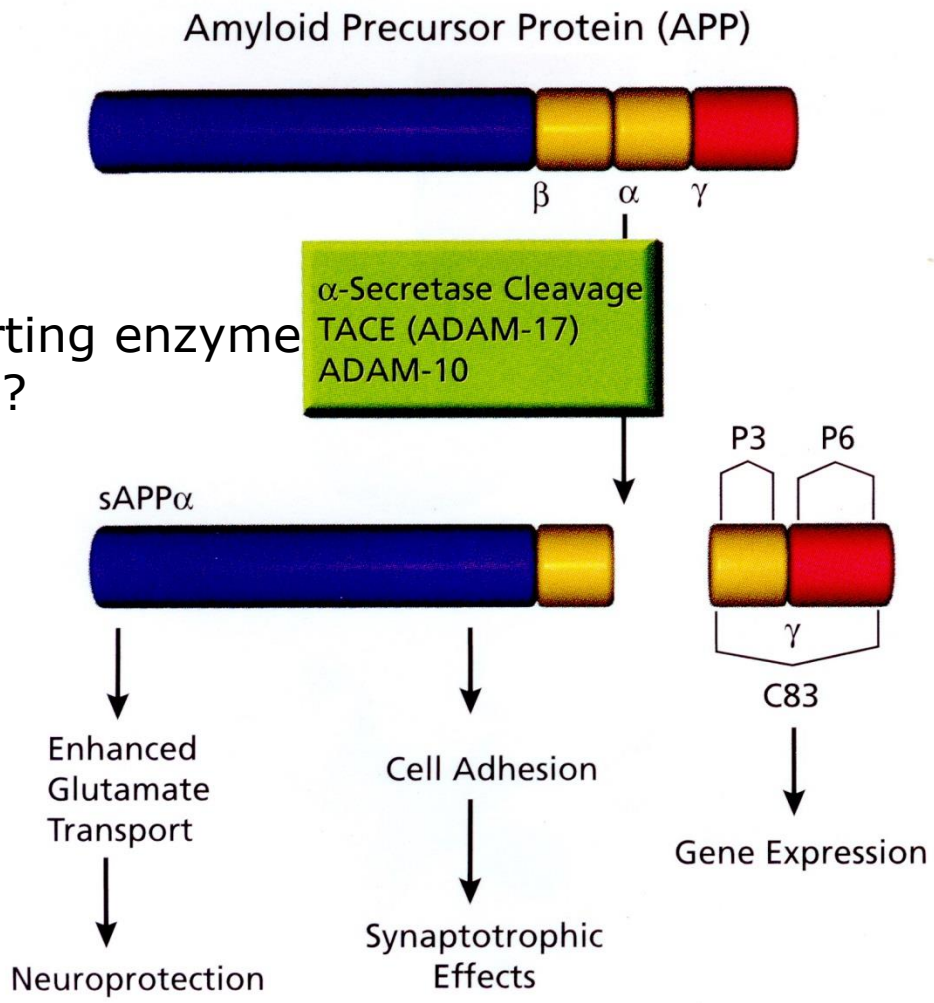
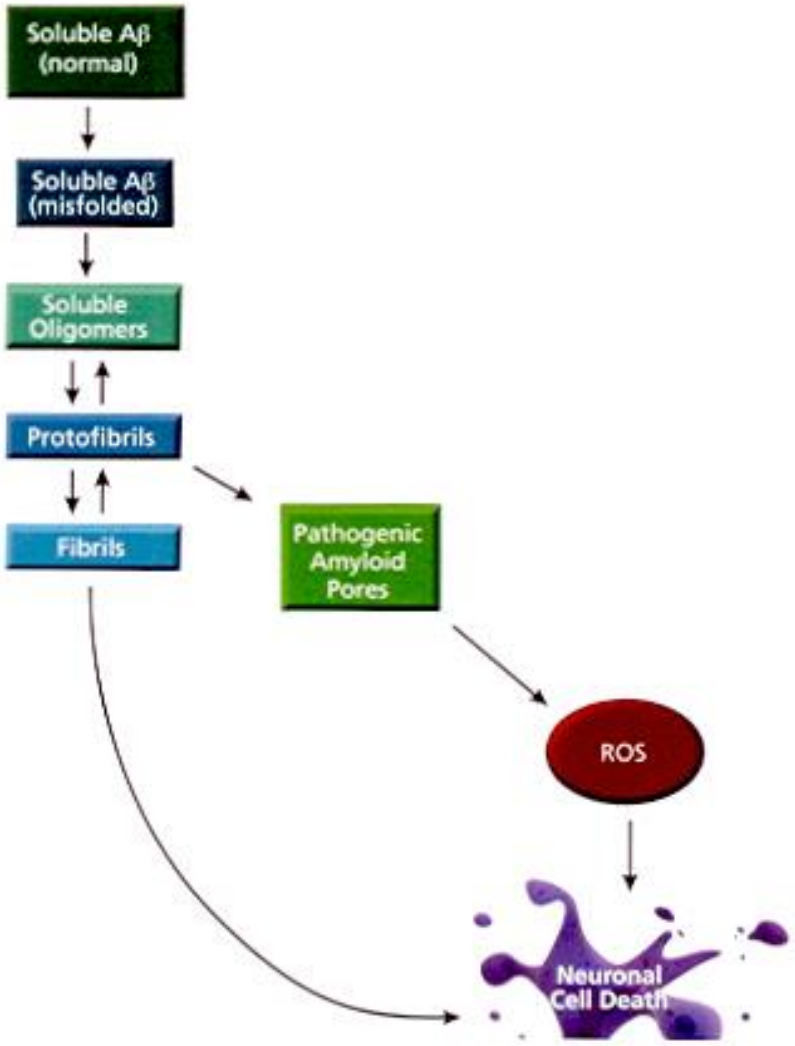
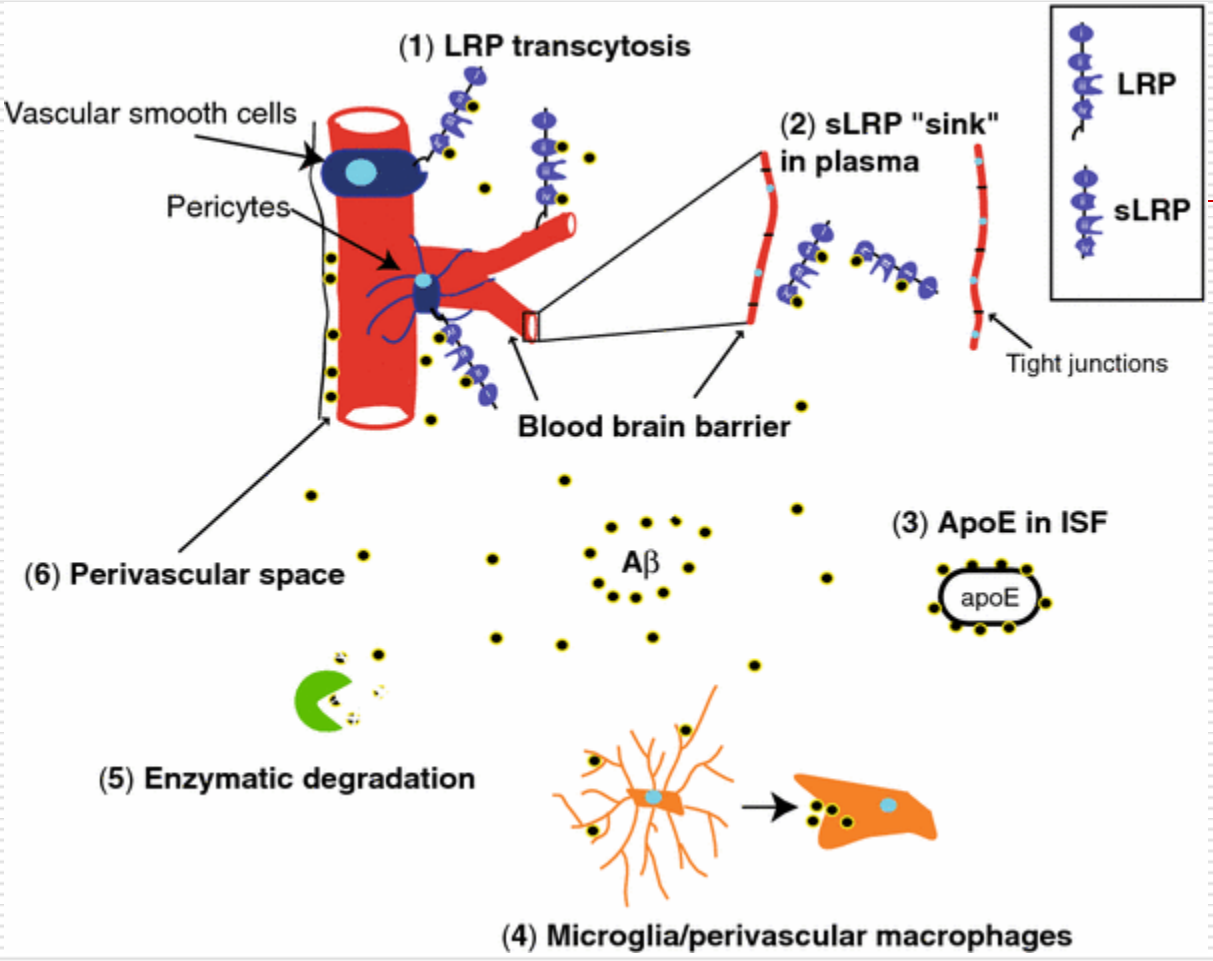


Figure 4. Possible Effects of Soluble Aβ Oligomers





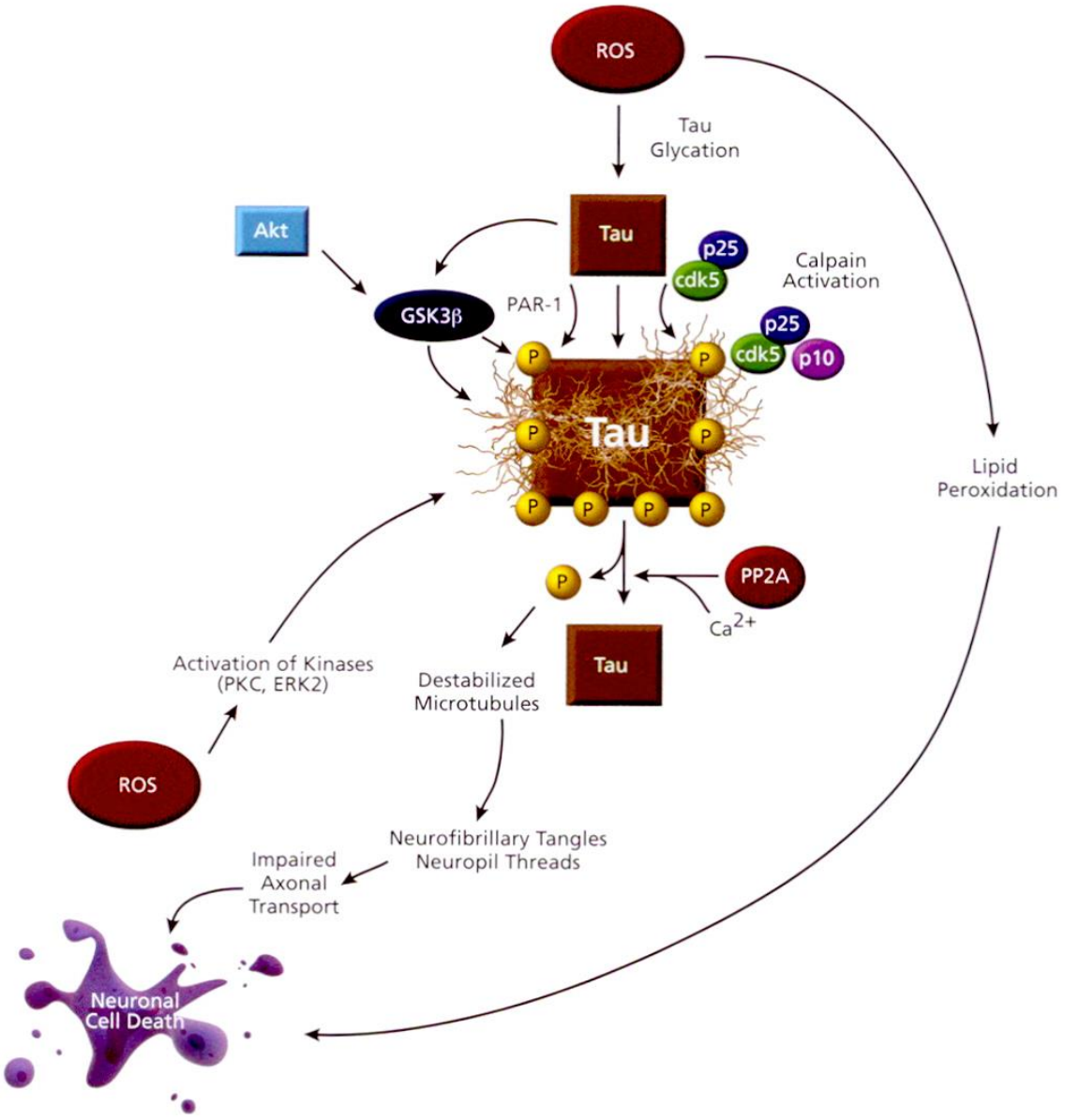
LRP=low-density lipoprotein receptor-related protein

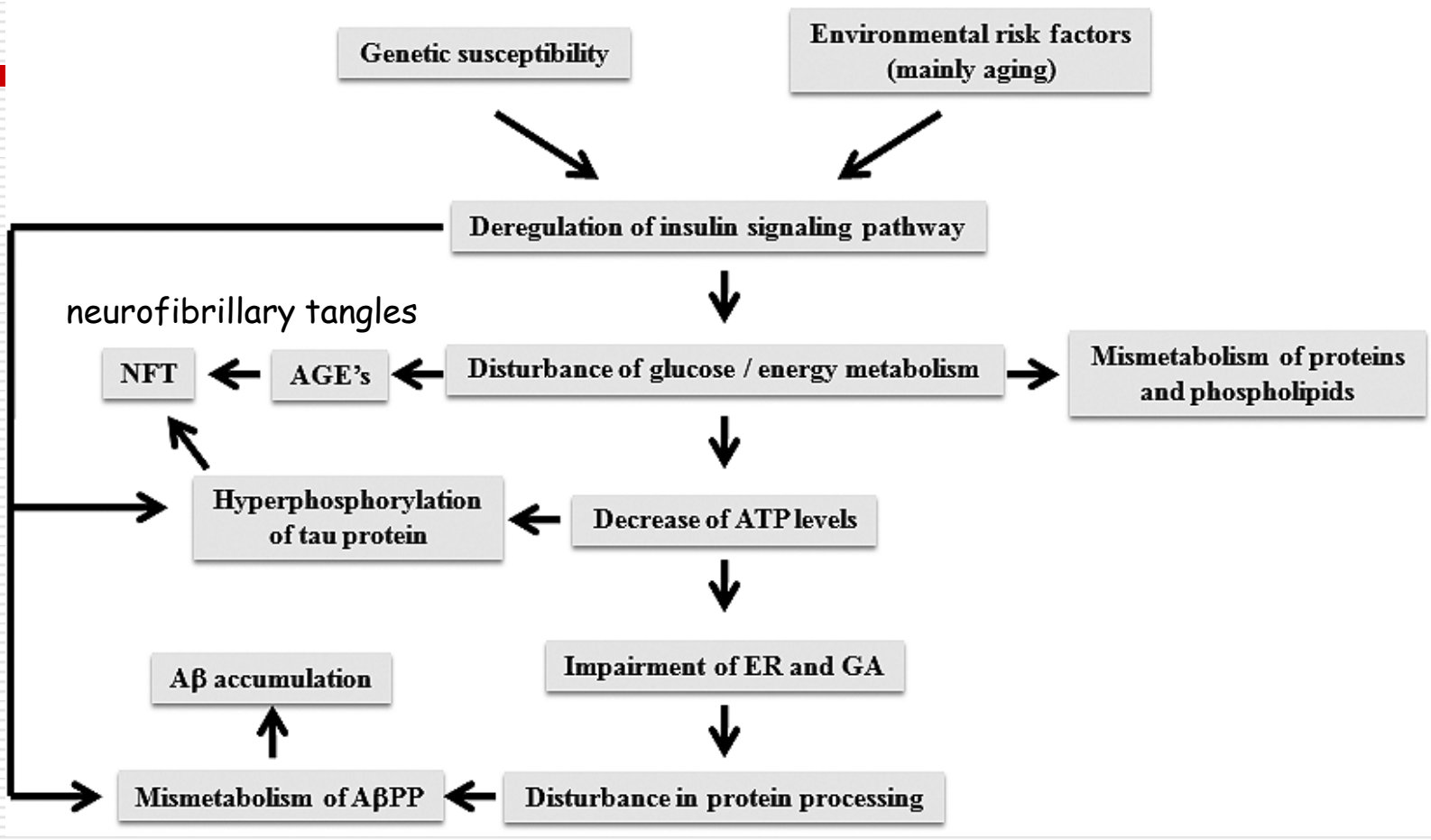
Clearance Aβ can be realised by several ways:
1 Transcytosis controlled by LRP (*purple*, receptor) through hematoencephalic barrier (red, capillaries) removes Aβ from CSF to blood. This degradation of Aβ in smoth muscle cells in blood vessels and perivascularly decreases Aβ also in exreacellular space (blue, cells,
2 solubile LRP (*purple*, solubile receptor) increases Aβ clearance and decreases levels of free Aβ in circulation
3 Aβ chaperones in CSF as ApoE isoforms can reduce Aβ clearance in dependence of ApoE isoform (apoE4 > apoE3 and/or apoE2)
4 clearance Aβ by microglial cells and perivascular brain macrophages (*orange*, cells) from brain parenchym and perivascular spaces,
5 direct enzymatic Aβ degradation in the brain (green, enzymes),
6 elimination of Aβ from perivascular spaces by a passive drenage in dependence on pulse arterial flow
7 others?

Tau Protein

- Phosphoprotein tau (68 kDa) is a natively unfolded protein related to microtubules. It is responsible for microtubules stabilization.
- Affinity to microtubules is done by a different phosphorylation state on 79 possible places.
- Neurofibrillary tangles are often found in patients with AD. They are protein fillaments in the form of stabile insoluble polymers of this tau protein. The value of tau protein in CSF:
- In AD patients 300 - 900 pg/mL
- in Creutzfeldt-Jakob´s disease(CJD) - 1300 pg/mL
- More commonly as a marker for neuronal loss

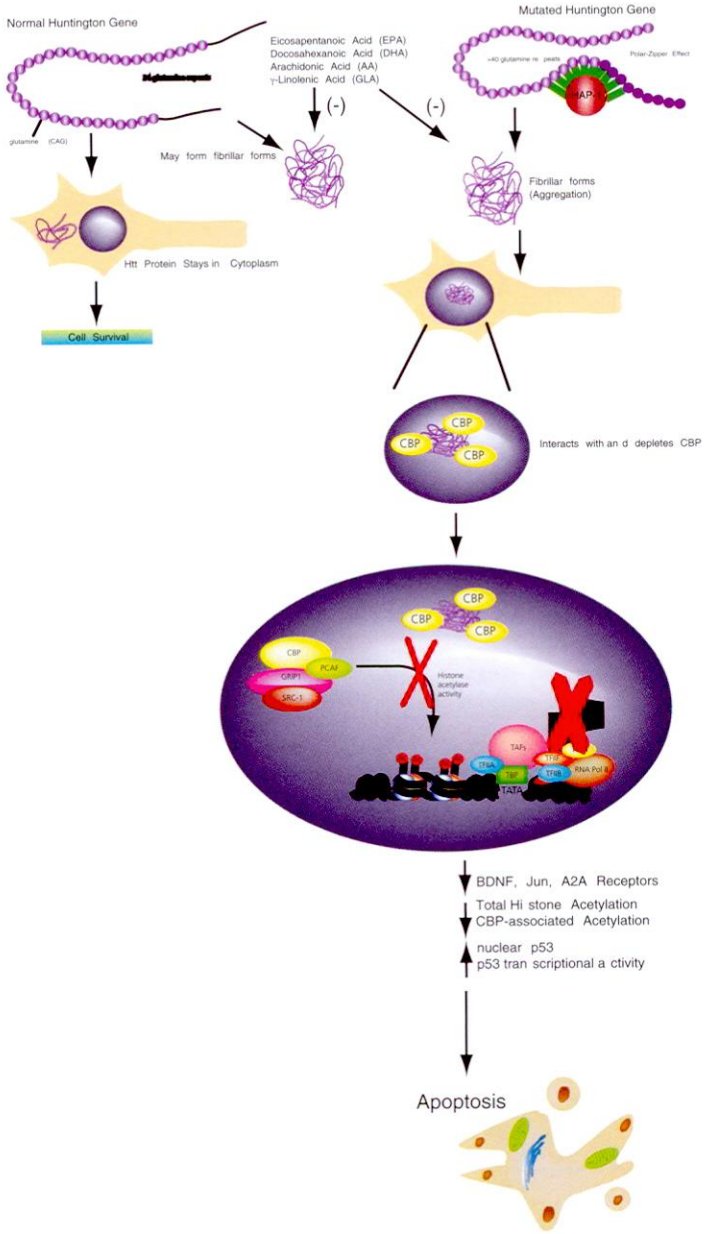
Figure 3. Tau Pathways





- ER – endoplasmic reticulum; GA – Golgiho aparát

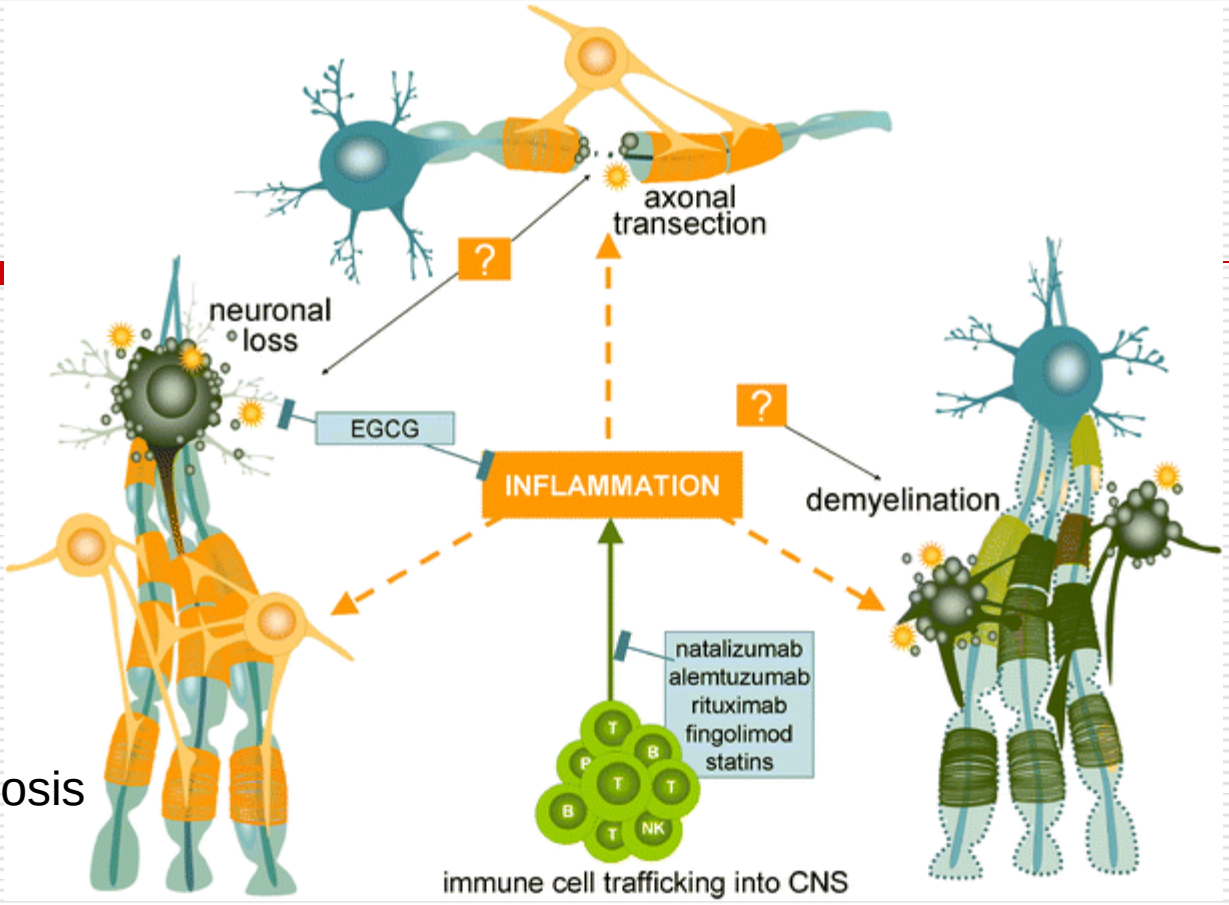
Figure 8. Huntington's Disease Pathway



Sclerosis multiplex

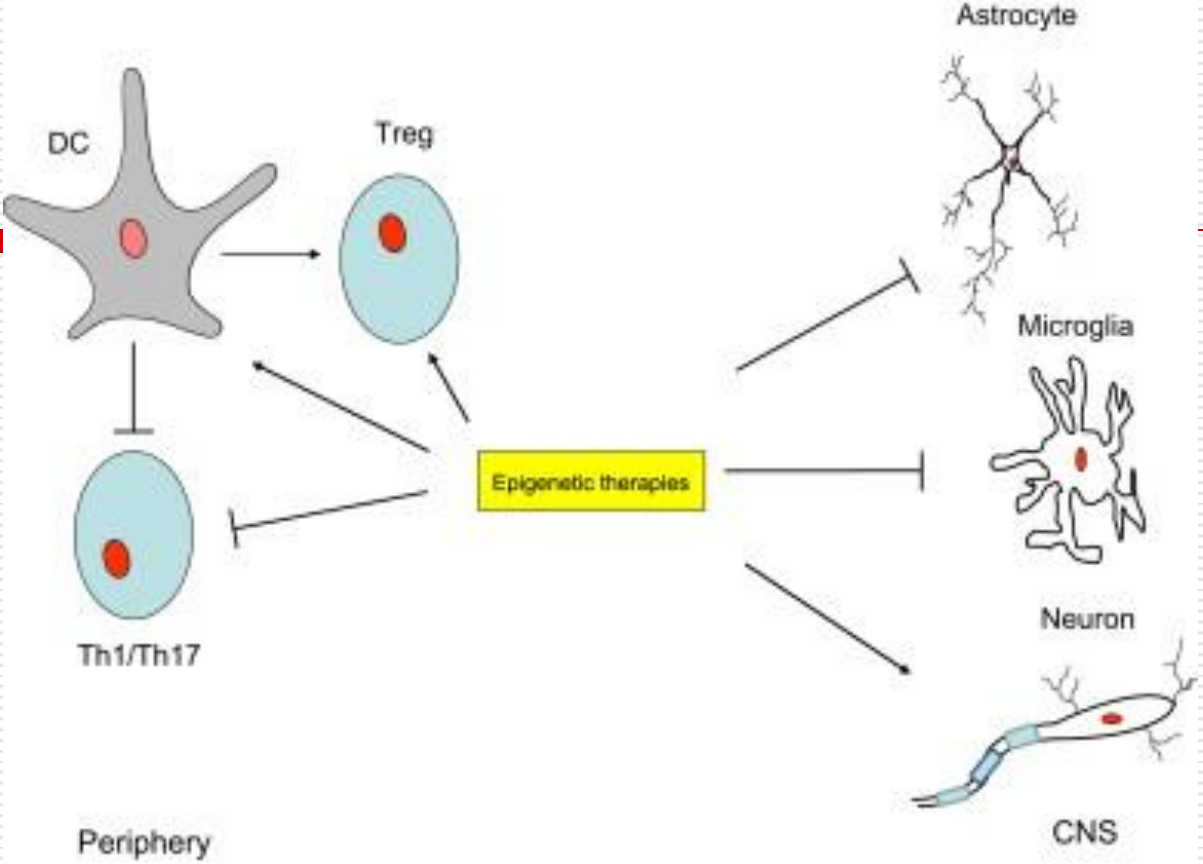
- The most frequent inflammatory disease of CNS
- Focal T cells, macrophage infiltrates, demyelinization and axonal loss.
- Several forms
- CD4+ autoreactive T cells.
- HLA-DR15 haplotype in Caucasians (DRB1 1501, DRB5 0101, DQA1 0102, DQB1 0602) brings the strongest genetic risk.

Multiple sclerosis



Current understanding of the pathogenesis of MS and potential therapeutic targets. Neuroinflammation has been classically described as the starting point in the pathology of MS. Myelin-specific T cells are believed to orchestrate the autoimmune attack that leads to oligodendrocyte damage and demyelination. Another hallmark of MS, however, is neuronal damage involving both axonal and neuronal loss. Demyelination, axonal transection, and neuronal loss are partly mediated by inflammation but might also occur independently of inflammatory activity. This current understanding of MS pathology impacts directly on therapy development. Ideally, patients need therapies that target both the process of inflammation and the process of neurodegeneration.

Multiple Sclerosis and Related Disorders
Volume 3, Issue 2, March 2014, Pages 163–175



Therapeutic potential of inhibitors of epigenetic processes in the treatment of multiple sclerosis.

Epigenetic drugs such as histone deacetylase inhibitors, lysine acetyltransferase inhibitors or DNA demethylating drugs have the capacity to rescue the distorted epigenetic processes that affect the expression of genes in MS. In this way these drugs mediate peripheral immunosuppressive activities either through skewing of dendritic cell function, or directly by inhibiting the activities of Th1/Th17 cells or by promoting the activities of Tregs. At the same time these drugs may also exhibit neuroprotective properties or interfere in disease-associated pathogenic processes in astrocytes or microglia.

Thank you for your attention